STATE OF KANSAS
OFFICE OF THE ATTORNEY GENERAL

KRIS W. KOBACH
ATTORNEY GENERAL

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August 19, 2026

Jessica Jensen
American Oversight
1030 15th Street NW
Suite B255
Washington, DC 20005

RE: Request for Records

Dear Ms. Jensen:

We have completed our review of records responsive to the search criteria in your request. As a reminder, you requested:

> All email communications (including emails, email attachments, complete email chains, calendar invitations, and calendar invitation attachments) between (a) any of the officials listed below, and (b) any of the external entities listed below, and (c) containing any of the key terms listed below, from May 1, 2025, through August 31, 2025.
>
> Office of the Attorney General Officials:
> a. Kris W. Kobach, Attorney General
> b. Joseph Sciarotta, Chief Deputy Attorney General
> c. Anthony Powell, Solicitor General
> d. James Rodriguez, Assistant Attorney General
> e. Michelle Schroeder, Chief of Staff
> f. Charles Dalton, Senior Advisor
> g. Anyone serving in the capacity of Chief of the Special Litigation and Constitutional Issues Division
> h. Anyone serving in the capacity of Chief of the Civil Division
> i. Anyone serving in the capacity of Chief of the Criminal Division
>
> External Entities:
> a. The Food and Drug Administration ("@fda.hhs.gov")
> b. The Department of Health and Human Services ("@hhs.gov")

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c. The White House ("who.eop.gov" or "whitehouse.gov")

Key Terms:
i. "abortion drug"
ii. "abortion medication"
iii. "abortion pill"
iv. "chemical abortion"
v. "in person dispensing"
vi. "in-person dispensing"
vii. "medication abortion"
viii. mifepristone-induced
ix. "Risk Evaluation and Mitigation"
x. "shield law"
xi. FAERS
xii. mifeprex
xiii. mifepristone
xiv. misoprostol
xv. REMS
xvi. "Louisiana v. FDA"
xvii. "LA v. FDA"
xviii. "Florida v. FDA"
xix. "FL v. FDA"
xx. "Missouri v. FDA"
xxi. "MO v. FDA"

Our search identified seven records responsive to the criteria set forth in your request. Those six records will be provided to you by electronic mail.

We hope this information is helpful. If you have any questions or require additional assistance, please contact the Office of the Attorney General at (785) 296-8495.

Sincerely,

OFFICE OF THE ATTORNEY GENERAL
KRIS W. KOBACH

Matt Bingesser
Administrative Counsel

AMERICAN OVERSIGHT

THE SECRETARY OF HEALTH AND HUMAN SERVICES

WASHINGTON, D.C. 20201

May 28, 2025

VIA ELECTRONIC MAIL

Dear Health Care Providers, Health Care Risk Managers, and State Medical Boards:

This letter advises you to read with care "Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices" (the Review) published by the U.S. Department of Health and Human Services (HHS) on May 1, 2025. The Review documents the "weak evidence and growing international retreat" (p. 205) from the use of puberty blockers, cross-sex hormones, and surgeries to treat gender dysphoria in minors and the "risk of significant harm" (p. 10). The Review explains that "many treatments (e.g., surgery, hormone therapy) can lead to relatively common and potentially serious long-term adverse effects" (p. 221). Given your "obligation to avoid serious harm" (p. 221) and the findings of the Review, HHS expects you promptly to make the necessary updates to your treatment protocols and training for care for children and adolescents with gender dysphoria to protect them from these harmful interventions.

The Review includes a methodologically rigorous assessment of evidence underpinning the use of surgical or endocrine interventions, including puberty blockers and cross-sex hormones, within the so-called "gender-affirming" model of care, while also drawing on international practice evaluations such as the U.K.'s Cass Review (April 2024). The Review documents serious concerns regarding the lack of reliable evidence of benefits and risks of significant harms for this model of care that have mounted in recent years, and points to psychotherapy (talk therapy) as a noninvasive alternative. As Sweden's national health authority has recommended, "[p]sychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures" (p. 247).

Providers should avoid relying on the World Professional Association for Transgender Health's (WPATH) *Standards of Care for the Health of Transgender and Gender Diverse People,* Version 8 (SOC-8). As the Review documents in detail, the creation of SOC-8 was fraudulent and marked "a clear departure from the principles of unbiased, evidence-driven clinical guideline development" (p. 172). To wit, in the context of developing its recommendations, WPATH suppressed systematic reviews of evidence, failed to manage conflicts of interest, and relied on legal and political considerations rather than clinical ones (p. 173). Health care risk managers should take note that a recent systematic review of international guideline quality did not recommend either the WPATH or the Endocrine Society guidelines for clinical use after determining they "lack developmental rigour and transparency" (p. 14). These and other guidelines based on the so-called "gender-affirming" model of care should not be relied upon to harm children any further (pg. 141).

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In contrast to WPATH SOC-8, the Review employs the tools of evidence-based medicine, widely recognized by health authorities worldwide as the foundation of high-quality care, and assesses the evidence underpinning the use of hormones and surgeries for minors. Specifically, it includes an "umbrella review," an overview of systematic reviews, which "found that the overall quality of evidence concerning the effects of these interventions on psychological outcomes, quality of life, regret, or long-term health, is very low" (p. 13). The Review also notes, based on what is known about human physiology and the effects and mechanisms of the pharmacological agents used, that there are risks of significant harms associated with the uses of puberty blockers, cross-sex hormones, and surgeries, including "infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret" (p. 10).

The Hippocratic Oath lays down the foundational commitment for the medical profession: "First, do no harm." The Review makes clear that "the evidence for benefit of pediatric medical transition is very uncertain, while the evidence for harm is less uncertain" (p. 15). For this reason, the Review states that when "medical interventions pose unnecessary, disproportionate risks of harm, healthcare providers should refuse to offer them even when they are preferred, requested, or demanded by patients" (ibid.).

The findings of the Review align with those of European countries, such as Sweden, Finland, and England, which have "sharply restricted" access to these interventions for minors following systematic reviews of evidence commissioned by their public health authorities, concluding that the risks outweighed the benefits (p. 246).

Health care providers are reminded, as the Centers for Medicare and Medicaid Services wrote in a Quality & Safety Special Alert memo on March 5, 2025, that "it is of utmost importance that all providers follow the highest standards of care and adhere closely to the foundational principles of medicine, especially as it comes to America's children." To this end, HHS published guidance on April 14, 2025, to protect whistleblowers who make reports concerning these harmful interventions for minors, including for waste, fraud, and abuse in HHS-funded programs, and created a portal to receive complaints at www.hhs.gov/protect-kids. HHS is committed to protecting whistleblowers to the full extent of the law. HHS may soon undertake new policies and oversight actions, consistent with applicable law, to ensure the protection of children, and to hold providers that harm children accountable.

Again, I urge you to read the Review and expect you to update your treatment protocols and training to ensure that our nation's children are protected from harm.

Sincerely,

/s/

Robert F. Kennedy, Jr.

Attachment: "Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices," U.S. Department of Health and Human Services, May 1, 2025, https://opa.hhs.gov/gender-dysphoria-report

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From: Jorgensen, Susan
To: Hutchison, Robert
Subject: FW: Letter to Health Care Providers on HHS Gender Dysphoria Report
Date: Monday, June 2, 2025 1:14:36 PM
Attachments: 5.28.25 Letter to Health Providers re Literature Review FINAL.pdf
Treatment for Pediatric Gender Dysphoria Review of Evidence and Best Practices.pdf

---

Robert –

Connie had mentioned to me that she was bringing the ACLU folder to you. You have probably already seen this but just in case I'm forwarding it. I have begun reading the 385-page document. In short from what I've gleaned so far: the hormone treatments can cause health problems:

- Doses are 40X what is naturally occurring in the recipient's body;
- Osteoperosis has been reported;
- The brain develops during pubescence so these drugs cause a halt in brain development;
- Infertility;
- Females may be sent into menopause-like symptoms;
- Regarding the psychological aspect, the treatment does not lessen the chance of suicide, and often young people with gender dysphoria have other accompanying mental health issues that may not be addressed.

I also found a great *short* article from Canada from a Pharmacist profession group – and I'm not just saying that because one of the authors is named Jorgensen– I'll forward that following this.

From: Dalton, Charles <Charles.Dalton@ag.ks.gov>
Sent: Thursday, May 29, 2025 4:23 PM
To: Jorgensen, Susan <Susan.Jorgensen@ag.ks.gov>
Subject: FW: Letter to Health Care Providers on HHS Gender Dysphoria Report

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Office of Kansas Attorney General Kris Kobach
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From: Stevens, Lee (OS/IEA) <Lee.Stevens@hhs.gov>
Sent: Wednesday, May 28, 2025 9:46 AM
To: Stevens, Lee (OS/IEA) <Lee.Stevens@hhs.gov>
Subject: Letter to Health Care Providers on HHS Gender Dysphoria Report

CAUTION: This email originated from outside of the Office of The Attorney General of Kansas organization. Do not click links or open attachments unless you recognize the sender and know the content is safe.

Dear State Partners,

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We appreciate your attention to this important information. Please do not hesitate to contact the Office of Intergovernmental and External Affairs if you have questions.

Darcie Johnston, Director
Office of Intergovernmental and External Affairs
US Department of Health and Human Services
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Attachment: "Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices," U.S. Department of Health and Human Services, May 1, 2025, https://opa.hhs.gov/gender-dysphoria-report

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Treatment for Pediatric Gender Dysphoria

Review of Evidence and Best Practices



Department of Health and Human Services

May 1, 2025

KS-AG-26-1037-A-000009

Minor corrections made May 15, 2025: see Errata

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Foreword

Over the past decade, the number of children and adolescents who question their sex and identify as transgender or nonbinary has grown significantly. Many have been diagnosed with a condition known as “gender dysphoria” and offered a treatment approach known as “gender-affirming care.” This approach emphasizes social affirmation of a child’s self-reported identity; puberty suppressing drugs to prevent the onset of puberty; cross-sex hormones to spur the secondary sex characteristics of the opposite sex; and surgeries including mastectomy and (in rare cases) vaginoplasty. Thousands of American children and adolescents have received these interventions.

While sex-role nonconformity itself is not pathological and does not require treatment, the use of pharmacological and surgical interventions as treatments for pediatric gender dysphoria has been called “medically necessary” and even “lifesaving.” Motivated by a desire to ensure their children’s health and well-being, parents of transgender-identified children and adolescents often struggle with how best to support them. Many of these children and adolescents have co-occurring psychiatric or neurodevelopmental conditions, rendering them especially vulnerable. When they seek professional help, they and their families should receive compassionate, evidence-based care tailored to their specific needs.

Society has a special responsibility to safeguard the well-being of children. Given that the challenges faced by these patients intersect with deeply contested issues of moral and social significance—including social identity, sex and reproduction, bodily integrity, and sex-based norms of expression and behavior—the medical practices that have recently emerged to address their needs have become a focus of significant controversy.

This Review is published against the backdrop of growing international concern about pediatric medical transition. Having recognized the experimental nature of these medical interventions and their potential for harm, health authorities in a number of countries have imposed restrictions. For example, the U.K. has banned the routine use of puberty blockers as an intervention for pediatric gender dysphoria.

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Health authorities have also recognized the exceptional nature of this area of medicine. That exceptionalism is due to a convergence of factors. One is that the diagnosis of gender dysphoria is based entirely on subjective self-reports and behavioral observations, without any objective physical, imaging, or laboratory markers. The diagnosis centers on attitudes, feelings, and behaviors that are known to fluctuate during adolescence.

Additionally, the natural history of pediatric gender dysphoria is poorly understood, though existing research suggests it will remit without intervention in most cases. Medical professionals have no way to know which patients may continue to experience gender dysphoria and which will come to terms with their bodies.

Nevertheless, the "gender-affirming" model of care includes irreversible endocrine and surgical interventions on minors with no physical pathology. These interventions carry risk of significant harms including infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret. Meanwhile, systematic reviews of the evidence have revealed deep uncertainty about the purported benefits of these interventions.

The controversies surrounding the medical transition of minors extend beyond scientific debate; they are deeply cultural and political. Public discourse is dominated by intensely polarizing narratives. Some view the medical transition of minors as a pressing civil rights issue, while others regard it as a profound medical failure and a sobering reminder that even modern medicine is vulnerable to serious error. In the midst of this highly charged debate, children and adolescents, and their families—who seek only to support their flourishing—have found themselves caught between competing perspectives. They require, and are entitled to, accurate, evidence-based information to guide their decisions.

This Review of evidence and best practices was commissioned pursuant to Executive Order 14187, signed on January 28, 2025. It is not a clinical practice guideline, and it does not issue legislative or policy recommendations. Rather, it seeks to provide the most accurate and current information available regarding the evidence base for the

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treatment of gender dysphoria in this population, the state of the relevant medical field in the United States, and the ethical considerations associated with the treatments offered.

The Review is intended for policymakers, clinicians, therapists, medical organizations and, importantly, patients and their families. It summarizes, synthesizes, and critically evaluates the existing literature on best practices for promoting the health and well-being of children and adolescents with distress related to their sex or to social expectations associated with their sex. Treatment of adults constitutes a separate topic and is not addressed in this Review. A summary of the Review's main findings is presented below.

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Executive Summary

Part I: Background

- Gender dysphoria is a condition that involves distress regarding one's sexed body and/or associated social expectations. Increasing numbers of children and adolescents in the U.S. and other countries are diagnosed with gender dysphoria. Internationally, there is intense disagreement about how best to help them.
- The term "rapid onset gender dysphoria" (ROGD) has been suggested to describe a new clinical presentation of gender dysphoria. Despite sharp disagreement about the concept's validity, symptoms consistent with ROGD have been recorded in clinics in the U.S. and other countries.
- In the U.S., the current approach to treating pediatric gender dysphoria aligns with the "gender-affirming" model of care recommended by the World Professional Association for Transgender Health (WPATH). This model emphasizes the use of puberty blockers and cross-sex hormones, as well as surgeries, and casts suspicion on psychotherapeutic approaches for management of gender dysphoria.
- The understandable desire to avoid language that may cause discomfort to patients has, in some cases, given rise to modes of communication that lack scientific grounding, that presuppose answers to unresolved ethical controversies, and that risk misleading patients and families. This Review uses scientifically accurate and neutral terminology throughout.
- In many areas of medicine, treatments are first established as safe and effective in adults before being extended to pediatric populations. In this case, however, the opposite occurred: clinician-researchers developed the pediatric medical transition protocol in response to disappointing psychosocial outcomes in adults who underwent medical transition.
- The protocols were adopted internationally before the publication of the first outcome studies. In recent years, in response to dramatic shifts in the number

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and clinical profiles of minor patients, as well as to multiple systematic reviews of evidence, health authorities in an increasing number of countries have restricted access to puberty blockers and cross-sex hormones, and, in the rare cases where they were offered, surgeries for minors. These authorities now recommend psychosocial approaches, rather than hormonal or surgical interventions, as the primary treatment.

- There is currently no international consensus about best practices for the care of children and adolescents with gender dysphoria.

Part II: Evidence Review

- Evidence-based medicine is widely recognized by health authorities worldwide as the foundation of high-quality care. Consistent with its principles, this Review undertook a methodologically rigorous assessment of the evidence underpinning pediatric gender medicine.
- Specifically, this Review conducted an overview of systematic reviews—also known as an "umbrella review"—to evaluate the direct evidence regarding the benefits and harms of treatment for children and adolescents with gender dysphoria. Existing systematic reviews of evidence, including several that have informed health authorities in Europe, were assessed for methodological quality. The umbrella review found that the overall quality of evidence concerning the effects of any intervention on psychological outcomes, quality of life, regret, or long-term health, is very low. This indicates that the beneficial effects reported in the literature are likely to differ substantially from the true effects of the interventions.
- Evidence for harms associated with pediatric medical transition in systematic reviews is also sparse, but this finding should be interpreted with caution. Inadequate harm detection in pediatric gender medicine may reflect the relatively short period of time since the widespread adoption of the medical/surgical treatment model; the failure of existing studies to systematically track and report harms; and publication bias. Despite the lack of robust evidence from population level studies, important insights can be drawn from established knowledge about

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human physiology and the effects and mechanisms of the pharmacological agents used.

- The risks of pediatric medical transition include infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret.

Part III: Clinical Realities

- In the U.S., the most influential clinical guidelines for the treatment of pediatric gender dysphoria are published by WPATH and the Endocrine Society. A recent systematic review of international guideline quality did not recommend either guideline for clinical use after determining they "lack developmental rigour and transparency."[1]
- Problems with the development of WPATH's *Standards of Care*, Version 8 (SOC-8) extend beyond those identified in the systematic review of international guidelines. In the process of developing SOC-8, WPATH suppressed systematic reviews its leaders believed would undermine its favored treatment approach. SOC-8 developers also violated conflict of interest management requirements and eliminated nearly all recommended age minimums for medical and surgical interventions in response to political pressures.
- Although SOC-8 relaxed the eligibility criteria for access to puberty blockers, cross-sex hormones, and surgeries, there is compelling evidence that U.S. gender clinics are not adhering even to those more permissive criteria.
- The "gender-affirming" model of care, as practiced in U.S. clinics, is characterized by a child-led process in which comprehensive mental health assessments are often minimized or omitted, and the patient's "embodiment goals" serve as the primary guide for treatment decisions. In some of the nation's

[1] Taylor, Hall, Heathcote et al. (2024a, p. 7).

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leading pediatric gender clinics, assessments are conducted in a single session lasting two hours.

- The voices of whistleblowers and detransitioners have played a critical role in drawing public attention to the risks and harms associated with pediatric medical transition. Their concerns have been discounted, dismissed, or ignored by prominent advocates and practitioners of pediatric medical transition.
- U.S. medical associations played a key role in creating a perception that there is professional consensus in support of pediatric medical transition. This apparent consensus, however, is driven primarily by a small number of specialized committees, influenced by WPATH. It is not clear that the official views of these associations are shared by the wider medical community, or even by most of their members. There is evidence that some medical and mental health associations have suppressed dissent and stifled debate about this issue among their members.

Part IV: Ethical Considerations

- The principle of autonomy in medicine establishes a moral and legal right of competent patients to refuse any medical intervention. However, there is no corollary right to receive interventions that are not beneficial. Respect for patient autonomy does not negate clinicians' professional and ethical obligation to protect and promote their patients' health.
- The evidence for benefit of pediatric medical transition is very uncertain, while the evidence for harm is less uncertain. When medical interventions pose unnecessary, disproportionate risks of harm, healthcare providers should refuse to offer them even when they are preferred, requested, or demanded by patients. Failure to do so increases the risk of iatrogenic harm and reduces medicine to consumerism, threatening the integrity of the profession and undermining trust in medical authority.
- Proponents of pediatric medical transition claim that regret is vanishingly rare, while critics assert that regret is increasingly common. The true rate of regret is

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not known and better data collection is needed. That some patients report profound regret after undergoing invasive, life-changing medical interventions is clearly of importance. However, regret alone (just like satisfaction alone) is not a valid indicator of whether an intervention is medically justified. Patients may regret medically justified treatments or feel satisfied with unjustified ones.

- A natural response to the absence of credible evidence is to call for more and better research. Even if high quality research such as randomized controlled trials on pubertal suppression or hormone therapy were feasible, however, conducting it may conflict with well-established ethical standards for human subjects research.

Part V: Psychotherapy

- The rise in youth gender dysphoria and the corresponding demand for medical interventions have occurred against the backdrop of a broader mental health crisis affecting adolescents. The relationship between these two phenomena remains a subject of scientific controversy.
- Suicidal ideation and behavior are independently associated with comorbidities common among children and adolescents diagnosed with gender dysphoria. Suicidal ideation and behavior have known psychotherapeutic management strategies. No independent association between gender dysphoria and suicidality has been found, and there is no evidence that pediatric medical transition reduces the incidence of suicide, which remains, fortunately, very low.
- There is a dearth of research on psychotherapeutic approaches to managing gender dysphoria in children and adolescents. This is due in part to the mischaracterization of such approaches as “conversion therapy.” A more robust evidence base supports psychotherapeutic approaches to managing common comorbid mental health conditions. Psychotherapy is a noninvasive alternative to endocrine and surgical interventions for the treatment of pediatric gender dysphoria. Systematic reviews of evidence have found no evidence of adverse effects of psychotherapy in this context.

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PART 1

BACKGROUND

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Chapter 1 Introduction

Currently, an estimated 3.3% of adolescents in the United States identify as transgender, and an additional 2.2% question whether they might be.[1] Many have received hormonal or surgical treatment for accompanying distress. A 2023 study published in the *Journal of the American Medical Association* found that between 2016 and 2020, 3,215 patients between the ages of 12 and 18 received surgical "breast or chest procedures" relating to their transgender identity.[2] A more recent study reported that approximately 0.1% of American 17-year-olds, or one in 1,000, was receiving cross-sex hormones between 2018 and 2022.[3] A national estimate of clinics offering pediatric medical transition interventions found at least 271 such institutions in the U.S. as of March 2023.[4]

This Review assesses the existing literature on best practices for promoting the health of children and adolescents with gender dysphoria (GD; serious distress at one's sexed body and associated social expectations[5]) or milder forms of such distress. Treatment of GD in adults is a separate topic and is not covered here.

In the United States, a number of institutions follow the guidelines of the World Professional Association for Transgender Health (WPATH) and the Endocrine Society (ES) for treating gender-dysphoric children and adolescents. This approach is usually called "gender-affirming care." Diane Ehrensaft, Director of Mental Health at UCSF's Child & Adolescent Gender Center, is a leading proponent. As Ehrensaft explains,

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[1] Suarez et al. (2024, Table 2).
[2] Wright et al. (2023).
[3] Hughes et al. (2025).
[4] Borah et al. (2023, p. 375-376). Some of these clinics were closed due to state age restriction laws.
[5] As an American Psychological Association report put it, quoting the American Psychiatric Association, gender dysphoria is an "aversion to some or all of those physical characteristics or social roles that connote one's own biological sex" (Schneider et al., 2009, p. 28). As explained in Zucker et al. (2016), "gender dysphoria" is a "technical term" that refers to symptoms of distress, but is also, as of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (2013), a "diagnostic term" (p. 218). Gender Dysphoria is a formal diagnosis in the current (text revision) version of the DSM-5, the DSM-5-TR (American Psychiatric Association, 2022). For the relevant diagnostic criteria for children, adolescents, and adults in the DSM-III, IV, and 5, and in the current *International Classification of Diseases* (ICD-11), see Appendix 2 of this Review. The term "gender dysphoria" is used throughout this Review to refer to sex-related distress or discomfort, unless the context makes clear that the formal diagnosis is the topic.

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> [gender-affirming care] is defined as a method of therapeutic care that includes allowing children to speak for themselves about their self-experienced gender identity and expressions and providing support for them to evolve into their authentic gender selves, no matter at what age. Interventions include social transition from one gender to another and/or evolving gender nonconforming expressions and presentations, as well as later gender-affirming medical interventions (puberty blockers, cross-sex hormones, surgeries).[6]

This Review is needed because—as later chapters will detail—the emphasis on medicalization makes the field of pediatric gender medicine (PGM) highly controversial. WPATH and ES guidelines recommend commencement of puberty blockers (drugs that halt pubertal development) at the earliest signs of puberty (i.e. Tanner Stage 2), which may begin as early as age 8 in girls and 9 in boys. According to these guidelines,[7] cross-sex hormones (CSH; estrogen for boys and testosterone for girls) are started sometime thereafter; surgeries (e.g., breast removal for girls) are also recommended for some adolescents.[8] All these interventions are associated with significant risks, and most cause irreversible physical or physiological effects.[9]

Do PBs, CSH, and surgeries constitute best practice for this population? Guidelines and policies promulgated by professional medical societies in the U.S. differ from some European guidelines that recommend psychotherapy, *not* hormones or surgeries, for children and adolescents with GD. This Review, then, is written against a backdrop of intense disagreement in the international medical community. The number of young people with GD has surged, and many are suffering, as are their families. The question of how to best help these patients hinges on a comprehensive assessment of the evidence base for different treatment approaches, together with ethical considerations. Bringing ethical principles to bear on the evidence is one goal of this Review. While the need for respect and compassion resonates with all reasonable Americans, an invasive

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[6] Ehrensaft (2017a, p. 62). The gender-affirming approach can be applied to adults too; this Review is entirely focused on the pediatric variety.
[7] Coleman et al. (2022); Hembree et al. (2017).
[8] The latest version of WPATH's clinical practice guideline has no recommended age limits for surgical procedures, with the exception of 18 years old for phalloplasty (the construction of a neophallus in females with skin taken from the patient's arm or leg).
[9] See Chapter 7.

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treatment with lifelong ramifications deserves the highest level of dispassionate scrutiny.[10]

The diagnostic description of GD has changed since the condition appeared in the third edition (1980) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), as has the terminology used to name it. But one thing has not changed. The DSM-III was clear that "Gender Identity Disorder of Childhood" was "not merely the rejection of stereotypical sex role behavior as, for example, in 'tomboyishness' in girls or 'sissyish' behavior in boys"[11]; the current DSM has a similar emphasis: "The diagnosis is not meant to merely describe nonconformity to stereotypical gender role behavior (e.g., "tomboyism" in girls, "girly-boy" behavior in boys, occasional cross-dressing in adult men)."[12] Non-conformity to sex-role stereotypes is as old as history, and present to some degree in every known culture.[13] This feature of the human experience is not pathological and needs no treatment. What may require treatment is the suffering experienced by those alienated from their sexed bodies.

PGM is a complex topic. This Review, therefore, will cover the field's history and evolution in some detail, from the inception of the medicalized approach in the Netherlands (Chapter 3)[14] to current treatment practices in the U.S. and other countries (Chapter 4, Chapter 9). The Review describes an international trend of retreat from the present "gender affirming" approach and reviews the reasons underlying it.

This Review finds that clinical practice in this field of medicine is exceptional and concerning (Chapter 11). The influential PGM guidelines followed in the U.S. are especially problematic. They were developed in ways that contravene best practices for

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[10] The U.K.'s Cass Review pointed out that although some conceptualize controversies about pediatric gender medicine primarily from political/social standpoints, healthcare guidance should "[work] in an evidence-based way" (Cass, 2024a, p. 20).
[11] American Psychiatric Association (1980, p. 264).
[12] American Psychiatric Association (2013, p. 458).
[13] See Chapter 3, Note 1.
[14] The general treatment paradigm of puberty blockers, cross-sex hormones, and surgeries originated in the Netherlands in the 1990s as an experimental research protocol, and, based on one small study that claimed to demonstrate significant benefits to mental health, was rapidly incorporated internationally into standard practice. As described in the Cass Review's interim report, the "affirmative model" is a "model of gender healthcare that originated in the USA which affirms a young person's subjective gender experience while remaining open to fluidity … This approach is used in some key child and adolescent clinics across the Western world" (Cass, 2022a, p. 78).

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guideline development (Chapter 9, Chapter 10). This Review also finds evidence of extreme toxicity and polarization surrounding this field of medicine. ("There are few other areas of healthcare where professionals are so afraid to openly discuss their views … where name-calling echoes the worst bullying behaviour."[15]) Additionally, this Review describes the inadequate response of professional medical and mental health associations to new evidence and controversies (Chapter 12).

Section 1.1 of this opening chapter emphasizes the exceptional nature of PGM. Section 1.2 outlines the role that evidence-based medicine (EBM) plays in the Review; Section 1.3 does the same for medical ethics.

1.1 Exceptionalism

The field of PGM is exceptional due to the convergence of several distinct features.

First, the *diagnostic criteria* for GD are based solely on subjective reports and behavioral observations in patients with no objective physical pathology; there are no verifiable physiological or biochemical markers–such as abnormal imaging, lab, or clinical findings–to confirm the GD diagnosis.[16]

Second, the condition's *natural course* (also known as "natural history")—i.e., what happens when the condition remains untreated—appears to tend toward resolution absent medical and/or social transition interventions for a significant number of affected youths (see Chapter 4). While the condition will persist in some affected adolescents into adulthood, the Cass Review, commissioned by England's National Health Service (NHS), found that while "a diagnosis of gender dysphoria has been the basis for initiating medical treatment … this is not predictive that the individual will go on to have longstanding trans identity."[17]

Third, the treatments recommended by the medicalized approach are invasive, usually irreversible, and their purported benefits are based on poor quality evidence. In addition

[15] Cass (2024a, p. 13).
[16] Laidlaw et al. (2019). The same goes for the ICD's diagnosis of "gender incongruence": for discussion, see Section 13.4.
[17] Cass (2024a, p. 146).

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to infertility and impairment of sexual function, the anticipated harms include adverse effects on bone health, cardiovascular function, and possible negative impacts on brain development (see Chapter 7).

When taken separately, *none* of these features is unique in medicine. Nearly all mental health and some physical health diagnoses are made on the basis of self-reports and behavioral observations. Also, there are other pediatric conditions such as mild ear infections and strep throat that are self-limiting but still treated to reduce discomfort, promote faster recovery, or prevent complications. Lastly, there are instances in which patients are offered treatments even if the benefits of those treatments are profoundly uncertain and harms are expected. For example, craniotomies are performed to remove certain malignant brain tumors, even though these interventions carry a high risk of permanent adverse effects and the overall prognosis remains poor even with treatment. (In such cases, however, the alternative to intervention is a significantly shorter life expectancy.) What makes PGM exceptional is not any one of these features, but their combination.

Is the fundamental goal of treatment to manage gender dysphoria, a condition recognized in the DSM's catalogue of mental disorders? Or is it to manage common comorbidities such as depression, anxiety, and suicidal ideation? Or, alternatively, is it to help individuals realize their "embodiment goals" (i.e., cosmetic desires)? The stated rationales for these interventions have shifted over time, following decades of research that failed to provide credible evidence of benefit (see Chapter 5). This unclarity surrounding the treatments' fundamental aims is yet another way in which PGM is exceptional. In contrast, there is broad consensus about the purpose of medical intervention for conditions like appendicitis, diabetes, or severe depression.

1.2 Evidence

When assessing a medical intervention, one of the most important questions is: Is it safe and effective? Does drug X reduce all-cause mortality for cancer patients? Does talk therapy alleviate depression? Does knee surgery relieve arthritis pain with few postoperative complications? Even if the treatment is effective, it may not be safe, and there may be better alternatives.

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In the case of invasive treatments for GD, medical authorities in the United States have issued statements indicating that the matter is settled. According to the American Medical Association (AMA):

> Improving access to gender-affirming care is an important means of improving health outcomes for the transgender population. Receipt of gender-affirming care has been linked to dramatically reduced rates of suicide attempts, decreased rates of depression and anxiety, decreased substance use, improved HIV medication adherence and reduced rates of harmful self-prescribed hormone use.[18]

In 2022, the then Assistant Secretary for Health at the U.S. Department of Health and Human Services, Admiral Rachel Levine, gave an even more unqualified endorsement:

> Gender-affirming care is medical care. It is mental health care. It is suicide prevention care. It improves quality of life, and it saves lives. It is based on decades of study. It is a well-established medical practice.[19]

However, according to the U.K.'s April 2024 Cass Review, the most comprehensive assessment of PGM to date:

> This is an area of remarkably weak evidence, and yet results of studies are exaggerated or misrepresented by people on all sides of the debate to support their viewpoint. The reality is that we have no good evidence on the long-term outcomes of interventions to manage gender-related distress.[20]

Whether the approach endorsed by the AMA is based on adequate evidence is the subject of intense controversy. What is considerably less controversial is the best framework for assessing the efficacy of treatments. That framework is EBM, adopted by this Review.

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[18] American Medical Association (2022).
[19] Levine (2022).
[20] Cass (2024a, p. 13).

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1.2.1 Evidence-based medicine

The physician and researcher Gordon Guyatt—who coined the term "evidence-based medicine" in 1991—describes EBM as follows:

> Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature.[21]

EBM sees carefully controlled clinical trials as especially important, along with "systematic reviews" (SRs), methodical syntheses and evaluations of all relevant available evidence. Various "hierarchies of evidence" have been proposed, with SRs at the top and the opinions of individual clinicians, which, although usually valuable, are subject to a variety of biases, at the bottom. EBM has been widely accepted by health authorities around the world.[22]

In keeping with EBM principles, this Review is informed by a methodologically rigorous assessment of the evidence underpinning PGM. An overview of SRs was conducted, and its findings are presented in Chapter 5 and in Appendix 4. In brief, the overview independently confirms Cass's observation that "this is an area of remarkably weak evidence."

Given its emphasis on clinical trials, EBM is less sensitive to evidence about known mechanisms of drug action or relevant biology more broadly. This limits the ability of SRs to uncover potential causal pathways or to understand observed associations or their absence (Chapter 6). Accordingly, Chapter 7 supplements the overview of SRs with evidence from basic science, including physiology. As detailed in that chapter, the risk of harm from the medicalized approach to treating pediatric GD is serious.

[21] Guyatt et al. (1992, p. 2420). See also Akobeng (2005).
[22] E.g. Darzi (2008); Margolis (2018); Carande-Kulis (2022).

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It is important to recognize that evaluating the evidence for a treatment's efficacy does not, on its own, determine whether the treatment ought to be offered. SRs or other sources of high-quality evidence are not rigid formulas for making medical decisions; rather, they are essential components of the decision-making process. The principle is explicitly acknowledged in EBM. Medical evidence is not sufficient to justify clinical recommendations or decisions; other considerations—such as patient values and preferences—also play a critical role.[23] However, as emphasized below, these preferences do not override physicians' ethical and professional duties.

1.2.2 History lessons

An unreasonable skepticism toward medical expertise can lead to patient harm and even death.[24] On the other hand, while physicians are often capable of remarkable healing, they are not immune to human error or bias. However well-intentioned, doctors are not infallible. Even the consensus of professional medical associations can, at times, be mistaken.

Peanut allergies are a recent example. In 2000, the American Academy of Pediatrics (AAP) advised that infants deemed "high risk" should avoid peanuts—and that breastfeeding mothers do the same. In practice, this guidance was widely interpreted as a recommendation for all infants to avoid peanuts as a precaution. Peanut allergies increased dramatically, and in 2017 the AAP reversed course, recommending early *introduction* of peanuts for the highest-risk infants.[25]

This is just one of many examples.[26] Medical error is more prevalent than many Americans realize. Consensus does not guarantee correctness—in fact, it can sometimes entrench error. Nor should it be assumed that all treatment recommendations are motivated by altruism, as the opioid overprescription crisis has starkly demonstrated. This is not to suggest that medical consensus is inherently untrustworthy, but rather that it should be approached with critical scrutiny, not

[23] Djulbegovic & Guyatt (2017, p. 416); see also Guyatt et al. (2000).
[24] Centers for Disease Control (2025).
[25] Makary (2024, Chapter 1).
[26] Apart from Makary (cited above), see Prasad & Cifu (2019, Chapters 1, 2) and Patashnik et al. (2017, Chapter 2).

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unquestioning acceptance. The physicians and researchers Vinay Prasad and Adam Cifu succinctly make this point:

> We expect that medical therapy will change and evolve with time. Good treatments will replace bad ones, and then better ones will replace those. Antibiotics have replaced arsenic, and anesthesia has replaced a bullet held bracingly between the teeth. Recently, however, change has occurred in surprising ways. If you have followed the news about prostate cancer screening, mammography for women in their forties, hormone replacement, cholesterol-lowering medications, and stents for coronary-artery disease, you might think doctors cannot get anything straight. These common practices were not replaced by better therapies; they were found to be ineffective. In some cases, they did more harm than good. You might be worried that some medical practices are nothing more than fads. In some cases, you would be right.[27]

1.3 Ethics

Finding safe and effective treatments is only part of medicine's mission. Questions of ethics–and the complex theoretical issues they raise–emerge immediately alongside clinical decision-making. What if a treatment is effective but the patient doesn't want it? When is informed consent needed before starting treatment? Should doctors ever lie to their patients? What is the difference between cosmetic procedures and those that alleviate a medical problem? What should we do when clinicians disagree with pediatric patients or their parents about the best medical course of action? These and numerous similar questions are the topic of the academic field known as *medical ethics*.[28]

EBM is only decades old, but medical ethics is as old as medicine itself. The Hippocratic Oath, originating in the fourth century BCE, and attributed to the ancient Greek physician Hippocrates, is a pledge to uphold ethical principles in medicine. The Hippocratic writings include: "I will use treatment to help the sick according to my ability

[27] Prasad & Cifu (2019, p. 11).
[28] An alternative name is *biomedical ethics*. *Bioethics* is a broader field encompassing ethical issues in the life sciences beyond healthcare. Although medical ethics is an academic discipline, medical ethicists often work in clinics and hospitals, supporting patients and their families, and assisting clinicians in developing policies.

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and judgment, but I will never use it to injure or wrong them."[29] This commitment laid the foundation for the medical maxim *Primum non nocere*: First, do no harm.[30] Together with the duty of non-maleficence (avoiding harm), the duty of beneficence (promoting the patient's well-being) "undergirds all medical and health care professions and their institutional settings."[31] These duties have been continually affirmed by professional medical societies. For example, the World Medical Association's Declaration of Geneva, first published in 1948 and last revised in 2017, requires physicians to respect the "autonomy and dignity" of patients but recognizes the primacy of non-maleficence and beneficence: "The health and well-being of my patient will be my first consideration."[32]

Importantly, the physician's duties of non-maleficence and beneficence are not overridden by the patient's desire for a particular course of treatment. In 2002, the American Board of Internal Medicine Foundation, the American College of Physicians Foundation, and the European Federation of Internal Medicine articulated this point in a "Physician Charter." Among the three "fundamental principles" of the charter is the "Principle of patient autonomy," defined as follows:

> Physicians must have respect for patient autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients' decisions about their care must be paramount, *as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care*.[33]

One central question this Review attempts to answer is whether pediatric medical transition—and in particular the provision of hormonal or surgical interventions to children and adolescents—is consistent with widely-accepted principles of medical ethics. This is examined in Chapter 13. Another treatment approach—psychotherapy (talk therapy)—is examined in Chapter 14.

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[29] Beauchamp & Childress (2019, p. 155). Graduating medical students today recite a variety of oaths, sometimes composing them themselves (Weiner, 2018).
[30] The Latin phrase does not trace back to ancient times: it may have been devised by the seventeenth century English physician Thomas Sydenham (1624-1689), the "English Hippocrates" (Smith, 2005).
[31] Beauchamp & Childress (2019, p. 155).
[32] Parsa-Parsi (2017, p. 1971).
[33] American Board of Internal Medicine Foundation (2002, emphasis added).

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The innovation and responsiveness of the U.S. medical system has made it the envy of the world. However, errors are unavoidable in healthcare. The test of a medical system is not its ability to avoid mistakes, but rather how it responds once mistakes become apparent.

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Chapter 2 Terminology in Pediatric Gender Medicine

The choice of words can affect medical decision-making. Medical providers have a professional duty to apprise their patients of their conditions and the treatment options in language that is accurate, ethically neutral, and in no way misleading.[1] In the case of pediatric gender medicine (PGM), language has distorted the clinical picture, obscuring important distinctions. This chapter addresses that issue. Section 2.1 examines commonly used terminology, while Section 2.2 clarifies the specific terms adopted in this Review.

2.1 Terminology in pediatric gender medicine

Concerns about proper terminology and disclosure of all relevant information are common in medicine generally, particularly in the context of physician-patient interactions.[2] PGM, however, presents unique challenges. In this context, the understandable desire to avoid exclusionary or pathologizing language—combined with beliefs firmly embedded in the field—has led to a vocabulary and a mode of communicating that is scientifically ungrounded, that presupposes answers to ethical controversies, and that is in other ways misleading.[3]

Nearly all the core terms used in PGM exhibit these kinds of issues. As mentioned in Chapter 1, the preferred label for the treatment approach endorsed by the World Professional Association for Transgender Health (WPATH), the Endocrine Society (ES), the American Academy of Pediatrics (AAP) and the American Medical Association (AMA) is "gender-affirming care." The surgical removal of breasts (mastectomy) in physically healthy females is called "gender-affirming chest surgery" or "top surgery."[4] "Affirming" has a positive connotation, and someone who objects to "gender-affirming

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[1] Importantly, accuracy and neutrality are not enough. "80% of patients given drug A recovered" is ethically bland; suppose it is also true. Absent further context that statement is misleading if 80% of patients *not* given drug A also recovered. Another example: if a physician truthfully tells a patient, "You either have cancer or a harmless cyst," knowing that the patient has cancer, the patient has been misled.
[2] Shaw et al. (2022).
[3] For related examples in the field of women's health, see Gribble (2025). See also Bartick et al. (2025); the authors make the point that "transgender and gender-diverse people need clear and unambiguous health communications, including those related to sex-based needs, conditions, and symptoms, as much as any other group" (p. 5).
[4] E.g. Coleman et al. (2022, p. S130).

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surgery" sounds lacking in compassion. The euphemisms "chest surgery" and "top surgery" gloss over the relevant fact that breasts are removed.

Word choices can obscure patients' young ages. Terms such as "people" or "folks" are sometimes used by proponents of medicalized interventions instead of "children" or "adolescents." It is frequently emphasized that prepubertal children are not prescribed hormones or surgeries. That is true. However, clinical guidelines recommend initiating puberty blockers (PBs) at pubertal onset, which can occur at 8 or 9 years old—meaning that such interventions may be started during childhood. In discussions of this recommendation, "young people" or "adolescents" are sometimes substituted for "children."[5] Again, this helps camouflage the fact that sometimes serious medical interventions are performed on children's healthy bodies.[6]

Some adolescents transition and later detransition, reverting to living as their sex, changing their name back and making other necessary social adjustments. If the adolescent has undergone some degree of medical transition, the process of detransitioning can present significant challenges.[7] These difficulties are sometimes downplayed through the use of "retransitioning"[8] instead of "detransitioning," or writing

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[5] E.g., from a National Association of Social Workers fact sheet: "MYTH: Gender-affirming hormones, or hormone replacement therapy (HRT), are given to *children*," and: "During and after puberty, some medical treatments may be available [for] the *youth*" (National Association of Social Workers, n.d., emphasis added). According to the AAP, childhood spans ages 2-12 (Hardin et al., 2017).

"Adolescent" is often used for children in the early stages of puberty, when a layperson would use "child." As a member of WPATH put it in an email: "I would avoid children and hormones, and stick to medical definitions: when a young person reaches … puberty, [they are] therefore classed as adolescents (whether they are 9 or 12)," quoted in Boe v. Marshall, No. 2:22-cv-00184: 557-9/700-2 (2024, p. 16). See also Ryan (2025): "Dr. Olson-Kennedy generally avoids using the words 'child,' 'children' or 'kids'"; and Levine et al. (2022b, p. 117). The Endocrine Society made a simple factual error when it stated that "medical intervention is reserved for older adolescents and adults" (Endocrine Society, 2023).

[6] Another phrase is "wrong puberty": e.g., "pubertal blockers … block the progression of puberty so the young person doesn't go through the wrong puberty" (Jacoby, 2022). Apart from presupposing the correct treatment, it is misleading to suggest that the "right puberty" induced by estrogen in males or testosterone in females amounts to a cross-sex version of puberty, because puberty centrally and definitionally involves maturation of the capacity for reproduction. The Endocrine Society guideline adopts this language, writing of the "induction of female puberty" in males (Hembree et al., 2017, Table 8); see also Section 7.4.1.

[7] MacKinnon, Expósito-Campos et al. (2023).

[8] Olson et al. (2022). "Retransitioning" does have a legitimate use, to describe the process of transitioning again, going from detransitioning to living as the other sex (MacKinnon, Expósito-Campos et al., 2023, p. 1).

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of “dynamic desires for gender-affirming medical interventions.”[9] This conceptualizes an experience that can be profoundly distressing for the patient as simply another stop along their “gender journey.”[10]

The lead author of the AAP’s 2018 policy statement (reaffirmed in 2023), “Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents,” has even described detransition as part of the “gender affirming” approach itself, thus making treatment failure impossible to conceive.[11]

The problems go deeper. The terminology of “sex,” “male,” and “female” is indispensable if the medical and ethical issues are to be discussed responsibly. And yet proponents of medicalization go to extraordinary lengths to avoid the plain use of these words, and related words such as “boy” and “girl.” When “sex” is defined, the definition is rarely correct,[12] and in any case the preferred phrase is “sex assigned at birth.” According to the ES’s “Clinical Practice Guideline for the treatment of Gender-Dysphoric/Gender-Incongruent Persons,” “the terms biological sex and biological male or female are imprecise and should be avoided.”[13] Pediatric female patients are not “girls” or “young women,” but rather “AFAB individuals” (people “assigned female at

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[9] Turban, Brady et al. (2022).

[10] Jorgensen (2023b): “we should be cautious about adopting euphemisms that might mask iatrogenic harm” (p. 2180).

[11] “Rafferty [the lead author of the AAP 2018 policy statement] told me patients who live with harms or regrets do not signal a failure of the affirmative care model. If a child or patient doesn’t like the effects of an intervention, or begins to feel different in their identity, then the provider continues to affirm by discontinuing treatment. ‘They’re not treatment failures if that’s what’s affirming’ he said” (Block, 2023d).

[12] E.g. the entry for “sex” in Hembree et al. (2017, Table 1) conflates sex with characteristics highly correlated with sex in humans (“sex chromosomes,” “sex hormones,” etc.); the entry in Rafferty et al. (2018, Table 2) erroneously says that sex is “an assignment that is made at birth.” For the orthodox conception of sex in biology, see, e.g., Dawkins (1976, pp. 183-184); Parker (2011); Futuyama & Kirkpatrick (2017, p. 249). The orthodox conception is in an Endocrine Society “Scientific Statement” (Bhargava et al., 2021), and in a Health and Human Services document (Health and Human Services, 2025).

[13] Hembree et al. (2017, Table 1). Hembree et al. don’t take their own recommendation completely to heart, writing at one point that “in females [i.e. “biological females”] … the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain” (p. 3880). This ES guideline is an update of “Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline,” published in 2009. In that earlier guideline the conventional meaning of sex is used, and the authors use the allegedly imprecise phrase “biological females” (Hembree et al., 2009, p. 3139). The AMA also claims that “sex assigned at birth” is “more precise” than “sex” (American Medical Association, 2021, p. 14).

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birth"). Some authorities in PGM say that the patients wanting mastectomies are in fact "young men."[14]

"Assigned sex at birth" is not a harmless euphemism. It suggests an arbitrary decision—not unlike "assigned seating"—rather than the observation of a characteristic present long before birth, namely the child's sex. Moreover, if the phrase "assigned sex" were intended merely as a gentler way of referring to sex in conversations with patients and families, one would expect more direct language to be used in the specialty medical literature. In professional contexts, where clarity is paramount, euphemisms are generally avoided. Yet "assigned sex" is ubiquitous in clinical and academic publications. Not only that: use of such terminology is now *mandated* by certain medical journals.[15] The American Psychological Association (APA) style guide, for example, classifies "birth sex" and "natal sex" as "disparaging terms" which problematically "imply that sex is an immutable characteristic."[16] As law professor Jessica Clarke observes, "'Sex assigned at birth' is not a euphemism for 'biological sex' but a critique of the very concept."[17]

The term "gender identity" is an especially important example of how words can sow confusion. When first introduced in the 1960s, it meant "the sense of knowing to which sex one belongs, that is, the awareness 'I am a male' or 'I am a female'."[18] Almost

[14] "I don't advocate removal [of] breast tissue from young women. I advocate for chest reconstruction in young men" (Olson-Kennedy, 2019, p. 38); this use of language has the effect of making mastectomies for adolescent girls sound unalarming. See also Ehrensaft (2017b, p. 7): "transgender boys are boys and transgender girls are girls."
[15] *The Lancet*'s "Information for Authors" mandates the use of "sex assigned at birth," instead of "biological sex," "birth sex," or "natal sex" because "it is more accurate and inclusive." The same document also incorrectly states that sex is not "binary," that it exists "along a spectrum," and that a person's sex can change (The Lancet, 2025).
[16] American Psychological Association (2024a).
[17] Clarke (2022, p. 1828). The language of "assigned sex" was used in the 1950s for exceedingly rare cases of disorders of sex development (DSDs), where a baby with ambiguous genitalia could be raised as either a boy or a girl (Money, 1955).
[18] Stoller (1964, p. 220); see also Greenson (1964, p. 217). For discussion see Byrne (2023b, 2023a); Haig (2023); D. F. Janssen (2023).

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everyone has a gender identity in this sense, and moreover one that is congruent with their sex: males know that they are male, and females know that they are female.[19]

However, today the phrase "gender identity" is used in a significantly different way. For example, WPATH defines "gender identity" in the glossary to their current clinical practice guideline (SOC-8) as:

> A person's deeply felt, internal, intrinsic sense of their own gender.[20]

This new definition is unclear. For instance, what does "gender" mean in this context? The glossary in SOC-8 offers little clarification—though it does correctly acknowledge that the word is highly ambiguous. One meaning of "gender" given in the glossary is "gender identity." But "gender" in the definition above cannot mean "gender identity," otherwise the definition would be circular. Another meaning provided is "gender expression," but this too leads to circularity, because "gender expression" is itself defined in the same glossary in terms of "gender."[21]

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[19] Some children distressed about their sexed bodies are mistaken about whether they are male or female, but some are not. Accordingly, being mistaken about one's sex is not required for a diagnosis of Gender Dysphoria in Childhood in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM): "A strong *desire* to be of the other gender" is enough. Although the diagnostic criteria for children also mention "an insistence that one *is* the other gender," this is not a necessary criterion, and is altogether absent from the DSM criteria for Gender Dysphoria in Adolescents and Adults (American Psychiatric Association, 2022, pp. 512-513, emphasis added).

[20] Coleman et al. (2022, p. S252). Along the same lines: "On one level, gender identity is something deeply felt and can be difficult to put into words. I often refer to this as one's *transcendent* sense of gender. You simply *feel* a certain gender" (Turban, 2024, p. 38); "Gender identity is a person's inner sense of belonging to a particular gender, such as male or female" (Ehrensaft, 2017b, p. 7). This latter definition would sound strange if "particular gender" was replaced by "particular sex": the implication would then be that there are more sexes beyond male and female.

[21] Another definition of "gender" given in SOC-8 is "social gender role, including understandings and expectations culturally tied to people who were assigned male or female at birth" (Coleman et al., 2022, p. S252). Consider the suggestion that this is the intended sense of "gender" in WPATH's definition of "gender identity." That is, "gender identity" is defined as: "a person's deeply felt, internal, intrinsic sense of their own social gender role." Now it is true that a person might have a sense of their "social gender role." A woman, say, might be aware that in her culture certain expectations apply to women. However, here the language of "deeply felt/internal/intrinsic" is quite inappropriate, which is one piece of evidence that the present suggestion is wrong. More importantly, there is no room for any "mismatch" between a person's sex and their social gender role. A woman may (perhaps rightly) disapprove of the expectations that her culture imposes on females; that is, she may disapprove of her social gender role. Since she has this gender role because she was "assigned female" at birth, her "gender" in this sense will *always* match her sex. But evidently WPATH wishes to define "gender identity" in such a way as to allow for *mismatches* with a person's sex. Hence, the "gender role" sense of "gender" is of no help in defining "gender identity" either. [Note continued on next page.]

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In short, “gender identity” as it appears in SOC-8 and related literature is ill-defined.[22] It may be true that a person’s gender identity is subjective, or undetectable by blood tests or neuroimaging,[23] or otherwise beyond the reach of science, but the more critical point is that no tolerably clear definition of “gender identity” has been offered in the first place.[24] This is a serious problem, because the term figures centrally in the justification for medical intervention.

The term “transgender” is typically explained in terms of gender identity. Transgender people are those whose gender identities do not “align with” or “match” their sex (or “sex assigned at birth”).[25] Since “each of us has a gender identity, though many of us never give it much thought,”[26] the rest of humanity have gender identities that match their sex; these people are said to be “cisgender.” It is important to realize that “transgender” is not a clinical term and does not correspond to a medical diagnosis.[27] Indeed,

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Another way of explaining “gender” is to give a list of representative “genders” with the expectation or hope that the reader will see the pattern. In principle, this sort of explanation can be satisfactory. However, WPATH’s previous guideline offered the following examples: “male (a boy or a man), female (a girl or woman) … boygirl, girlboy, transgender, genderqueer, eunuch” (Coleman et al., 2012, p. 221). Notice that the list includes the category *transgender*, which is itself explained in terms of gender identity and hence gender, introducing a circularity. Another point is that if *eunuch* is a (contemporary) gender, then “gender” as it figures in WPATH’s definition of “gender identity” cannot possibly be explained in terms of “social gender role” (see the first paragraph of this note). Eunuchs had a special social role in Imperial China; they have no such role today. WPATH’s current guideline has an entire chapter on eunuchs, so clearly WPATH thinks the gender *eunuch* is not an anachronism.

[22] Here is another example. The AAP’s 2018 policy statement defines gender identity as “[a] person’s deep internal sense of being female, male, a combination of both, somewhere in between, or neither” (Rafferty et al., 2018, Table 1). The policy statement also says that a “transgender” person is someone “whose gender identity does not match their assigned sex.” Clearly “gender identity” as the AAP defines it cannot mean what it originally did, because a transgender man, for instance, might not be mistaken about being female. How to interpret “female” and “male” in the AAP’s definition is far from clear.

[23] See, e.g. Baldinger-Melich et al. (2020); Levin et al. (2023); Bakker (2024).

[24] The original 1960s explanation of gender identity (see above) was perfectly clear, but that is not the contemporary conception in gender medicine.

[25] Boe v. Marshall, No. 2:22-cv-00184: 558-16 (2024); Ehrensaft (2017b); Olson-Kennedy (2022). According to the previous WPATH guideline (SOC-7): “The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth” (Coleman et al., 2012, p. 221). Remarkably, sometimes “transgender” is defined to include commonplace gender non-conformity, *regardless* of any “mismatched” gender identity. For instance, according to SOC-8, if a person’s “gender expressions are not what is typically expected for the sex to which they were assigned at birth,” they are transgender (Coleman et al., 2022, p. S252).

[26] Forcier et al. (2020, p. 2). Similarly: “Gender identity … is a core and *universal* component of human identity” (Boe v. Marshall, No. 2:22-cv-00184: 592-12, 2024, p. 6, emphasis added).

[27] Thus a recent article on assessing “transgender and gender diverse adolescents” for puberty suppression recommends reassuring patients that the goal is not to determine whether they “are actually transgender” (Turban et al., 2025, p. 14). But see Section 13.3.

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proponents of the medicalized approach emphasize that some transgender people neither desire nor need medical or surgical interventions of any sort.

It is often claimed that gender identity is "innate or fixed at a young age," and so "cannot be changed."[28,29] Putting that idea together with the definition of "transgender," the result is that being transgender is a close-to-immutable trait. (The same goes for being cisgender.) A "transgender child," in this framework, is a child whose unalterable gender identity does not align with their sex, while cisgender children are the other kind.[30] Once this binary paradigm of "trans kids" and "cis kids" is accepted, therapeutic exploration of the underlying causes of a child's discomfort with his or her sexed body is readily dismissed as "conversion therapy," an unethical attempt to interfere with the development of the child's authentic self.[31,32]

According to many authorities in PGM, there is a test to determine whether a child is transgender or cisgender. This is because children "know who they are." Specifically, they know their "gender."[33] If a child's "gender" matches their "assigned sex," they are cisgender; if not, they are transgender. So, to determine whether a child is transgender or cisgender, one only need ask.

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[28] Adkins (2016, p. 4); Ehrensaft (2017b, p. 7); Olson-Kennedy (2022, p. 9). However, an earlier paper on the PMT approach, which has Ehrensaft and Olson-Kennedy as co-authors, states that it is a "myth" that gender identity is "immutable" (Hidalgo et al., 2013, p. 288), indicating at least some confusion about key terms.

[29] In his expert witness report for *Boe v. Marshall*, Aron Janssen, a gender clinician and vice chair of clinical affairs at Lurie's Pritzker Department of Child and Adolescent Psychiatry, wrote that gender identity, "a person's innate sense of their gender," "cannot be altered through medical or psychological interventions" (Boe v. Marshall, No. 2:22-cv-00184: 592-12, 2024, p. 6).

[30] Some PMT authorities would dispute this characterization and claim that a transgender child's gender identity *does* match their sex—what it *doesn't* match is their "birth-assigned sex" (Ehrensaft, 2017b, p. 9).

[31] "Psychotherapy may be beneficial but should not be a requirement for gender-affirming treatment, and conversion treatment should not be offered" Coleman et al. (2022, p. S10). On "conversion therapy," see Section 14.5.2.1.

[32] Two books that discuss the "transgender child" are Gill-Peterson (2018) and Meadow (2018). On Gill-Peterson, see Byrne (2024b, pp. 243-244). For an early expression of skepticism, see Brunskell-Evans & Moore (2018).

[33] [R]esearch substantiates that children who are prepubertal and assert an identity of TGD [transgender and gender-diverse] *know their gender* as clearly and as consistently as their developmentally equivalent peers who identify as cisgender and benefit from the same level of social acceptance" (Rafferty et al., 2018, emphasis added). Also: "Individuals whose sex assigned at birth is opposite to the gender they *know themselves to be* are often referred to as *transgender*" (Turban & Ehrensaft, 2018, p. 1, first emphasis added); "studies show that trans children and adolescents know themselves and their gender" (Ashley, 2022b, p. 15).

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An immediate problem is posed by the undeniable phenomenon of temporary youthful transgender identification. (See Section 4.3.1.4.) Attempting to address this difficulty, Aron Janssen, vice chair of clinical affairs at the Pritzker Department of Child and Adolescent Psychiatry at Lurie Children's Hospital in Chicago, and chair of the American Academy of Child and Adolescent Psychiatry's Sexual Orientation and Gender Identity Issues Committee, stated in a deposition that although gender identity is "static" and "fixed," "one's understanding of it can evolve over time."[34]

Dysphoric children and socially transitioned children are routinely referred to as "transgender children." In some cases, this is for convenience or as a gesture of respect.[35] However, its use may subtly influence clinical reasoning. The label "transgender" implies a mismatch between gender identity and the person's sexed body, and that mismatch can supposedly cause gender dysphoria.[36] Since an adolescent's gender identity cannot be changed, the obvious solution to relieve the distress is to change their body.[37]

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[34] Boe v. Marshall, No. 2:22-cv-00184: 558-16 (2024, pp. 104-110). Some PMT clinicians maintain that such change in understanding is not likely: "there is [a] small but non-zero possibility of one's understanding of their gender identity evolving over time" (Turban et al., 2025, p. 2). According to UCSF's Diane Ehrensaft, "My own clinical experience told me that you could discern one group of children from the other prior to adolescence, not with 100% accuracy, but not far from it" (Ehrensaft, 2014, p. 578). As Ehrensaft puts it in her book *The Gender Creative Child*, "we can tell the apples (the transgender children) from the oranges (the gender-nonconforming but not trans kids), sometimes as early as when they are three years old. So, why hold the apples back if they already know who they are?" (Ehrensaft, 2016, p. 55). Put without the framing of "trans kids," the clinical issue is whether one can discriminate between gender dysphoric children whose dysphoria will resolve without any medical intervention, and those whose dysphoria will persist into adulthood (see Section 4.3.2).

[35] E.g. Olson et al. (2022).

[36] According to WPATH, gender dysphoria is "distress that is *caused by* a discrepancy between a person's gender identity and that person's sex assigned at birth" Coleman et al. (2012, p. 221, emphasis added). The quotation continues, "(and the associated gender role and/or primary and secondary sex characteristics)"; so at least in theory, one way of relieving gender dysphoria would be to change the "associated gender role."

[37] The AAP policy statement includes more young people as candidates for medicalization that just those with mismatched or incongruent gender identities. The title of the policy statement is "Ensuring Comprehensive Care and Support for Transgender *and Gender-Diverse* Children and Adolescents" (Rafferty et al., 2018, emphasis added). Transgender youth, the policy statement says, are "a subset of gender-diverse youth." The policy statement explicitly equates "gender diverse" with "gender nonconforming" (the latter term being deprecated only because of its allegedly pejorative connotation). Thus, gender-nonconforming youth *in general* are singled out as potential recipients of sex-related hormone therapy and surgery. The same points apply to WPATH's SOC-8, *Standards of Care for the Health of Transgender and* Gender Diverse *People*, which also deprecates the use of "gender-nonconforming" (Coleman et al., 2022, p. S11, emphasis added); SOC-7 (Coleman et al., 2012) has "gender-nonconforming" in its title.

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2.2 Terminology in this Review

While communication with patients and families must always be sensitive and compassionate, describing sex as a matter of "assignment" is, at best, confusing and accordingly not truly respectful. Patients and their legal caregivers are entitled to the facts regarding their medical situation; this is essential for informed participation in the medical decision-making process. Just as importantly, evidence assessments must use accurate and precise language when referring to sex, in order to maintain scientific integrity and support sound clinical judgment.

Treatment of children and adolescents with GD presents an especially complex case of doctor-patient communication because doctors understandably do not want to alienate their patients; trust is the bedrock of shared decision-making.

There is growing international awareness of the importance of using accurate sex-based language. As the recent U.K.'s *Review of Data, Statistics and Research on Sex and Gender* (RSG) asserts:

> Analysts must be able to use clear and familiar language in reporting findings on sex. Terms such as women, men, boys and girls are synonymous with (respectively) adult human females and males and children of each sex. Similar considerations apply to terms such as mothers and fathers, sons and daughters.[38]

The RSG also recommends against using the phrase "sex assigned at birth," remarking that it is "misleading."[39]

The RSG notes that the word "gender" has "multiple distinct meanings, including: a synonym for sex; social structures and stereotypes associated with sex; and gender identity."[40] For this reason, the RSG cautions against using the word when misunderstandings could arise. A prime example is WPATH's definition of "gender identity" discussed above, which uses the word "gender" without an adequate

[38] Sullivan (2025, p. 11). The Review was commissioned by the previous Conservative government and welcomed by the present Labour Secretary of State for Health and Social Care (Scott, 2025).
[39] Sullivan (2025, p. 7).
[40] Sullivan (2025, p. 5).

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explanation. Because of its unclarity and ambiguity, “gender” will generally be avoided in this Review. “Gender identity” inherits the obscurity of “gender” and will not be used either.[41] As discussed, the term “transgender child” suggests that medical intervention is the default or primary course of action. For this reason, it will be avoided.[42]

The Review will use “social transition” for the process of changing one’s sex-associated name, presenting oneself as a member of the other sex, being referred to with third-person pronouns for the other sex,[43] and so on.

“Gender dysphoria” (GD) is in the DSM and at present has no accepted alternative; therefore, it will be used despite problems with the word “gender.” “Gender nonconformity” is a familiar and well-understood phrase, so it will also be used (although some may prefer “sex-stereotype nonconformity”). As already indicated, “pediatric gender medicine” (PGM) will be used for the clinical field that treats children and adolescents with GD, sometimes with medical interventions. Instead of the term “gender-affirming care” this Review will use “PMT” (pediatric medical transition), as in phrases such as “the PMT approach.” This is more accurate and carries no positive or negative connotation. The PMT approach does not always involve hormones or surgeries, but some of its proponents do tend to view even social transition as an initial step toward medical transition. The older term “cross-sex hormones” (CSH)[44] is more neutral and informative than “gender-affirming hormone therapy.” Surgeries to alter sex characteristics[45] for adolescents will be given medically standard, clinical, neutral descriptions—e.g. “mastectomy.” Finally, the older term “sex reassignment surgery” (SRS) will be used rather than the more recent “gender confirmation surgery.”

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[41] Also relevant from the RSG: “Questions on gender identity should recognize that the concept of gender identity as such will be unfamiliar, unclear or irrelevant to some respondents, and that many respondents may not perceive themselves as having a gender identity. Questions should not assume that respondents will agree that they have a gender identity” (Sullivan, 2025, p. 9). The RSG illustrates how “gender identity” is now firmly embedded, not just in gender medicine, but also in social statistics (and, it could be added, pedagogy). For an illuminating discussion of the history, see Brubaker (2025).

[42] Needless to say, terminology that makes other treatment pathways prominent is equally undesirable.

[43] Or *they* or neo-pronouns (*xe*/*xem* and the like).

[44] Even this terminology is not perfect: estrogens are normally present in males, although at lower levels than in females; vice versa for androgens (including testosterone).

[45] Sex characteristics are either *primary* (the external and internal reproductive organs), or *secondary* (characteristics that emerge at puberty, such as breasts in females and facial hair in males).

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Chapter 3 History and Evolution of Adult and Pediatric Gender Medicine

Medical transition for gender dysphoric youth is a comparatively recent practice and grew out of the clinical experience of transitioning mature adults. It is common in medicine to extend medical treatments to children once they have been proven safe and effective in adults. In this case, however, the opposite occurred. The rationale for transitioning adolescents emerged from the observation that medical transition in adults often failed to produce the desired positive outcomes. This chapter explains how this came about and provides additional historical context.

Sections 3.1, 3.2, and 3.3 briefly review the history of medicalized transitions, which are barely a century old. Sections 3.4 and 3.5 explain how the observed failure of medical transition to produce positive psychosocial outcomes for adults led clinicians in the Netherlands to propose an early intervention model, resulting in the "Dutch Protocol." The final section describes how the Dutch Protocol evolved into the "gender affirming care" approach to pediatric medical transition (PMT), a shift that was accompanied by significant changes in the pediatric patient population presenting with GD—both in terms of size and demographic composition.

3.1 *The Transsexual Phenomenon*

Extremely gender-nonconforming people, including those who live their lives either as members of the other sex, or as a so-called "third gender," have been documented throughout human history.[1] One famous example is the French diplomat and spy Chevalière d'Eon (1728-1810), who dressed and "passed" as a woman during the final 32 years of his life. Everyone was convinced, including the last king of France, Louis XVI.[2] In the early 20th century, the English physician and sexologist Henry Havelock Ellis coined *eonism*, after the Chevalière, for "people who took pleasure in behaving and

[1] See, e.g., Bullough et al. (1997); R. Green (1966); Herdt (1996); Peled (2016); Vasey & VanderLaan (2014). Many earlier cultures and some contemporary ones have "third genders": some people of one sex (typically feminine same-sex attracted males) occupy social roles (somewhat) similar to those of the other sex. It is a mistake to take this phenomenon to be akin to the contemporary Western "transgender moment"—see Vasey (2022).
[2] Kates (2001, p. 218).

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dressing like the opposite sex and yet were not sexually inverted; that is, their sexual feelings were not directed towards persons of their own sex."[3] "Eonism" later came to label a broader category, including individuals with strong cross-sex wishes who were same-sex attracted.[4] In 1949, an American physician, David Cauldwell, used the term "transexual" to label "individuals who are physically of one sex and apparently psychologically of the opposite sex."[5]

"Transsexualism" was popularized by Harry Benjamin, a German-American endocrinologist and the father of transgender medicine. Benjamin's 1966 book, *The Transsexual Phenomenon*, was the first comprehensive English-language discussion of medicalized treatment for people who "want to undergo corrective surgery … so that their bodies would at least resemble those of the sex to which they feel they belong and to which they ardently want to belong."[6] Cross-sex hormones (CSH) followed by surgery, Benjamin thought, could "change a miserable and maladjusted person of one sex into a happier and more adequate, although by no means neurosis-free, personality of the opposite sex."[7]

In the first half of the 20th century, there were few recorded instances of transsexuals. One of the first people to undergo sex-reassignment surgery (SRS) was Einar Wegener, a Danish artist who modeled while cross-dressed for his wife Gerda Gottlieb, a talented painter. In pursuit of the body modifications he so desperately desired, Wegener sought help from the sexologist Magnus Hirschfeld, a long-time friend of Harry Benjamin's and founder of the Institute for Sexual Science in Berlin.[8] Castration, penectomy, and ovarian implantation were performed on Wegener in Berlin and Dresden in 1930, with

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[3] Havelock Ellis (1937, p. 1, Part Two); quoted in Byrne (2024b, pp. 113-114). According to d'Eon's biographer, the historian Gary Kates, "d'Eon was neither a transvestite nor a transsexual … there is simply no indication that d'Eon hated his own body or that he wanted, or even imagined he would be better off with, the body of a woman" (Kates, 2001, p. xxii); quoted in Byrne (2024b, p. 229).
[4] See, e.g., Hamburger et al. (1953) (a report on Christine Jorgensen's case; see the following section). See also Benjamin (1967b, p. 107) and Blanchard (1989, p. 240).
[5] Quoted in Meyerowitz (2009, p. 44). This quotation is from Cauldwell's 1950 *Questions and Answers on the Sex Life and Sexual Problems of Trans-Sexuals*, which hyphenates "transsexual." Cauldwell used "psychopathic transexual" (one "s") in 1949 (Cauldwell, 2006, p. 41).
[6] Benjamin (1966, p. 14)
[7] Benjamin (1966, p. 164).
[8] Li (2023).

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additional procedures the following year. These were unsuccessful. Einar Wegener, transformed into Lili Elbe, died in September 1931, after an "abyss of suffering."[9]

3.2 From George to Christine

Transsexualism was not then a phenomenon. That changed in 1952, when the news broke that George Jorgensen, a 24-year-old American of Danish descent had undergone sex reassignment surgery (SRS) in Denmark:

> [H]er celebrity began December 1, 1952, when a banner headline screaming "EX-GI BECOMES BLONDE BEAUTY: OPERATIONS TRANSFORM BRONX YOUTH" greeted readers of the *New York Daily News*. Hearst Publications' popular Sunday newspaper supplement, *American Weekly*, subsequently paid twenty thousand dollars for an exclusive interview with Jorgensen that brought her story to millions of American homes, and whetted the appetite of the world press. When she returned to the United States in 1953, an unprecedented three hundred reporters were on hand to meet her plane at New York International Airport … Her "sex-change" was viewed by many as a miracle of God in which not Christ, but Christine—Man reborn as Woman—heralded a new dispensation of human history.[10]

Jorgensen met Harry Benjamin in New York that year, and they enjoyed a long friendship. In a 1965 letter, just before the publication of *The Transsexual Phenomenon*, Benjamin wrote: "Without you, Christine, none of this would have happened."[11]

Growing up in the Bronx, the young George was teased for his "girlish qualities," and was greatly conflicted by his homosexuality:

> One question was especially troubling for George: He had learned at church and from his school friends that homosexual relationships were considered sinful and immoral. In the Jorgensen household, the word was never spoken. Among his

[9] Elbe et al. (2020, p. 203); quoted in Joyce (2021, p. 17). Lili apparently had no regrets, writing in June 1931, "The price which I have paid seems to me very small" (Elbe et al., 2020, p. 198). On regret, see Section 13.4. The 2015 movie *The Danish Girl*, starring Eddie Redmayne, is loosely based on Einar/Lili's story.
[10] Stryker (2000, pp. v-vi).
[11] Jorgensen (1967, p. xi).

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> neighbors, “homos” or “queers” were thought to be unacceptable, even dangerous people. Hence, a series of romantic attractions to other young men became his greatest teenage conflict. Try as he might to avoid these crushes, George persistently fell in love with other male youths of his age. This conflict would contribute to episodes of depression, low self-esteem, low aspiration for success, and much personal unhappiness.[12]

George himself fixated on a hormonal explanation for his femininity and same-sex attraction—a “glandular imbalance”[13]—and was also (wrongly) convinced that his genitals were “underdeveloped.”[14] It is a plausible conjecture that George found an English translation of Lili Elbe’s autobiography while hunting in New York City libraries, “hoping to find other keys to my dilemma.”[15] In any event, in search of the hormonal and surgical treatment he felt he needed, George went to Denmark on a one-way ticket in 1950. There the “Bronx youth” became a patient of Christian Hamburger, a Copenhagen endocrinologist:[16]

> Perhaps Hamburger felt a special compassion for homosexuals because his sister was a lesbian. Despite Denmark’s comparatively liberal national policies, Hamburger surely knew from his sister’s experience how discrimination against gays and lesbians could be profoundly troubling for a homosexual. He could offer no medical intervention to help his sister, but he believed there might be some steps he could take to help George Jorgensen, and he was willing to try.[17]

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[12] Docter (2013, pp. 25-26).
[13] Docter (2013, p. 63).
[14] Docter (2013, p. 46).
[15] Jorgensen (1967, p. 80); for the conjecture, see Docter (2013, p. 38).
[16] Hamburger had a distinguished career (Pedersen-Bjergaar, 1964). Contrasting with Hamburger’s academic record, before Benjamin became interested in transsexuality he was a prominent proponent of endocrine “rejuvenation therapy,” a medical fad. In 1931 he sued the editor of the *Journal of the American Medical Association* (*JAMA*) “for calling his treatment quackery,” and lost (Pettit, 2013, p. 1070).
[17] According to Hertoft & Sørensen (1979), a “sex change” was not the original plan: “the Danish team regarded Chris Jorgensen as a homosexual man suffering from his homosexuality and since he himself asked for castration, they would not deny him this operation. Not until afterwards, when the press published the case, did the team behind the procedure accept it as a sex change. The rest of the story is well known” (p. 168). Hamburger is said to have denied that Jorgensen was a homosexual in Christine’s autobiography (Jorgensen, 1967, p. 101). See also Docter (2013, p. 81).

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In a case report he later wrote for the *Journal of the American Medical Association* (*JAMA*) Hamburger described George's desire "with medical assistance to be able to obtain permission to live on 'as nearly a woman as possible.'"[18] Hamburger prescribed estrogen, and George's application for castration to the Danish Ministry of Justice was approved in 1951.[19] Castration was followed by penectomy and a later unsatisfactory attempt at creating an artificial vagina. "As a nationally recognized personality, Christine Jorgensen's flame burned with exceptional brilliance for about thirty years,"[20] dimming in the 1980s. A heavy drinker and smoker, Christine died of cancer in 1989, at the age of 62.

3.3 "Dear Dr. Hamburger"

After the "sensational publicity" over George Jorgensen's metamorphosis into Christine, Hamburger received "a unique collection of letters from a considerable number of men and women who desire to change their sex."[21] He analyzed all 756 of them, from 465 people, and published the results in a European endocrinology journal, *Acta Endocrinologica*. His correspondents wrote from all over the world. Over three quarters were men, and some of the letter writers were young teenagers. Not everyone mentioned their sexual orientation, but the women were the most forthcoming, with 71% offering at least some information. Fewer than half the men gave "any information about their sexual impulses."[22] Homosexuality predominated[23] among the men and was universal among the women:

> It is remarkable that not one single woman admits to heterosexuality, which is the case in 22 per cent of all male letter writers … Not a single woman mentions attraction to men; on the contrary. Women who have experienced shorter or longer periods of married life, felt the physical part of matrimony to be intolerable. Completely different are the transvestic men: they do not appear to have felt any

[18] Hamburger et al. (1953, p. 393).
[19] Jorgensen (1967, pp. 114-116).
[20] Docter (2013, p. 255).
[21] Hamburger (1953, p. 361).
[22] Hamburger (1953, p. 368).
[23] Of the 45% of men who disclosed information about their sexual orientation, Hamburger classified 65% as homosexual (Hamburger, 1953, Table 3).

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> aversion to the female body, although the erotic attraction, if any, is stated to have declined with passing years, or to have led to impotence.[24]

A 16-year-old American girl wrote:

> I've always acted like a boy and did the things they did. When I was smaller I used to wear my brothers [sic] clothes and I even do now sometimes when no one is home. This isn't the worst of it though, ever since I've been in High School I've been in love with a girl! and as much as I try to forget this love the more I realize I don't want to forget it. - - - I've also read about transvestites who only wanted to dress like the opposite sex but that's not how I feel. I want to dress like a boy yes, but it's not so bad that I can't control it.[25]

Childhood gender-nonconformity is strongly associated with later homosexuality.[26] Because childhood- or early-onset gender dysphoria (GD)[27] involves extreme gender-nonconformity, young children distressed by their sexed bodies will likely grow up to be same-sex attracted. As the current *Diagnostic and Statistical Manual* (DSM-V-TR) puts it, "Studies have shown a high incidence of sexual attraction to those of the individual's birth-assigned gender, regardless of the trajectory of the prepubescent child's gender dysphoria."[28] Harry Benjamin put his own spin on George Jorgensen's homosexuality: "since the psychological status of a transsexual male is that of a female, it is natural that sex attraction centers on a male."[29]

Despite the sensational publicity, in the 1960s the "transsexual phenomenon" was still in its infancy. By 1965, Benjamin had seen 307 cases of which he deemed 220 "true transsexuals," the remainder being classed as "transvestites." Almost 90% of the transsexuals were male. Only 62 males and 11 females had had surgery.[30] Reflecting

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[24] Hamburger (1953, p. 369).
[25] Hamburger (1953, p. 370).
[26] Bailey & Zucker (1995); R. Green et al. (1987); Steensma et al. (2013).
[27] Ristori & Steensma (2016); Singh et al. (2021). For other forms of GD, see Bailey & Blanchard (2017); Zucker et al. (2016). See also Section 4.3.1.
[28] American Psychiatric Association (2022, p. 516).
[29] Benjamin (1967a, p. ix).
[30] Benjamin (1966, p. 163).

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this imbalance, *The Transsexual Phenomenon* had only one slim chapter on "the female transsexual."

By 1979, the demand for "sex change" became significant enough for clinicians caring for this patient population to form a professional association, the Harry Benjamin International Gender Dysphoria Association (HBIGDA), which published the first *Standards of Care* in 1979. In that short typewritten document, "Principle 2" of 32 was: "Hormonal and surgical sex reassignment are procedures requiring medical justification and are not of such minor consequence as to be performed on an elective basis."[31]

In the third edition of the DSM in 1980, the disorder of "transsexualism" was said to be "apparently rare."[32] In 1994 DSM-IV reported: "Data from smaller countries in Europe with access to total population statistics and referrals suggest that roughly 1 per 30,000 adult males and 1 per 100,000 adult females seek sex-reassignment surgery."[33] The "transgender tipping point"[34] had not yet arrived.

3.4 Outcomes of adult transitions

Pediatric medical transition began in the Netherlands, which had offered adult treatment in an academic hospital starting in the 1970s, with the costs of a medical transition reimbursed through the Dutch national health insurance system.[35] The availability of comprehensive and reliable medical records gave clinicians the opportunity to study how patients fared, and a paper detailing the results was published in 1988: "Sex reassignment surgery: A study of 141 Dutch transsexuals." The research was led by the psychologist Peggy Cohen-Kettenis, who had worked earlier with adult transsexuals at the Department of Sexology at Utrecht University. In 1987 she moved to the Department

[31] Harry Benjamin International Gender Dysphoria Association (1979).
[32] For the diagnostic criteria, see Appendix 2. The first two versions of the DSM fleetingly included "transvestism" (American Psychiatric Association (1952, p. 39) and "transvestitism" (American Psychiatric Association (1968, p. 44). See also Drescher & Yarbrough (2024).
[33] American Psychiatric Association (1994, p. 535). See also Dhejne et al. (2014). According to the first *Standards of Care*, "As of the beginning of 1979, an undocumentable estimate of the number of adult Americans hormonally and surgically sex-reassigned ranges from 3,000 to 6,000" (Harry Benjamin International Gender Dysphoria Association, 1979).
[34] The title of a *Time* cover story in 2014 (Steinmetz, 2014).
[35] Bakker (2021, p. 29).

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of Child and Youth Psychiatry at the Academic Hospital Utrecht (now UMC Utrecht), where she began to see children and adolescents with GD.[36]

Cohen-Kettenis and her co-author and student Bram Kuiper sent recruitment letters to all 229 patients diagnosed by the Netherlands Gender Care Foundation (NGCF) as "transsexuals and who … had at least started hormone therapy." The 141 who agreed to participate were "36 FMs (female-to-male transsexuals) and 105 MFs (male-to-female transsexuals)."[37] They were at varying stages of medical transition. Some had completed surgery, while others had just started on CSH; follow-up time from the start of treatment ranged from one month to more than 10 years. The patients' average ages were late-20s (the FMs) and mid-30s (the MFs). They were assessed by interview, and all but three were interviewed in their homes.

On the positive side, 65% reported feeling happy or very happy, while 11% said they were unhappy or very unhappy. Almost all the FMs and nearly 80% of the MFs described their ability to "pass as a member of the newly assumed gender" as good or very good. None of those who had had surgery "felt any significant doubts about the decision to get rid of their own primary and secondary sex characteristics and to have the body surgically adjusted to the characteristics of the opposite sex," except for one FM who nonetheless had no regrets about living as a man.[38]

On the other hand, while the self-reported subjective outcomes were good, objective measures told a different story. One in seven MFs and one in 36 FMs had attempted suicide after treatment began. (Of the total number of patients seen at the NGCF in the previous 10 years, three had committed suicide after treatment.) 60% of the MFs and 37% of the FMs were unemployed and 59% of the MFs and 33% of the FMs had no romantic partners.[39] Commenting on previous studies of SRS, the researchers noted: "it is possible to discern a trend in these reports that the subjective well-being of the

[36] Bakker (2021, p. 113).
[37] Kuiper & Cohen-Kettenis (1988, p. 442).
[38] Kuiper & Cohen-Kettenis (1988, p. 450).
[39] Kuiper & Cohen-Kettenis (1988, p. 447).

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transsexuals has increased, whereas an 'improvement' in their actual life situation is not always observed."[40]

Did medical transition at least alleviate gender dysphoria? Interestingly, there was no relationship between reported happiness and stage of transition:

> Although a fair number of persons attribute their feelings of happiness to SRS, there appears to be no direct relation between the subjective well-being and the phase of therapy. Those who have completed SRS are not happier or less happy than those who are still in the initial phase of therapy. In other words, a person's positive evaluation of his/her life-in-its-totality is not directly related to his/her progress in physical adjustment to the opposite sex.[41]

The researchers speculated that this might be due to an expectation effect:

> However, it does not seem justifiable to conclude that it is irrelevant to a person's happiness whether physical adjustment has or has not taken place and that the operations could therefore just as well have been omitted. One has to bear in mind that in general the [FMs and MFs who had not completed treatment] are happy in the knowledge that the operations will be performed within a reasonable time. They are taking a loan on the future.[42]

Although the researchers claimed that "there is no reason to doubt the therapeutic effect of sex reassignment surgery," they were clear that there were significant costs:

> SRS is no panacea. Alleviation of the gender problems does not automatically lead to a happy and lighthearted life. On the contrary, SRS can lead to new problems.[43]

Why were the MFs, in particular, doing so poorly? Three possible explanations were floated. One was that "passing" is easier for FMs, because of the power of

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[40] Kuiper & Cohen-Kettenis (1988, p. 440). Dhejne et al. (2011) examined the long-term outcomes of 324 people in Sweden receiving sex-reassignment surgery (SRS) over the period 1973-2003 (191 MFs, 133 FMs). Dhejne et al. concluded: "Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population."
[41] Kuiper & Cohen-Kettenis (1988, p. 454).
[42] Kuiper & Cohen-Kettenis (1988, p. 454).
[43] Kuiper & Cohen-Kettenis (1988, p. 455).

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testosterone.[44] Second, "society in general is inclined to take a milder view of women who dress and/or behave like men."[45] Finally, the MFs had transitioned later and were more likely to have married and to have children, with a consequent "heavier burden of a past life as a person of the original gender."[46,47]

One possibility that the Dutch researchers did not consider was that the FMs were doing better because their romantic relationships were easier to preserve after transition. As Hamburger reported from his correspondence in 1953, "No less than 10 women say, in so many words, that they want their sex changed in order to be able to marry their female friend or to have the relationship legalized."[48] Also apparently ignored was the related possibility that transition may appeal to young gay men and lesbians suffering from social disapproval of their homosexuality.[49]

3.5 The rationale for youth gender transition

Medically transitioning earlier gave patients a better chance to "pass" and reduced the "burden of a past life," so perhaps intervening at younger ages would improve transsexuals' quality of life. Cohen-Kettenis thought so. As sociologist Michael Biggs explains,

> Cohen-Kettenis believed that transsexuals would experience better outcomes if they started treatment before adulthood. By the mid-1990s, she was referring some patients aged 16 and 17 to the Amsterdam clinic for endocrinological intervention prior to cross-sex hormones … Johanna, for example, "fulfilled all necessary requirements for early treatment": she did not favor girly things (though neither did her sisters), she was fond of soccer, she never dated in school (perhaps not surprising given that she was homosexual), and her parents discovered her wearing a tight t-shirt to conceal her breasts … Brought to the clinic at 17, she was prescribed progestin for four months and then testosterone.

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[44] This works both ways. First, testosterone can dramatically transform the female body; second, the effects of pubertal testosterone on the male body are hard or impossible to undo. See Section 7.4.
[45] Kuiper & Cohen-Kettenis (1988, p. 455).
[46] Kuiper & Cohen-Kettenis (1988, p. 456).
[47] See also Smith et al. (2005, p. 97).
[48] Hamburger (1953, p. 370).
[49] See Barnes (2023, pp. 159-164).

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> Within two years Jaap (as Johanna had become) underwent mastectomy, hysterectomy, and oophorectomy, and obtained a new birth certificate.[50]

In 1991 Cohen-Kettenis and her colleague Louis Gooren lowered the eligible age for CSH to 16, but Cohen-Kettenis was not yet recommending puberty blockers (PBs).[51] The Dutch pediatric endocrinologist Henriette Delemarre-van de Waal had treated the first patient with blockers some years earlier, in 1987. "FG" was a girl with early-onset gender dysphoria:

> From the age of 5, FG "had made it very clear that I was supposed to be a boy." It later transpired that FG was sexually attracted to women. FG's father, an Italian with traditional views on gender, disapproved of his daughter's masculinity, and serious conflict ensued. Extensive psychotherapy did not improve matters; FG wrote a suicide note at the age of 12.[52]

At age 13, FG was prescribed puberty blockers and remained on them until age 18, after which many surgeries followed, including mastectomy and hysterectomy.

FG had come to the Utrecht gender clinic three years after starting PBs; as Cohen-Kettenis recounts:

> I'll never forget that first boy treated with Decapeptyl[53] by Henriette Delemarre. He made an impression with his boyish appearance at 16—naturally, because he hadn't entered puberty. Henriette and I embarked upon the adventure. No one knew what the long-term effects of administering puberty blockers would be. Yes, I was nervous: suppose you've got it wrong with an adolescent like that and you have to reverse it![54]

With the collaboration of Cohen-Kettenis and Delemarre-van de Waal, the "Dutch Protocol" for youth medical transition was born.[55] As of 1997, for carefully selected

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[50] Biggs (2023b, p. 350).
[51] Bakker (2021, p. 118).
[52] Biggs (2023b, p. 350).
[53] The brand name of triporelin, a gonadotropin releasing hormone agonist (GnRHa); triptorelin acts on the pituitary gland, blocking puberty in adolescents. See Section 7.3.
[54] Bakker (2021, p. 115).
[55] Delemarre-van de Waal & Cohen-Kettenis (2006).

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"juvenile transsexuals," with early-onset GD worsening at puberty, PBs could be given as early as 12.[56] Cross-sex hormones could be administered at 16, with surgeries at 18.[57] Patients were required to be otherwise mentally healthy and have family support.

FG was followed up 22 years later at age 35:[58]

> FG did not regret transition, but scored high on the measure for depression. Owing to "shame about his genital appearance and his feelings of inadequacy in sexual matters," he could not sustain a romantic relationship with a girlfriend. Ironically, a "strong dislike of one's sexual anatomy" is one of the diagnostic criteria for gender dysphoria in children (according to DSM-5), and so in this respect it is not clear how the dysphoria had been resolved … Now aged 48, FG has given two recent interviews. FG's situation seems to have improved, and he now has a serious girlfriend. He describes puberty suppression as "life-saving" in his case … but also recommends that it should require a significant assessment process.[59]

3.6 The spread of the Dutch Protocol and the rise of "gender-affirming care"

In the United States, HBIGDA endorsed puberty blockers in their sixth version of their clinical guideline, the *Standards of Care* (SOC-6, 2001):

> Two goals justify this intervention: a) to gain time to further explore the gender identity and other developmental issues in psychotherapy; and b) to make passing easier if the adolescent continues to pursue sex and gender change. In order to provide puberty delaying hormones to an adolescent, the following criteria must be met:

[56] Bakker (2021, p. 121).
[57] In fact, surgery was mandatory until 2014 (Gregory, 2021).
[58] Cohen-Kettenis et al. (2011).
[59] Biggs (2023b, p. 355).

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1. throughout childhood the adolescent has demonstrated an intense pattern of cross-sex and cross-gender identity and aversion to expected gender role behaviors;

2. sex and gender discomfort has significantly increased with the onset of puberty;

3. the family consents and participates in the therapy.[60]

SOC-6 also erroneously characterized PBs as "fully reversible" (see Chapter 7). As Biggs points out, "the published evidence for the benefits of puberty suppression then comprised a single case study of one patient—FG—awaiting final surgery."[61]

In the U.S., PBs were first prescribed for GD at Boston Children's Gender Management Service (GeMS, now Gender Multispeciality Service) around 2007, with the U.K.'s Gender Identity Development Service (GIDS) following four years later.[62] GeMs did not set a minimum age limit, and in 2015 neither did the U.K.'s National Health Service.[63] The relatively strict gatekeeping of the Dutch Protocol soon gave way to a more patient-led approach (see Section 4.1. and Chapter 11). This occurred not just in the U.S. but other countries, including the U.K.:

> From 2014, puberty blockers moved from a research-only protocol to being available through routine clinical practice … In addition, the strict inclusion criteria of the Dutch protocol were no longer followed, and puberty blockers were given to a wider range of adolescents … These included patients with no history of gender incongruence prior to puberty, as well as those with neurodiversity and complex mental health presentations.[64]

HBIGDA became the World Professional Association of Transgender Health (WPATH) in 2007. Reflecting in 2009 on the "new paradigms [that] have emerged about the nature

[60] Harry Benjamin International Gender Dysphoria Association (2001, p. 10).
[61] Biggs (2023b, p. 353).
[62] GIDS was closed in March 2024; see also Barnes (2023).
[63] Biggs (2023b, p. 354).
[64] Cass (2024a, p. 73).

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of transgender identity and experience," Lin Fraser, then President-elect of WPATH, wrote:

> The new model views gender as a continuum rather than a male/female dichotomy and calls for individualized gender trajectories, which may or may not include hormonal therapy and sex reassignment surgery.[65]

The seventh version of the *Standards of Care* (SOC-7) was published in 2012 and was a significant departure from SOC-6, moving away from medical gatekeeping and towards the "gender-affirming" model. For example, SOC-6 recommended that CSH be given only to patients aged 18 or older, who either had "real-life experience" ("living in the desired gender") or had been in psychotherapy for at least three months. SOC-7 had no age limit for CSH, only requiring that the adolescent give "informed consent" and that the parents or guardians have also "consented to the treatment and are involved in supporting the adolescent." Recommendations for psychotherapy or real-life experience were absent. SOC-7 effectively relegated the role of mental health professionals to provide assessments needed by insurance companies for reimbursement.

Another change was apparent from SOC-7's title. SOC-6 was the standards of care "for Gender Identity Disorders," but SOC-7 was "for the Health of Transsexual, Transgender, and Gender Nonconforming People." "Non-binary" would have to wait its turn, appearing for the first time in the current guideline, SOC-8 (2022), with a chapter dedicated to it.[66] The first version of the *Standards of Care* was authored by just six people and comprised slightly over 3,000 words; SOC-8 has more than 100 contributors and more than 100,000 words.

In 2011, Cohen-Kettenis and colleagues published a follow-up study of 70 adolescent patients who received PBs in the Netherlands between 2000 and 2008. The results

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[65] Fraser (2009, pp. 113-114, citations omitted). One of the citations omitted from the quotation is *The Apartheid of Sex: A Manifesto on the Freedom of Gender*, by Martine Rothblatt. Chapter 1 of that book is called "Five Billion Sexes," and begins: "There are two sexes, male and female, right? Wrong! In fact, there is a continuum of sex types, ranging from very male to very female, with countless variations in between" (Rothblatt, 1995, p. 1).

[66] A 2020 survey of U.S. youth aged 13-24 who identified as LGBTQ found that, of the 11,914 who identified as transgender or non-binary, more than 60% identified as the latter (A. E. Green et al., 2022, p. 645).

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were interpreted as encouraging: “Behavioral and emotional problems and depressive symptoms decreased, while general functioning improved significantly during puberty suppression.”[67] A 2014 study of the same patient cohort after sex reassignment surgery—but with just 55 of the original 70 subjects—contained a similarly positive conclusion: “After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved.”[68] These two studies form the foundational evidence base of the Dutch Protocol, and are widely cited to support it. (As subsequent analysis revealed, they do not: see Section 4.3.6.)

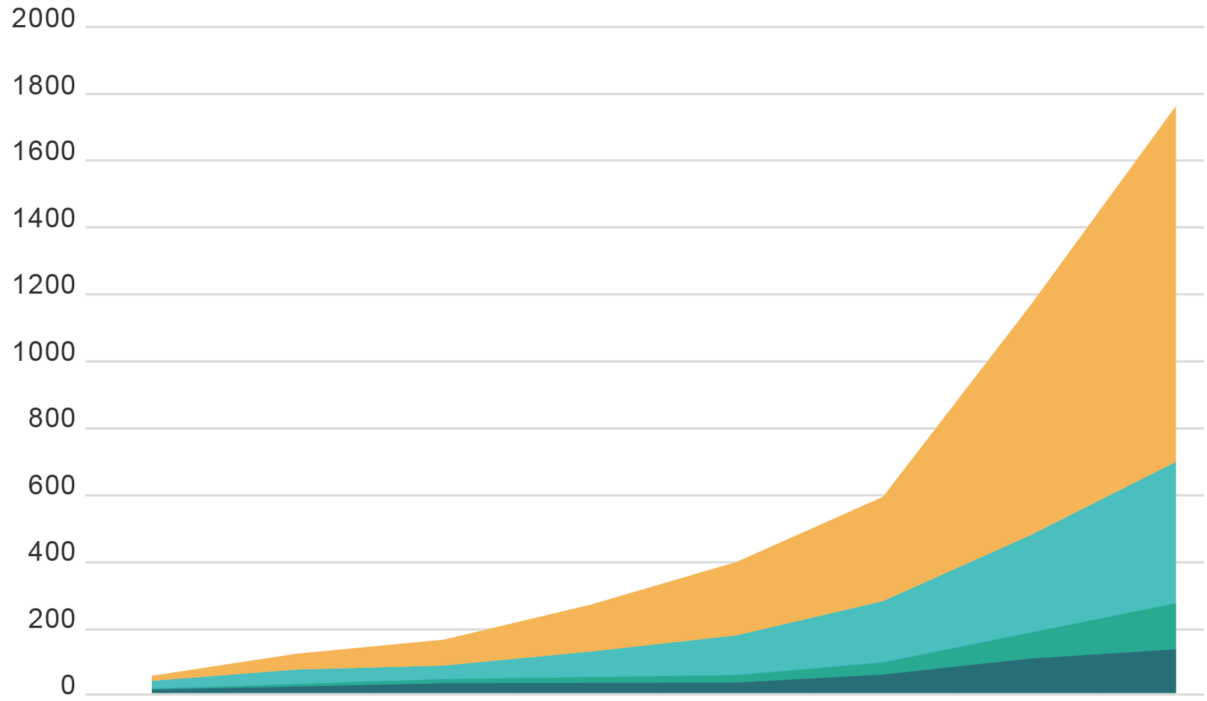
The previously observed tendency for early-onset GD patients to be gay continued with the Dutch cohort. Of the initial group of 70, only one reported heterosexuality; the other 69 reported either homosexuality (62), bisexuality (six), or “don’t know yet” (one).[69] (See also Section 13.3.1.)

Around the time Cohen-Kettenis and colleagues published their first study, clinicians started to observe a rapid increase in the pediatric patient population. More notably, the demographic profile of these patients was shifting, with adolescent females emerging as the predominant group. This trend is illustrated in Figure 3.1, which charts referrals to GIDS from 2009 to 2016.

[67] de Vries et al. (2011, p. 2276).
[68] de Vries et al. (2014, p. 696).
[69] de Vries et al. (2011, Table 1).

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Figure 3.1: Sex ratio in children and adolescents referred to GIDS in the U.K. (2009-16)[70]



	2009	2010	2011	2012	2013	2014	2015	2016
Adolescent F	15	48	78	141	221	314	689	1071
Adolescent M	24	44	41	77	120	185	293	426
Children F	2	7	12	17	22	36	77	138
Children M	10	19	29	30	31	55	103	131

In a related trend, Western countries began reporting a growing number of adolescents who, often unexpectedly, disclosed a transgender identity—frequently to the surprise of their parents.[71] The number of pediatric patients seeking medical transition can only be roughly estimated,[72] but the demand in European countries has outstripped supply, with waitlists approaching 2 years or longer. In response to the growing demand, the U.S.—characterized by its decentralized and privatized healthcare system—saw the

[70] Reproduced from Cass (2024a, p. 70); original in de Graaf et al. (2018, Figure 1).
[71] See Section 4.3.1.4.
[72] According to the Human Rights Campaign (HRC), "there are more than 300,000 high school-aged (ages 13-17) transgender youth in the United States today, *many of whom need gender-affirming care*" (Human Rights Campaign, n.d.), emphasis added). See also Williams Institute (2024).

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emergence of many new specialty gender clinics, along with a proliferation of independently practicing clinicians.[73] According to a recent conservative estimate, as of March 2023 there were 271 clinics offering PMT in the U.S., though 70 were inactive due to legislative restrictions.[74]

As clinical experience with treating youth with GD across the world has grown, concerns about the PMT model have become increasingly apparent. In response, public health authorities in several European countries have launched formal investigations into the practice. The most comprehensive is the U.K.'s 2024 Cass Review, mentioned in Chapter 1. As a result of such inquiries, some European health authorities are now restricting eligibility for medical transition and implementing new research requirements and safeguards. In the U.S., where government health authorities play a more limited role, and medical practice is primarily regulated at the state level, many states have turned to legislative measures to restrict or prohibit pediatric medical transition.[75]

As Hilary Cass observed in 2022, "it is not helpful to exceptionalise gender identity issues."[76] The consensus in pediatric gender medicine (PGM) of 10 years ago was driven by that exceptionalization, which has now begun to change. The following chapter explains why this change is underway.

[73] Levine et al. (2022a, p. 708).
[74] Borah et al. (2023, pp. 375-376).
[75] Harmon (2024).
[76] Cass (2022b).

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Chapter 4 International Retreat from the "Gender-Affirming" Model

Since the publication of the Dutch Protocol in 2006, the practice of "gender-affirming" (or "affirmative" care) has rapidly expanded. Now, a global reversal is underway. Several national health authorities have restricted hormonal and surgical interventions for minors. Section 4.1 provides a brief overview of the rise of pediatric medical transition (PMT) as the primary response to childhood and adolescent gender dysphoria (GD). Section 4.2 summarizes the ongoing practice reversal that is now taking place in an increasing number of countries. Section 4.3 explores the reasons behind these reversals.

4.1 The rise of the affirmative care model

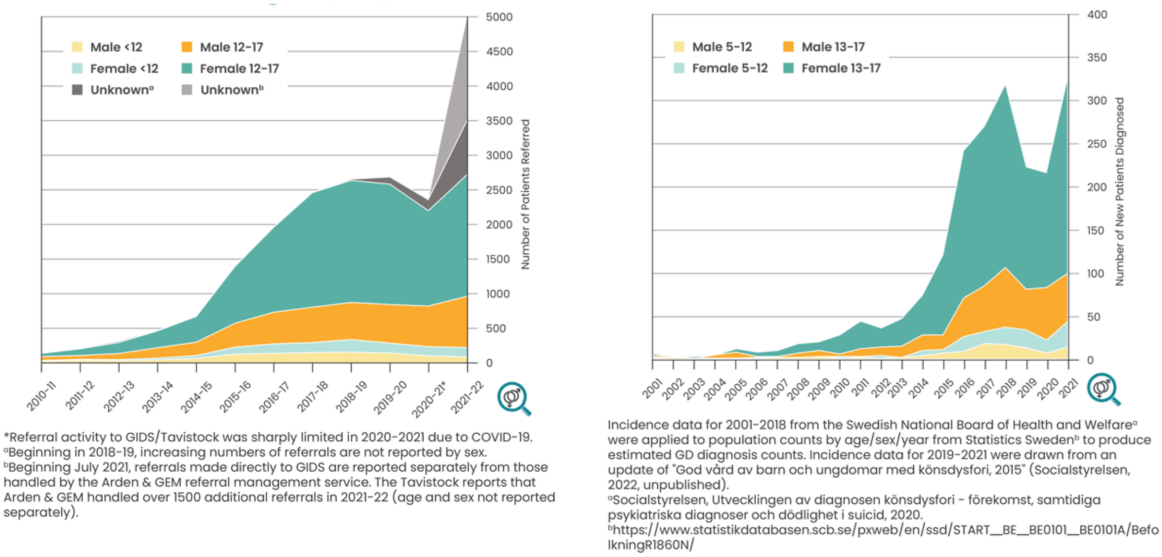
Following the publication of the Dutch Protocol in 2006,[1] puberty blockers (PBs) and cross-sex hormones (CSH) were incorporated into the Endocrine Society's 2009 clinical practice guideline (CPG),[2] which recommended that hormonal interventions should be used for certain pediatric patients with GD. This approach was also recommended by the World Professional Association for Transgender Health's (WPATH) guidelines in 2012.[3] Notably, these endorsements occurred before the final analysis of psychological outcomes from the original Dutch cohort was published in 2014[4]—and several years before the first systematic reviews of evidence (SRs) commissioned by public health authorities began to appear in 2019 and 2020.[5] During this same period, the number of children and adolescents reporting symptoms of GD and seeking medical intervention surged—a trend that has since become widespread across Western countries. At the same time, the epidemiological profile of patients changed markedly: while earlier

[1] Delemarre-van de Waal & Cohen-Kettenis (2006). Outcomes from the first patient cohort treated according to the protocol were published in 2011 and 2014 (de Vries et al., 2011, 2014).
[2] Hembree et al. (2009).
[3] The 2012 guidelines were the organization's seventh CPG (Coleman et al., 2012). The fifth and sixth CPGs, published in 1998 and 2001, briefly mentioned the potential use of "LHRH agonists" (Levine et al., 1998; Harry Benjamin International Gender Dysphoria Association, 2001), but the use of PBs as the central part of the treatment for adolescents did not emerge until the seventh version.
[4] de Vries et al. (2014).
[5] National Institute for Health and Care Excellence (2020b, 2020a); Pasternack et al. (2019).

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cohorts consisted mainly of prepubertal boys, more recent referrals have been dominated by teenage girls (see Figure 4.1 below).

Figure 4.1: Child and adolescent referrals for GD (U.K., left; Sweden, right)[6]



*Referral activity to GIDS/Tavistock was sharply limited in 2020-2021 due to COVID-19.
[a]Beginning in 2018-19, increasing numbers of referrals are not reported by sex.
[b]Beginning July 2021, referrals made directly to GIDS are reported separately from those handled by the Arden & GEM referral management service. The Tavistock reports that Arden & GEM handled over 1500 additional referrals in 2021-22 (age and sex not reported separately).

Incidence data for 2001-2018 from the Swedish National Board of Health and Welfare[a] were applied to population counts by age/sex/year from Statistics Sweden[b] to produce estimated GD diagnosis counts. Incidence data for 2019-2021 were drawn from an update of "God vård av barn och ungdomar med könsdysfori, 2015" (Socialstyrelsen, 2022, unpublished).
[a]Socialstyrelsen, Utvecklingen av diagnosen könsdysfori - förekomst, samtidiga psykiatriska diagnoser och dödlighet i suicid, 2020.
[b]https://www.statistikdatabasen.scb.se/pxweb/en/ssd/START__BE__BE0101__BE0101A/BefolkningR1860N/

The scientific foundation for the rapid expansion of PMT was largely underpinned by two Dutch studies, published in 2011 and 2014,[7] which followed the same patient cohort. The first study, which focused on the use of PBs,[8] reported psychological outcomes in 70 adolescents who had completed the PB phase and were beginning CSH. The findings suggested modest "pre-post" improvements in some mental health measures following PB treatment—but notably, no improvement in GD itself, as assessed by the newly developed Utrecht Gender Dysphoria Scale (UGDS).

For more than a decade, many of the study's methodological flaws remained largely overlooked. One of the study's limitations was its retrospective selection of 70 subjects from a larger "intent-to-treat" group of 111 using non-randomized methods. This selection process inadvertently biased the sample toward cases with the most favorable prognoses, thereby limiting the generalizability of the study's findings.[9]

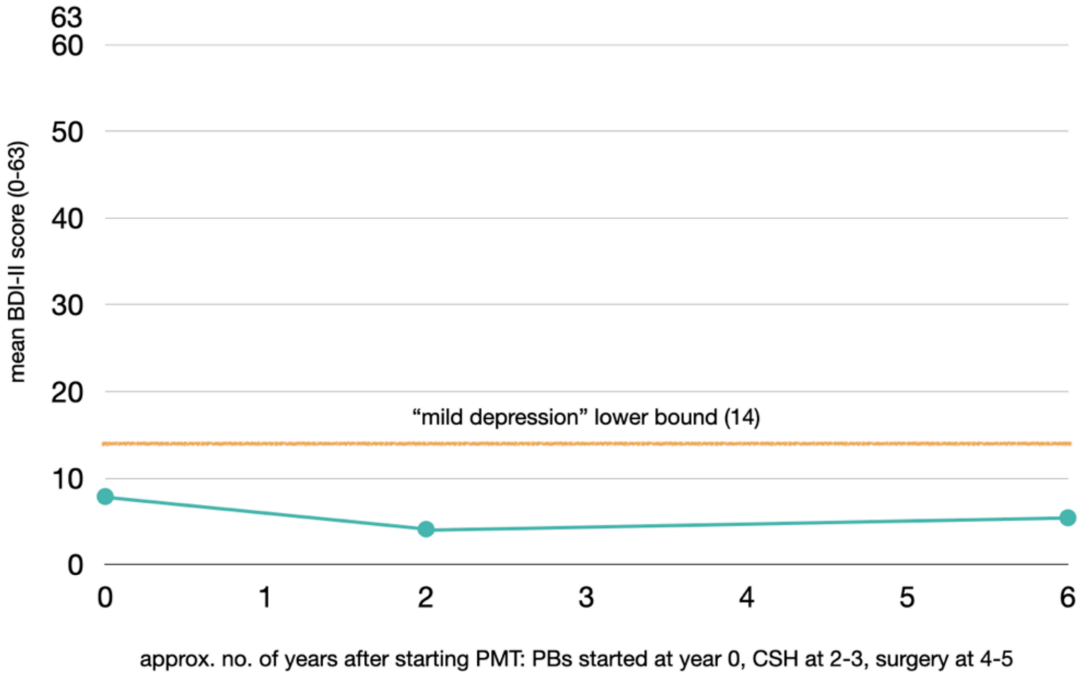
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[6] Source: Society for Evidence-Based Gender Medicine (SEGM).
[7] de Vries et al. (2011, 2014).
[8] de Vries et al. (2011).
[9] The study's inclusion criteria defined eligibility for analyzing the effects of puberty blockers (PBs) based on the start date of the subsequent phase—CSH. This approach introduced significant bias by excluding,

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In 2014, a follow-up study was published assessing the participants' functioning after CSH and surgery.[10] The sample size was further reduced to just 55 participants, and critical measures of psychological health—such as depression, anxiety, and overall functioning—were assessed in as few as 32 participants. Moreover, although the reported improvements reached statistical significance, their clinical relevance was limited (see the depression scores plotted in Figure 4.2: the orange line indicates the *threshold* for "mild depression," with 63 being the maximum score; mean scores remained below the mild depression threshold at baseline and throughout treatment).

Figure 4.2: Depression scores in Dutch cohort[11]



Noting the high-functioning status of the adolescent/young adult cohort at the end of the study, the authors concluded that the Dutch Protocol provided patients with "the

from the outset, any subjects who discontinued treatment, underrepresenting psychologically complex cases who remained in the "diagnostic" PB phase for longer periods, and skewing the sample toward older subjects. Because eligibility hinged on starting CSH at 16, only those who reached this threshold were included—potentially explaining why the average age for initiating PBs in the study was 15, despite the protocol recommending initiation around age 12 (Abbruzzese et al., 2023).

[10] de Vries et al. (2014).

[11] Graph of data contained in de Vries et al. (2011) and de Vries et al. (2014).

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opportunity to develop into well-functioning adults."[12] The study failed to consider that the subjects were already high-functioning at baseline—comparable to Dutch peers without GD.[13] This was likely attributable, at least in part, to the original Dutch Protocol's stringent selection criteria.

Moreover, the study failed to account for or appropriately consider potential signals of harm. One participant died due to post-surgical treatment complications associated with early pubertal suppression,[14] at least three were diagnosed with uncontrolled diabetes or morbid obesity while on hormones, and at least one subject discontinued treatment.

These and other serious limitations—including subject selection bias and methodological flaws (such as the post-treatment reversal of the UGDS[15])—remained largely unacknowledged, even as the study became the foundational pillar[16] of PMT protocols worldwide. Attempts to replicate the Dutch findings regarding PBs in the U.K. were unsuccessful[17]—and the publication of those unfavorable results was delayed for several years.[18] It has also been reported that the attempts to replicate the benefits of PBs in a National Institutes of Health (NIH)-funded study in the U.S. yielded less-than-favorable results.[19]

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[12] de Vries et al. (2014, p. 696).
[13] As explained in Abbruzzese et al. (2023), the requirement of psychological stability was built into the protocol, and earlier research from the same clinic had stated that "when both pre- and posttest group means were compared with Dutch normative data, all scores turned out to be within the average range" (Smith et al., 2001, p. 277).
[14] de Vries et al. (2014) noted that "1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis" (p. 697). A 2023 analysis of the original Dutch papers found that the researchers "did not mention the fact that this death was a consequence of puberty suppression: the patient's penis, prevented from developing normally, was too small for the regular vaginoplasty and so surgery was attempted with a portion of the intestine, which became infected" (Biggs, 2023b, p. 8). See also Negenborn et al. (2017).
[15] The reversal of the GD scale post-surgery may have entirely invalidated the study's key finding of the resolution of GD post-treatment (Abbruzzese et al., 2023). Of note, another clinical research study in this field (López de Lara et al., 2020) also switched GD and body image scales.
[16] One of the authors of the original Dutch research noted, in 2022, that those papers are "still used as main evidence for provision of early medical intervention including puberty blockers in transgender youth" (de Vries, 2022, p. 109). The Cass Review's final report described that instead of the usual, slow evolution of clinical practice over "many years before strongly positive research findings are incorporated … the reverse happened in the field of gender care for children. Based on a single Dutch study … the practice spread at pace to other countries …" (Cass, 2024a, p. 13).
[17] Carmichael et al. (2021).
[18] See Chapter 6.
[19] Ghorayshi (2024c).

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Spurred on by the belief in the success of the Dutch Protocol and its central premise—reliance on PBs —the expanding availability of PMT services was met by a surge in demand: "first gradually, then suddenly."[20] By 2015, nearly every European country was reporting a dramatic increase in the number of gender-dysphoric youth seeking hormonal interventions at pediatric gender medicine (PGM) clinics—a trend whose underlying cause remains the subject of ongoing debate. The endorsement of PMT was further solidified by the publication of the 2017 Endocrine Society (ES) guidelines,[21] co-authored by psychologist Peggy Cohen-Kettenis—the pioneer of the original Dutch Protocol—who had first introduced the recommendations for PMT into the 2009 ES guidelines, and later reinforced them in the 2012 WPATH *Standards of Care 7* guidelines (SOC-7).[22]

One striking characteristic of the surge of adolescents presenting with a wish to undergo medical transition is the disproportionate number of female adolescents without prior childhood history of GD who present with high rates of comorbid mental health conditions. This pattern drew the attention of Finnish researchers, who were the first to publish on these changing demographics and to raise concerns that the Dutch Protocol might not be helping—and might even be harming—patients.[23] Finland subsequently became the first country to revise its national guidelines,[24] sharply limiting medical interventions based on the findings of an SR.[25] In the years that followed, other countries began conducting their own evaluations of the evidence and arrived at similar conclusions. A global trend has since emerged, away from use of PBs, CSH, and surgeries in youth with GD. This ongoing reversal is explored in greater detail in the following section.

4.2 The international practice reversals

Starting in 2020, PMT began to face growing scrutiny from public health authorities worldwide, resulting in substantial reversals of clinical protocols in an increasing number

[20] Abbruzzese et al. (2023, p. 12).
[21] Hembree et al. (2017).
[22] Coleman et al. (2012); Hembree et al. (2009).
[23] Kaltiala et al. (2020); Kaltiala-Heino et al. (2015).
[24] Council for Choices in Health Care Finland (2020a, 2020b, 2020c).
[25] Pasternack et al. (2019).

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of countries. The most influential effort to date has been the Cass Review—a four-year independent evaluation of PGM that was published in April 2024.[26] The findings of the Cass Review led to the closure of the U.K.'s PGM clinic, the Gender Identity Development Service (GIDS), which had been given a rating of "inadequate" by the Care Quality Commission in 2021.[27] The Cass Review recommended a restructuring of the care delivery model—away from the centralized "gender clinic" model of care toward a more holistic framework centering psychosocial support, to be delivered through regional hubs. The Cass Review's findings also led the U.K. to ban the use of PBs outside clinical trials,[28] and to significantly restrict CSH.[29] While CSH are still officially an available treatment, the National Health Service (NHS) recently revealed that since the Cass Review was published, no minor has been found eligible to receive CSH according to the updated policy.[30] In the U.K., minors have never received GD-related surgery through the NHS.

Finland was the first country to curtail PMT, issuing revised national guidelines in 2020.[31] In 2022, Sweden's National Board of Health and Welfare concluded that, for most young people, the potential harms of hormonal interventions outweigh the benefits, and subsequently restricted both to research settings or exceptional cases.[32] Denmark followed Sweden's lead in 2023, restricting the use of endocrine intervention in minors,[33] and Norway's public health agency (the Norwegian Healthcare Investigation Board) advised that PBs and CSH should be considered experimental treatments.[34] Most recently, hormonal interventions have been restricted in Brazil,[35] Chile,[36] the province of Alberta in Canada,[37] and the state of Queensland in Australia.[38]

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[26] Cass (2024a).
[27] Care Quality Commission (2021).
[28] Department of Health and Social Care (2024).
[29] National Health Service England (2024c).
[30] Spencer (2025).
[31] Council for Choices in Health Care Finland (2020a, 2020b, 2020c).
[32] Socialstyrelsen (2022a, 2022b, 2022c).
[33] Hansen et al. (2023). See also Society for Evidence-Based Gender Medicine (2023b).
[34] Block (2023b).
[35] AFP (2025).
[36] Lane (2024).
[37] Government of Alberta (2024).
[38] Australian Associated Press (2025).

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At the same time, several other countries are in the process of determining how best to care for youth with GD. In Australia, following Queensland's statewide pause in January 2025 on initiating PBs and CSH for new patients under 18, the Australian Government commissioned the National Health and Medical Research Council with developing new clinical practice guidelines for youth with GD. The guidelines are expected to be completed within three years, with interim recommendations on PBs available in 2026.[39] In Italy, the Italian Bioethics Committee updated its position on the use of PBs for GD,[40] and a formal guideline development process is underway.[41] France is expected to release new national guidelines in 2025, which are expected to spark considerable debate due to anticipated endorsement of PMT[42]—a position previously criticized by the French National Academy of Medicine.[43]

Germany recently published guidelines[44] that continue to generate considerable debate in German-speaking countries, including Austria and Switzerland. The controversy stems from concerns about the non-evidence-based nature of the recommendations, their *a priori* reliance on WPATH positions, and deep divisions in the professional community[45] regarding the appropriate approach to caring for youth with GD. Even the Netherlands—the birthplace of the Dutch Protocol—has not been immune to debate.[46] In May 2024, the Dutch Minister for Medical Care formally requested that the Health Council of the Netherlands produce an independent scientific advisory report on healthcare for minors with GD. This ongoing review will include an evaluation of the Dutch Protocol and a comparison with other countries' guidelines.[47]

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[39] Australian Government National Health and Medical Research Council (2025).
[40] Italian National Bioethics Committee (2024). See also Society for Evidence-Based Gender Medicine (2024d).
[41] Curridori (2024).
[42] Sugy (2024).
[43] Society for Evidence-Based Gender Medicine (2022a).
[44] German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP) (2025).
[45] Zepf, Buchmann, et al. (2024).
[46] Society for Evidence-Based Gender Medicine (2023c).
[47] Health Council of the Netherlands (2024).

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4.2.1 The Cass Review and its reception

The Cass Review has had a profound influence on international debates. Commissioned by NHS England, the Cass Review assessed the safety, efficacy, and delivery of PGM services for children and adolescents. Conducted over four years under the leadership of Hilary Cass, pediatrician and a past president of the Royal College of Paediatrics and Child Health, the review engaged a broad range of stakeholders and relied on SRs from the National Institute for Health and Care Excellence (NICE)[48] and the University of York,[49] as well as additional research. The Cass Review identified significant limitations in the evidence base for PBs and CSH. It recommended that PBs be offered only as part of a clinical trial until further data are available, and that all potential interventions should be tested within a research context.[50] The review emphasized a multidisciplinary, developmentally-informed model of care for youth with GD that prioritizes psychological support and the development of "an explicit clinical pathway … for non-medical interventions."[51]

Recent criticisms of the Cass Review—particularly claims that it fails to meet CPG standards—reflect a misunderstanding of the Cass Review's purpose and scope. The Cass Review was not a CPG; it was an "independent review." This is a U.K.-specific process of conducting a service-level evaluation intended to inform policy, not prescriptive clinical decisions. Such processes are invoked when an area of clinical care begins to operate in ways that compromise care quality and threaten patient safety.[52]

Criticism of the Cass Review appears to stem largely from a U.S.-based group of motivated advocates for the continued legality of PMT.[53] The critiques are ridden with

[48] National Institute for Health and Care Excellence (2020a, 2020b).
[49] Hall et al. (2024); Heathcote et al. (2024); Taylor, Hall, Heathcote et al. (2024a, 2024b); Taylor, Hall, Langton et al. (2024a, 2024b); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024).
[50] "The overarching conclusion from the evidence presented in this Review is that the puberty blocker trial, which is already in development, needs to be one part of a much broader research programme that seeks to build the evidence on all potential interventions, and to determine the most effective way of supporting these children and young people" (Cass, 2024a, p. 197). See "Recommendation 6" (Cass, 2024a, p. 35).
[51] Cass (2024a, p. 157).
[52] Cheung et al. (2025).
[53] Of these, the white paper McNamara et al. (2024), produced by the Yale Integrity Project, has been most influential.

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misrepresentations of the Cass Review and contain multiple factual errors.[54] In the U.K., the Cass Review has been widely accepted as a foundational document for realigning pediatric gender medicine (PGM) with the principles of evidence-based medicine (EBM) and child safeguarding.[55] It has been welcomed by both major political parties in the U.K., and was fully accepted by the NHS for implementation, which is well underway.[56]

4.3 Rationale for international reversals

A defining feature of these global reversals has been the rejection of the "gender clinic" model, which typically promotes PMT. Internationally, this model is increasingly being supplanted by more traditional, holistic approaches to adolescent distress. Rather than referring youth with GD to specialty clinics oriented toward transition, emerging models emphasize standard mental health services, where young people receive comprehensive psychosocial and psychotherapeutic support—and, when indicated, psychiatric care.

The global reversals away from PMT can be attributed to six main factors: a significant shift in the patient population; uncertainty surrounding the natural history and prognosis of GD; increasing recognition of the risks associated with medical interventions; a more accurate understanding of the suicide risk; the collapse of the original treatment rationale; and a weak underlying evidence base. The following subsections (1-6) examine each of these factors in turn.

4.3.1 Changes in the patient population

The population of young people for whom the Dutch Protocol was originally developed differs significantly from those presenting for care today.

4.3.1.1 Epidemiological shifts

Over the past decade, the population presenting to PGM clinics has changed in two key ways: a rapid increase in numbers and a significant shift in demographic composition. Before hormonal interventions became widely available, pediatric referrals for GD were

[54] Cheung et al. (2025); McDeavitt et al. (2025).
[55] Abbasi (2024).
[56] National Health Service England (2024a).

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relatively rare,[57] and the majority were prepubertal boys with early-onset GD.[58] Over the past decade, the increase in patients has been described as exponential,[59] a trend driven primarily by adolescent females who typically have no childhood history of GD.[60]

4.3.1.2 Mental illness and neurodevelopmental diagnoses

The current patient population has a high rate (relative to the general population) of comorbid mental health problems, including depression, anxiety, suicidality, self-harm, and eating disorders; as well as neurodevelopmental conditions like autism spectrum disorder (ASD).[61] Importantly, register-based research conducted in Finland, which has national databases, found that 75% of patients presenting to PGM clinics in the mid-2010s had severe mental health problems that appeared to have *predated* the emergence of GD.[62] High rates of comorbid mental illness have been documented in the U.S. and other countries.[63]

The high prevalence of ASD among youth presenting with GD has been recognized for some time.[64] At the U.K.'s clinic, ~35% of patients had comorbid moderate-to-severe autistic traits (compared to <2% of the general population).[65] Although some researchers have postulated that the social difficulties in youth with these co-occurring conditions may not result from ASD but instead from GD and may be ameliorated by targeting this distress,[66] limited research thus far has not supported this hypothesis.[67] In

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[57] For example, the U.K.'s clinic saw 12 total patients in 1994 and 24 in 1996; it saw 150 total patients between its opening in 1989 and the year 2000 (Barnes, 2023, pp. 15-16).
[58] Steensma et al. (2018).
[59] E.g. Coleman et al. (2022, p. S9, S43); Baker & Restar (2022); de Vries et al. (2021); Olson-Kennedy, Okonta et al. (2018). The figure in McDeavitt et al. (2025) shows that the rate of increase in referrals to the U.K.'s clinic (for example) is well-approximated by an exponential. A Reuters investigation did not describe exponential growth but did find that referrals to PGM clinics have sharply increased in the U.S. (Respaut & Terhune, 2022).
[60] See Kaltiala-Heino et al. (2015, 2018); Taylor, Hall, Langton et al. (2024b); Thompson et al. (2022a); Wagner et al. (2021); Wood et al. (2013); Zhang et al. (2021). One study in this field claimed that there was no disproportionate increase in female adolescents (Turban, Dolotina et al., 2022). However, this finding was based on a survey in which there was "uncertainty as to whether transgender students responded to the sex question with their sex or gender identity" (Johns et al., 2019).
[61] See Becerra-Culqui et al. (2018); Kaltiala-Heino et al. (2015), (2018); Kozlowska et al. (2021); Taylor, Hall, Langton, Fraser, et al. (2024b); Thompson et al. (2022b).
[62] Kaltiala-Heino et al. (2015).
[63] E.g., Becerra-Culqui et al. (2018); Kozlowska et al. (2021).
[64] E.g. de Vries et al. (2010); Strang et al. (2018).
[65] Barnes (2023, p. 156).
[66] E.g., Ehrensaft (2016); Edwards-Leeper & Spack (2012); J. L. Turban (2018).
[67] Russell et al. (2021).

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2018, recognizing the clinical entity of co-occurring GD and ASD traits, researchers published preliminary guidelines for this specific population of children and adolescents,[68] recommending that "due to differences in social communication, insight and flexible thinking … extended diagnostic periods should be considered in cases where [ASD] is suspected or diagnosed."[69]

4.3.1.3 Nonbinary identities

The original Dutch research did not study patients with nonbinary identities; such patients were not deemed to be appropriate candidates for medical transition.[70] However, nonbinary identities now feature prominently in contemporary clinical settings and research populations. In a 2020 research project funded by the Trevor Project, for example, 63% of the 11,914 survey respondents identified as nonbinary.[71] In a study of youth who received mastectomies, 11% identified as nonbinary or "other."[72] This creates a new set of ethical challenges, as patients seek interventions that have never before been contemplated, including keeping patients in puberty-suppressed states for extended periods of time to allow them to maintain a sex-ambiguous appearance. The risks of such interventions may be considerable.[73]

4.3.1.4 Social influence

The role of social influence is a likely factor in these epidemiological changes. In 2018, physician and researcher Lisa Littman popularized the phrase "rapid onset gender dysphoria," or ROGD, in the peer-reviewed literature, describing the clinical picture of

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[68] Strang et al. (2018).
[69] See description in Russell et al. (2021, p. 2074). In contrast to the 2018 Dutch guidelines that recommended more caution for patients with co-occurring ASD, leading specialists in the United States have criticized parents who are reluctant to consent to PMT for their autistic children. They have proposed clinicians "depend on drawings" for severely autistic, nonverbal adolescents who cannot speak but are able to draw pictures (Transparency Podcast, n.d.). See also: whistleblower account of therapist Tamara Pietzke (Section 11.4.3).
[70] de Vries et al. (2006, p. 88): "Adolescents whose wish for sex reassignment seems to originate from factors other than a genuine and complete cross-gender identity are served best by psychological interventions."
[71] A. E. Green et al. (2022).
[72] Ascha et al. (2022).
[73] In 2020, researchers published a case report in which clinicians considered the possibility of keeping an "agender" patient with low bone density on PBs for at least seven years in order to provide affirmation for this identity (Pang, Notini, et al., 2020). Contemporary WPATH guidelines have eliminated barriers to hormonal interventions and surgeries for minors with nonbinary and other identities.

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"adolescent-onset or late-onset gender dysphoria where the development of gender dysphoria is observed to begin suddenly during or after puberty in an adolescent or young adult who would not have met criteria for gender dysphoria in childhood."[74] This phenomenon has also been described in research from the U.K.,[75] the Netherlands,[76] Finland,[77] and Canada.[78] Other terms have been used—e.g. "adolescent onset gender dysphoria," "postpuberty adolescent-onset transgender histories"[79]—for pubertal-onset gender dysphoria disproportionately affecting female adolescents.

Research into experiences of detransition and regret (detransition refers to stopping or reversing transition after having received medical and/or surgical interventions; it can overlap with but is not synonymous with regret) have suggested social influence or pressure have played a role in the transient transgender identifications of some patients.[80] Concerns about the possible role of social influence underlying epidemiological shifts in presentations have been articulated elsewhere in the literature,[81] including by some proponents of PMT.[82] WPATH's guidelines note that "susceptibility to social influence impacting gender may be an important differential to consider" for some adolescents; the guidelines also acknowledge "situations in which a young person experiences very recent or sudden self-awareness of gender diversity and a corresponding gender treatment request, or when there is concern for possible excessive peer and social media influence on a young person's current self-gender concept."[83]

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[74] Littman (2018, p. 2). This research surveyed 256 parents of children with adolescent-onset GD, finding that in roughly half the cases, the rapid onset of GD appeared to have coincided with the onset of similar distress within the children's friend groups, and with an increase in social media/Internet use. "Rapid onset gender dysphoria" appeared in scholarly work a year earlier, in a poster abstract by Littman in the *Journal of Adolescent Health* and (following Littman's research) also in Marchiano (2017).
[75] de Graaf et al. (2018); Hutchinson et al. (2020).
[76] de Vries (2020).
[77] Kaltiala-Heino et al. (2018); Kaltiala-Heino & Lindberg (2019).
[78] Zucker (2019).
[79] Kaltiala-Heino & Lindberg (2019); de Vries (2020).
[80] Littman (2021); Littman et al. (2024).
[81] Bailey & Diaz (2023); Wood et al. (2013).
[82] Edwards-Leeper & Anderson (2021); Shrier (2021b).
[83] Coleman et al. (2022, p. S45, S58).

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4.3.2 Unclear natural history and prognostic uncertainty

Prior to the widespread availability of hormonal interventions, most cases of childhood GD resolved naturally by the end of puberty, with the majority of patients having a homosexual sexual orientation in adulthood.[84] The Dutch Protocol was developed on the assumption that only GD that persisted into adolescence would likely be permanent.[85] As referrals shifted toward patients with adolescent-onset distress, this assumption of permanence was generalized to all adolescent GD regardless of whether it *intensified* in adolescence or *appeared for the first time* in adolescence. The belief that any GD in adolescence is likely permanent and warrants medical treatment remains "central to the rationale for medical intervention" in adolescents.[86]

4.3.2.1 New evidence about the natural history of gender dysphoria

Recent close examination of the literature has called into question the assumptions regarding the permanence of adolescent GD.[87] Although the natural history of GD—i.e., its course absent medical interventions—is currently impossible to measure given the wide availability of interventions, new evidence suggests that GD has a low diagnostic stability. For example, a German longitudinal analysis of an insurance claims database showed that over 70% of adolescent females aged 15-19 no longer had the diagnosis

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[84] The largest such study was Singh et al. (2021), which included a comprehensive overview of prior research on persistence of childhood GD (pp. 2-4). Some have argued that changes to diagnostic criteria—from the older "Gender Identity Disorder" (for which dysphoria, described as "discomfort," was a criterion) to the contemporary "Gender Dysphoria" diagnosis—render findings of older studies irrelevant (Temple Newhook et al., 2018). These arguments have been effectively countered (Zucker, 2018). (For the diagnostic criteria, see Appendix 2.) Low persistence rate of childhood GD has been recognized in the literature: e.g. "gender variant children, even those who meet the criteria for GID prior to puberty, for the most part are not gender dysphoric at a later age" (de Vries & Cohen-Kettenis, 2012, p. 306); also see Ristori & Steensma (2016, p. 6); Cohen-Kettenis & Gooren (1999).

[85] E.g. Cohen-Kettenis & Pfäfflin (2003); de Vries et al. (2006); de Vries & Cohen-Kettenis (2012); de Vries et al. (2014).

[86] Rosenthal (2021a, p. 585): "Longitudinal studies have indicated that the emergence or worsening of gender dysphoria with pubertal onset is associated with a very high likelihood of being a transgender adult. This observation is central to the rationale for medical intervention in eligible transgender adolescents."

[87] Byrne (2024a).

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five years later.[88] Another recent study from the Netherlands found that "gender non-contentedness" continues to decline steadily into the early twenties.[89]

4.3.2.2 Concerns about identity development

There is considerable concern that "pubertal suppression may alter the course of gender identity development, essentially 'locking in' a gender identity that may have reconciled with biological sex during the natural course of puberty."[90] This concern is not new. Some early critics of the Dutch approach pointed out that initiation of hormonal interventions in early to mid-puberty "might affect the further development of gender identity, or … even iatrogenically induce persistence [of GD]."[91] In 2024, the European Academy of Pediatrics cautioned that puberty suppression may undermine long-term autonomy by creating a path dependency that leads to cross-sex hormones and surgery.[92] Several studies have suggested continuation rates from PBs to CSH exceed 90%.[93] The perception of PBs has shifted—from being seen as a reversible "pause button" to more like a "gas pedal" that accelerates medical transition.

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[88] Bachmann et al. (2024) was an insurance claims study looking at the International Classification of Diseases, tenth version (ICD-10) code F64 ("Gender Identity Disorder"), which was the billing code used in Germany over the course of the study period (Society for Evidence-Based Gender Medicine, 2024c). A recent *BMJ* analysis of claims data and medical records concluded that for some groups, including young people, "GD is not a permanent diagnosis" (Sun et al., 2023).

[89] Rawee et al. (2024, p. 1813). "Gender non-contentedness" was defined based on endorsement of item 110 in the Youth Self Report/Adult Self Report (YSR/ASR), "Wishes to be the opposite sex." Although item 110 is not synonymous with the diagnosis of GD, it is frequently used as a rough proxy for the clinical diagnosis as it captures the primary criterion of the desire to be the opposite sex. See Zucker (2005).

[90] Jorgensen et al. (2022, p. 1005). See also the Cass Review's final report: "Blocking [puberty] means that young people have to understand their identity and sexuality based only on their discomfort about puberty and a sense of their gender identity developed at an early stage of the pubertal process. Therefore, there is no way of knowing whether the normal trajectory of the sexual and gender identity may be permanently altered" (Cass, 2024a, p. 178).

[91] Korte et al. (2008, p. 839).

[92] Brierley et al. (2024).

[93] E.g., Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018). Some have claimed that "the most likely explanation for why most youth who receive early, supportive interventions [i.e., puberty blockers] continue onto gender-affirming hormone therapy [is] that they are indeed transgender. It is not ... puberty-pausing medications that drive a persistent transgender identity" (McNamara et al., 2024, pp. 20-21). However, the very research studies that comprise the evidence base in this area recognized the possibility that the intervention may induce persistence; e.g., "Due to the observational character of the study, it is not possible to say if [puberty blocker] treatment itself influenced the outcome" (Brik et al., 2020, p. 2611); "[there is] the potential that treatment could influence the continuation of their GD" (Carmichael et al., 2021).

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Social transition in childhood may have similar effects, with some low-quality studies suggesting the majority of children who socially transition[94] before puberty progress to medical interventions.[95] These patients "are likely [to] seek blockers or hormones."[96] Prepubertal transition was not recommended in the original Dutch approach (the researchers actually recommended *against* the practice),[97] but was originally championed by American clinicians.[98]

Prepubertal social transition is now recommended for certain patients, including in the Netherlands.[99] However, there are no reliable methods to distinguish which patients will experience long-term GD.[100] There is growing concern about administering irreversible treatments that may lead to lifelong medical dependency for a condition that, in many cases, may naturally resolve.

4.3.3 Concerns about treatment-associated risks and harms

Awareness of the risks and potential harms of PMT is growing.[101] Concern has been raised about the unknown or potentially harmful effects of suppressing normally timed puberty on adolescent physical and mental health, especially with regard to bone mineralization and brain development.[102] Hormonal interventions can lead to infertility and impaired sexual function, and in some cases, if the patient proceeds to genital

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[94] In this context, social transition refers to "a 'complete' binary social transition ... including changing their pronouns to the binary gender pronouns that differed from those used at their births" (Olson et al., 2022, p. 2), not to changes in hairstyle, clothing, etc.
[95] Olson et al. (2022, 2024). See also Society for Evidence-Based Gender Medicine (2022b).
[96] Olson et al. (2022, p. 4).
[97] E.g., "In a qualitative follow-up study, several youths indicated how difficult it was for them to realize that they no longer wanted to live in the role of the other gender and to make this clear to the people around them… Another reason we recommend against early transitions is that some children who have done so (sometimes as preschoolers) barely realize that they are of the other natal sex. They develop a sense of reality so different from their physical reality that acceptance of the multiple and protracted treatments they will later need is made unnecessarily difficult. Parents, too, who go along with this, often do not realize that they contribute to their child's lack of awareness of these consequences" (de Vries and Cohen-Kettenis, 2012, p. 308).
[98] E.g. Ehrensaft (2016); Olson et al. (2016).
[99] Bazelon (2022a).
[100] Cass (2024a, pp. 22, 134, emphasis added). "… clinicians have told us *they are unable to determine with any certainty* which children and young people will go on to have an enduring trans identity … Many clinicians, both nationally and internationally, have [acknowledged] that there is *no reliable way to accurately predict* which young people might benefit from a medical transition and which might benefit from alterative pathway(s) or interventions(s)."
[101] See Chapter 7 for detailed discussion.
[102] E.g., Baxendale (2024); Biggs (2021).

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procedures, riskier operations.[103] Surgical procedures themselves carry the risk of complications.

The emergence of detransitioners has brought renewed attention to a risk acknowledged in the original Dutch Protocol, which is that initiating medical transition while a young person's identity is still developing carries the risk of "false positives"—patients who undergo irreversible hormonal and/or surgical interventions but ultimately do not continue to identify as transgender.[104] In the past five years, a growing body of research and peer-reviewed literature has examined the phenomena of detransition and regret.[105] Personal accounts from detransitioned patients who report having been harmed by PMT have played a significant role in drawing public and regulatory attention to these issues.[106]

4.3.4 More appropriate understanding of suicide

Proponents of PMT often describe it as lifesaving.[107] Some physicians recommending PMT have urged anxious parents to consent to irreversible interventions for their distressed children, warning that not doing so may increase the risk of suicide.[108] Such claims are not supported by the evidence and have been criticized as unethical.[109]

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[103] See Lee et al. (2023), for example.
[104] Delemarre-van de Waal & Cohen-Kettenis (2006, p. S132). "It is conceivable that lowering the age limit increases the incidence of 'false positives.'"
[105] E.g. Entwistle (2020); Littman (2021); MacKinnon, Expósito-Campos et al. (2023); Roberts et al. (2022).
[106] According to a Reuters investigation, a patient told her gender clinic at age 16 that she was "sure of my identity … I thought nothing would change my mind." After starting CSH she experienced worsening mental health and had several suicide attempts and psychiatric hospitalizations. She detransitioned at age 20 and identifies as a lesbian: "I do wish my doctors had said to me, 'It's OK to feel disconnected from your body. It's OK to like girls. It's OK to be gender non-conforming'" (Respaut et al., 2022). For an overview of the role of detransitioner Keira Bell in drawing regulatory attention to pediatric gender medicine in the U.K., see Cass (2024a, pp. 78-80).
[107] E.g., ACLU (2021); Boerner (2022, 3/31/2025 update); Georges et al. (2024); Lee & Rosenthal (2023); Sandhu et al. (2025); Szilagyi (2022b); The Lancet Child & Adolescent Health (2021). See also Section 1.2.
[108] In 2011, Johanna Olson-Kennedy, pediatrician and leader in the field of pediatric gender medicine, told ABC News that "We often ask parents, would you rather have a dead son than a live daughter?" (ABC News, 2011). See also Singal (2018).
[109] E.g., Clayton (2023); Levine et al. (2022a).

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Adolescents and adults with GD do exhibit higher rates of suicidality—including suicidal thoughts, self-harm, and suicide attempts—compared to the general public.[110] However, completed suicide among adolescents with GD remains rare.[111] Moreover, there is no evidence that elevated suicidality can be attributed solely to GD, as it frequently co-occurs with other mental health conditions. A 2020 report by the Swedish National Board of Health and Welfare (Socialstyrelsen) concluded that "people with gender dysphoria who commit suicide have a very high rate of co-occurring serious psychiatric diagnoses, which in themselves sharply increase risks of suicide … it is not possible to ascertain to what extent GD alone contributes to suicide."[112]

Further, the evidence for whether PMT reduces *suicidality*-related outcomes in adolescents—such as self-reported frequency of suicidal thoughts, or healthcare utilization for self-harm or suicide attempts—is inconsistent.[113] When the focus turns to preventing *suicide mortality*, there is no evidence that hormonal interventions are effective. A large, register-based study from Finland found that overall suicide mortality in patients with GD was rare and that when mental health comorbidities were controlled for, the rate did not differ from that of the general population. The study authors concluded that hormonal interventions did not appear to have impacted suicide risk.[114] An SR of suicide prevention for youth with GD rated the evidence as low quality,[115] and WPATH's own SR of mental health outcomes, which focused on adult populations, acknowledged that "It was impossible to draw conclusions about the effects of hormone

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[110] E.g., Biggs (2022); Erlangsen et al. (2023); Heino et al. (2023); Marconi et al. (2023); Van Cauwenberg et al. (2021); Wiepjes et al. (2020).
[111] Biggs (2022); Ruuska et al. (2024); Society for Evidence-Based Gender Medicine (2023a).
[112] Socialstyrelsen (2020); see also Ruuska et al. (2024). Additionally, de Graaf et al. (2022) found that adolescents with GD or transgender identification had similar self-reported suicidality measures to comparator adolescents without GD who were receiving specialized mental healthcare for other psychiatric diagnoses.
[113] Small to medium-size studies have reported improvement over time in self-report scores related to suicidality (Achille et al., 2020; Allen et al., 2019) or decrease in healthcare utilization for suicidal or self-harm behavior (Kaltiala et al., 2020; Khatchadourian et al., 2014); other larger studies found the percent of patients with suicidal thoughts/behaviors increased after initiating PBs/CSH (Kuper et al., 2020) and increases in healthcare utilization related to suicidality (Hisle-Gorman et al., 2021). Kuper et al.'s before-after comparison is compromised by the unequal time periods over which suicidality was measured.
[114] Ruuska et al. (2024).
[115] Christensen et al. (2025). Similar findings were also reported in a recent narrative review focused on adults (Jackson, 2023). With respect to surgeries, evidence is limited. A recent systematic review of mastectomies in young females found very low certainty evidence with respect to effect on death by suicide (Miroshnychenko et al., 2024).

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therapy on death by suicide."[116] As summarized in the Cass Review's final report, "it has been suggested that hormone treatment reduces the elevated risk of death by suicide in this population, but the evidence found [does] not support this conclusion."[117] Consequently, claims that PMT is "lifesaving" appear to be unsupported by the evidence.

These findings also have been confirmed by the Appleby Report, commissioned by the U.K. government, which reviewed suicides among young people with GD. The report strongly criticized the way suicide and GD have been discussed on social media, characterizing it as insensitive, distressing, dangerous, and in violation of established guidance on the safe reporting of suicide. Appleby emphasized that many of the public claims made about suicide do not meet basic standards for statistical evidence. The report also urged a shift away from viewing PBs as the primary marker of supportive care, warning that such a narrow focus oversimplifies complex clinical needs.[118]

4.3.5 Collapse of clinical rationale

An original rationale for prescribing PBs, as outlined in the Dutch Protocol, was to provide adolescents with "time to think" by pausing puberty, thereby allowing for the exploration of identity without the added distress of physical development.[119] However,

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[116] Baker et al. (2021, p. 12). Another more recent systematic review also found very low certainty evidence for the effect of CSH on death by suicide (Miroshnychenko, Ibrahim et al., 2025).
[117] Cass (2024a, p. 33). An example of commonly cited evidence—e.g., American Psychological Association (2024b); The Lancet Child & Adolescent Health (2021), via reference to Rew et al., (2021); Turban (2020)—in support of this suggestion is Turban, King et al. (2020), a cross-sectional analysis of Internet-based survey data that found that respondents who had accessed PBs had lower lifetime suicidal ideation when compared to those who had wanted PBs but not accessed them. The online survey, the 2015 U.S. Transgender Survey (USTS) (James et al., 2015), had multiple methodological weaknesses. For example, it was a convenience sample, likely not representative of transgender adults in the U.S, and respondents may have confused PBs for CSH (Biggs, 2020; Clayton et al., 2021). Additionally, the survey relied on adult respondents' retrospective recall of childhood and adolescence, and such memories "are subject to confabulation, modification, bias, and simply forgetting;" for example, "31% of respondents recalled realizing they were transgender by age 5, including some who recalled they were transgender at the age of 1 and 2—long before autobiographical memories begin" (Kulatunga Moruzi & Lawler, 2024, pp. 11, 4). The Turban et al. study has also been criticized for its inaccurate assumption that PBs for GD were available in the U.S. starting in 1998, and it has been pointed out that on multivariate analysis, there were no statistically significant between-group differences on five other measures of suicidality, including history of suicide attempts (Biggs, 2020; Clayton et al., 2021).
[118] Appleby (2024).
[119] Delemarre-van de Waal & Cohen-Kettenis (2006).

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data suggest that adolescents who start PBs go on to take CSH.[120] This means that PBs may not function as a neutral pause, but rather the first step on the path to medical transition. This has prompted many experts to abandon the "time to think" rationale, a reversal reflected in more recent WPATH guidelines and professional statements.[121] PBs and CSH are now understood to be a continuous treatment pathway.[122]

Given the risk profile of PBs as outlined in Chapter 7, and the possibility that their use may lead to lifelong medical dependency carrying additional long-term risks, their role in the current treatment paradigm is unclear. In male patients, testosterone suppression can be achieved with anti-androgens alongside estrogen for feminization. In female patients, testosterone alone effectively suppresses estrogen, while also inducing masculinization. Therefore, if PBs are not being used to provide time to think, their rationale in this context remains uncertain.[123]

4.3.6 Lack of reliable evidence of benefit

The original intent behind the use of hormonal interventions in pediatrics was to improve mental health outcomes[124] by preventing sexual development and causing the development of physical characteristics typical of the other sex. This approach was

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[120] Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).

[121] Although WPATH's 2012 guidelines stated (consistent with the original Dutch research) that PBs would "[give] adolescents more time to explore their gender nonconformity and other developmental issues," (see Coleman et al., 2012, p. 177), this clinical rationale is absent in the latest version of the organization's guidelines, Coleman et al. (2022). A recent article by leaders in the field about eligibility and screening evaluations for patients interested in PBs made no mention of the "time to think" rationale (Turban et al., 2025). See also amicus brief acknowledging that PBs and CSH should not be considered separate treatment pathways because they constitute a "care continuum" and "the vast majority of adolescents with gender dysphoria who receive puberty blockers progress to cross-sex hormone therapy" (U.S. v. Skrmetti (No. 23-477), Expert Researchers and Physicians, Amicus curiae brief, 2024).

[122] There are exceptions to this understanding; some research papers and organizations still claim PBs provide time to think (e.g. Fisher et al., 2024; U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief, 2024, p. 13).

[123] The Cass Review found that although there may be "a very narrow indication for the use of puberty blockers in birth-registered males as the start of a medical transition pathway in order to stop irreversible pubertal changes," there were no other reasonable, proven rationales for use of PBs, and, notably, no indication for use of PBs in females (Cass, 2024a, p. 180). Experts have questioned "the rationale for depriving an adolescent of sex hormones for years during puberty and risking the effects on bones and brains" (Ryan, 2024b).

[124] Researchers were originally motivated to initiate hormonal interventions in children and adolescents because they were concerned about poor mental health in adult patients and hoped to mitigate this by preventing development of sex characteristics that were distressing for these adults (discussed in more detail in Chapter 3).

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based on the hypothesis that avoiding "an unfavorable physical appearance"[125] would "improve the ability to 'pass' as the desired gender."[126] While these interventions do alter physical appearance, SRs have not found credible evidence that they lead to meaningful improvement in mental health.[127] Multiple SRs have concluded that the evidence supporting the benefits of pediatric transition interventions—from PBs to CSH and surgery—is of "very low certainty." (See Chapter 5.) This means that findings from studies reporting mental health improvements[128] are not considered reliable. In contrast, all medical interventions carry the potential for harm.

Ultimately, medical interventions should be used when the balance of benefits clearly outweighs the risks. Every public health authority that has conducted a systematic review of the evidence has concluded that the benefit/risk profile of PMT is either unknown or unfavorable.

[125] Delemarre-van de Waal & Cohen-Kettenis (2006).
[126] Costa et al. (2015).
[127] The other original clinical rationale was decreasing need for future surgeries. One study has reported that female patients who started PBs early in puberty were less likely to receive mastectomies than patients who started PBs later, suggesting relative lack of breast tissue precluded need for mastectomy. However, this study also found greatly increased odds of intestinal vaginoplasty in male patients who received PBs in early puberty (van de Grift et al., 2020). One adolescent mastectomy study suggested chest-related dysphoria increased after testosterone use (Olson-Kennedy, Warus, et al., 2018). Theoretically, increasing chest dysphoria could lead to pursual of mastectomy. In the adult literature there have been reports of females undergoing hysterectomy due to pelvic pain caused by reproductive organ atrophy (e.g., Zwickl et al., 2023).
[128] Across the studies looking at mental health outcomes, statistically significant improvements have been inconsistently reported. Of longitudinal mental health outcome studies in this field, some reported improvements in one or more mental health outcomes (Achille et al., 2020; Allen et al., 2019; Chelliah et al., 2024; Chen et al., 2023; de Vries et al., 2011, de Vries et al., 2014; Fisher et al., 2024; Kaltiala et al., 2020; Kuper et al., 2020; Lavender et al., 2023; López de Lara et al., 2020; Olson-Kennedy et al., 2025); the largest study found worsening in mental health outcomes (Hisle-Gorman et al., 2021), while others reported no change (Becker-Hebly et al., 2020; Cantu et al.. 2020; Carmichael et al., 2021; Eisenberg et al., 2024; Khatchadourian et al., 2014; Russell et al., 2021; Tordoff et al., 2022). One study reported similar improvement in a group treated with PBs and a group treated with psychotherapy only (Costa et al., 2015).

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PART 2

EVIDENCE REVIEW

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Chapter 5 Overview of Systematic Reviews

This chapter reviews the best available information regarding the risks, benefits, and uncertainties of interventions commonly used to address gender dysphoria (GD) in youth. It summarizes the findings of the overview of systematic reviews (SRs) (also known as an "umbrella review") conducted for this Review. Section 5.1 defines some terminology and describes the methodology used to produce the overview of SRs. Sections 5.2-5.6 summarize the overview's findings for the following interventions: social transition; puberty blockers (PBs); cross-sex hormones (CSH); surgery; and psychotherapy. The chapter concludes with a discussion section (5.7).

Chapter 6 explains the limitations of SRs and the need—especially in the context of pediatric gender medicine (PGM)—to consider other types of scientific evidence. Chapter 7 is an overview of those other types of evidence, including evidence from basic science, from known mechanisms of drug action, and from endocrinological disorders that approximate the effects of medical transition. This broader base of evidence allows for a more comprehensive assessment of potential harms. Chapter 8 briefly summarizes the implications of these findings for decision-makers.

5.1 Methodology

A fundamental principle of evidence-based medicine (EBM) is that optimal decision-making "requires awareness of the best available evidence, which ideally will come from systematic summaries of that evidence."[1] The cornerstone of EBM is the *systematic review*,

> [which] attempts to collate all empirical evidence that meet prespecified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.[2]

[1] Guyatt et al. (2015, p. 10).
[2] Higgins et al. (2019, p. xxiii).

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The conclusions of any individual study will be limited by study design and other factors. Collating, synthesizing, and assessing all relevant studies on the topic of interest, using systematic and reproducible methods to minimize biases and mistakes, makes possible more reliable conclusions.

SRs sit atop of the "hierarchy of evidence."[3] However, not all literature reviews are SRs, even when titled as such, so it is important to evaluate the process used in the production and reporting of any evidence review that claims to be an SR. For example, the "Cornell Review" has been extensively cited in the field of PGM to support a claim of low regret, but that review's findings do not support that conclusion.[4]

An overview of SRs essentially applies the methodology of SRs to SRs themselves, making the SRs the unit of analysis, rather than individual primary studies. In the present case, an overview of SRs was prepared because the field is already saturated with SRs, many of which evaluate the same studies. By assessing the quality of these SRs, an overview allows for a clearer understanding of the overall strength, consistency, and gaps in the evidence base.

The methodology of the overview followed the recommendations for overviews of SRs in the *Cochrane Handbook for Systematic Reviews of Interventions*.[5,6] Medline, Embase, and the psychological database PsycINFO were searched for SRs on the effects of social transition, PBs, CSH, surgeries, and psychotherapy for youth with GD up to age 26 years.[7] A complementary literature search was also conducted for "grey

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[3] See Appendix 3.
[4] Cornell University & What We Know Project (2017). The Cornell Review claimed that "regrets are most likely to result from a lack of social support after transition or poor surgical outcomes using older techniques." But this review did not properly synthesize evidence from included studies, nor assess the quality of the evidence. The review findings should therefore be interpreted with caution. The Cornell Review was not included in the present overview because the target population was mature adults, and thus is not clearly applicable to children and adolescents with GD (see Section 4.3.1.1).
[5] Higgins et al. (2019).
[6] See Appendix 4 for the detailed methodology and results of this overview.
[7] SRs in this area have usually involved patients under 18 or under 26. To encompass the inclusion of those aged 18, the Review made the decision to search for SRs for patient populations below the age of 26. This balances the comprehensiveness and the directness (applicability) of evidence review. Though there is concern regarding the directness of evidence, the evidence for <18 and patients who are older than 18 years did not identify any significant differences in outcomes.

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literature"[8] and reference lists of eligible SRs. Two reviewers independently screened titles and abstracts, and then full texts, to determine study eligibility. Reviewers resolved disagreement by discussion. The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) was used to assess the included SRs.[9] Data extraction and risk of bias assessment were completed by one reviewer and checked by a second. ROBIS assesses the quality of the SR in four domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis of findings. Additionally, ROBIS assesses the overall risk of bias in an SR's process. SRs with concerns identified in the four domains can still be assessed at low risk of bias if the SRs have properly addressed those concerns in the evidence interpretation.

The following five sections of this chapter summarize the outcome data across SRs published in English and classified at low risk of bias. The evidence synthesis was organized by the outcomes of interest for each treatment strategy. These outcomes included GD, mental health and well-being, physiologic effects (e.g., suppression of sex hormones for PBs), need for or progression to further treatment, safety outcomes including side effects and adverse outcomes, and regret. For each outcome, this overview summarized the effect estimates and the quality of evidence (the confidence in the effect estimates), following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

In GRADE, quality of evidence is equivalent to certainty of evidence.[10] Quality of evidence can be downgraded for various reasons: risk of bias (study limitations), inconsistency (unexplained variation in results), indirectness (evidence not directly applicable), imprecision (wide confidence intervals or small samples), and publication bias (selective reporting).[11] Conversely, quality may be upgraded if there is a large

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[8] "Gray literature" refers to research and information produced outside of traditional academic publishing channels and therefore may not be formally peer-reviewed or indexed in major databases.
[9] Whiting et al. (2016).
[10] "The quality of evidence is very low" is equivalent to "the certainty of evidence is very low" (Balshem et al., 2011; Guyatt et al., 2008).
[11] Balshem et al. (2011); Guyatt et al. (2008); Guyatt, Oxman, Kunz, Brozek et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter et al. (2011); Guyatt, Oxman, Kunz,

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effect size, a clear dose-response relationship, or if confounding factors would likely reduce the observed effect but the effect was nonetheless observed.[12]

Evidence is then classified into four categories by level of quality: high, moderate, low, or very low.[13] High quality evidence means that "we are very confident that the true effect lies close to that of the estimate of the effect." Very low quality evidence indicates that "we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect." This overview summarizes the GRADE ratings from the original SRs for the respective outcome wherever it is available. Nevertheless, two modifications were made:

1. Where a formal GRADE appraisal had not been performed by the SR, but expressions such as "we are very uncertain" or "no conclusions could be drawn" were used in the SR's conclusions, these were considered equivalent to a "very low quality" GRADE assessment.[14]
2. Where SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale.

After screening, 17 SRs met the inclusion criteria. These examined the effects of social transition (n = 2),[15] PBs (n = 9),[16] CSH (n = 8),[17] surgery (n = 3),[18] and psychotherapy (n = 5)[19] among children or adolescents with GD. Of the 17 included SRs, ten were rated

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Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou et al. (2011); Guyatt, Oxman, Montori, et al. (2011); Guyatt, Oxman, Vist et al. (2011).
[12] Guyatt, Oxman, Sultan et al. (2011).
[13] Balshem et al. (2011). See also Appendix 3.
[14] Balshem et al. (2011); Santesso et al. (2020).
[15] Dopp et al. (2024); Hall et al. (2024).
[16] Chew et al. (2018); Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan et al. (2025); Ramos et al. (2021); Rew et al. (2021); Taylor, Mitchell, Hall, Heathcote et al. (2024); Thompson et al. (2023); Zepf, König et al. (2024).
[17] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024); Thompson et al. (2023); Zepf, König et al. (2024).
[18] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[19] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).

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as having a low risk of bias overall.[20] SRs rated as a "low risk of bias" nevertheless may still have limitations in one or more domains. Seven SRs were rated as having a high risk of bias overall,[21] often due to limited or poorly defined research questions and eligibility criteria, lack assessment for risk of bias, and inadequate synthesis of findings. The variation in methodological rigor highlights the need for cautious interpretation of findings, especially from reviews rated at high risk of bias.

Of note, this overview excluded two SRs performed by the National Institute for Health and Care Excellence (NICE) in October 2020 to inform the Cass Review.[22] These were excluded because several subsequent SRs commissioned from the University of York to inform the Cass Review were published. The latter SRs are more comprehensive and updated the findings of the two NICE SRs.

This overview also excluded the 2021 SR by Baker et al.,[23] because participants in most of the included studies for that SR were mature adults. Notably, the Baker et al. review was cited to support Statement 2.1 in the World Professional Association for Transgender Health's *Standards of Care for the Health of Transgender and Gender Diverse People*, Version 8 (WPATH SOC-8).[24] That statement—"We recommend health care systems should provide medically necessary gender-affirming health care for transgender and gender diverse people"—was then cited in support of the recommendations in SOC-8's Adolescent chapter. Because of the way this SR has been relied on in the field of PMT, Baker et al. was subjected to a separate ROBIS analysis which found it to be at high risk of bias due to limitations in ROBIS domains of "data collection and study appraisal" and "synthesis and findings." The ROBIS assessment of Baker et al. is included in Section 2.3 of Appendix 4, while Appendix 3 provides an

[20] Dopp et al. (2024); Hall et al. (2024); Heathcote et al. (2024); Ludvigsson et al. (2023); Miroshnychenko et al. (2024); Miroshnychenko, Ibrahim et al. (2025); Miroshnychenko, Roldan et al. (2025); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024); Zepf, König et al. (2024). SRs conducted by the same research group generally followed the same methodology approach.
[21] Chew et al. (2018); Expósito-Campos et al. (2023); Karalexi et al. (2020); Malpas et al. (2022); Ramos et al. (2021); Rew et al. (2021); Thompson et al. (2023).
[22] National Institute for Health and Care Excellence (2020b, 2020a).
[23] Baker et al. (2021).
[24] Coleman et al. (2022).

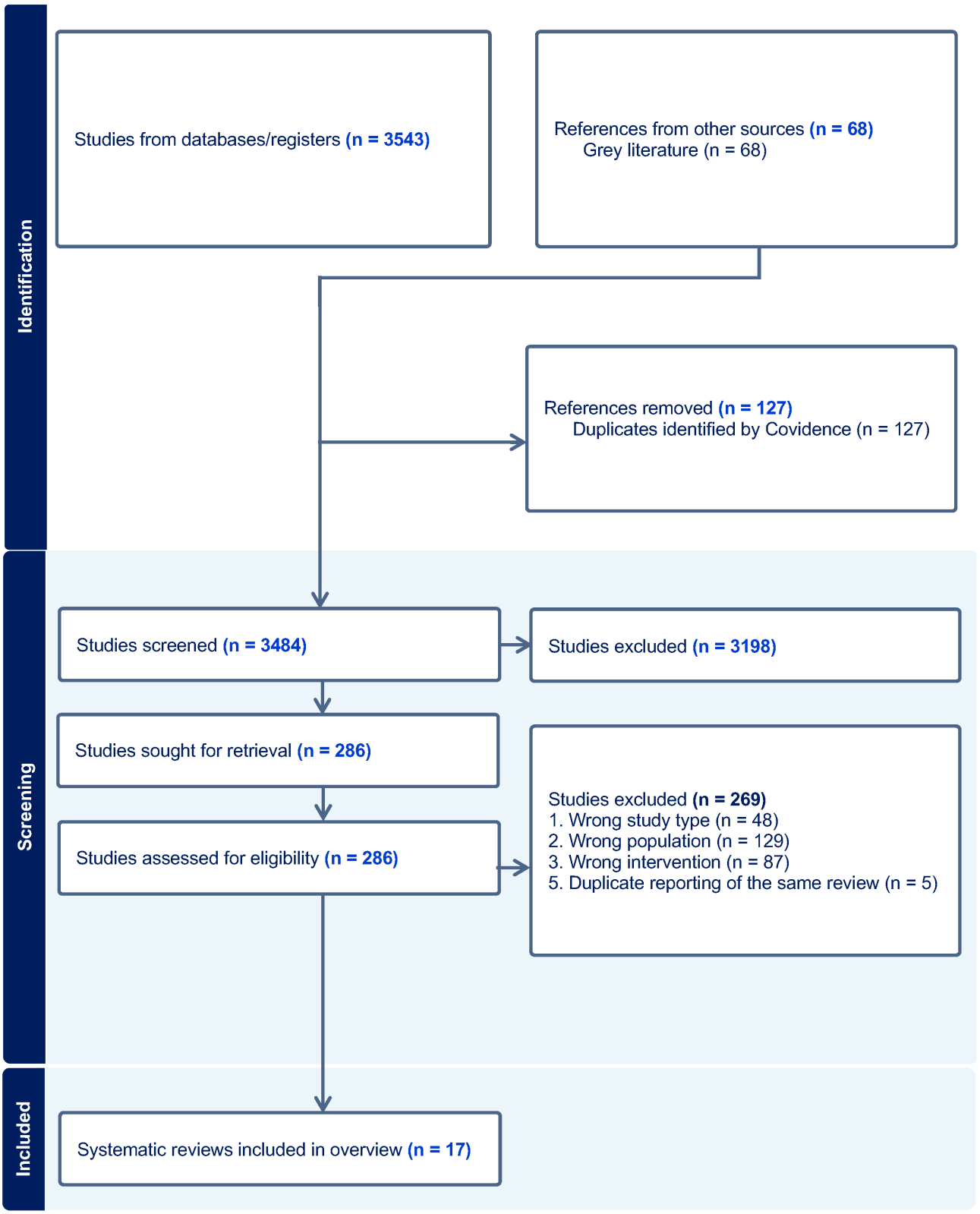
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introduction to SRs and EBM. Figure 5.1 below provides a flow diagram for the searching, screening, and inclusion process.

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Figure 5.1 Searching, screening, and inclusion process



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5.2 Outcomes of social transition

Social transition involves changing one or more aspects of one's presentation or expression, such as name, appearance, or behavior, with the goal of being perceived and treated as a member of the other sex, or to avoid being perceived and treated as a member of one's own sex. As noted in the Cass Review, even though social transition is undertaken outside healthcare settings, "it is important to view [social transition] as an active intervention because it may have significant effects on the child or young person in terms of their psychological functioning and longer-term outcomes."[25]

This overview identified two SRs evaluating the impact of social transition. Both are assessed at low risk of bias.[26] The results suggest that the impact of social transition on long-term GD, psychological outcomes and well-being, and future treatment decisions such as hormones or surgeries remains poorly understood. Evidence on regret associated with social transition is extremely limited. The certainty of evidence for these outcomes is very low.

Significant evidence gaps remain in the evaluation of social transition as an intervention for children and adolescents with GD. Most available studies are cross-sectional and there are no prospective longitudinal studies with appropriate comparison groups, making it unclear whether observed associations reflect the effects of social transition or other underlying factors. Additionally, published studies often do not disentangle the effects of social transition from concurrent interventions such as psychotherapy or medical treatments, further complicating interpretation.

5.3 Outcomes of puberty blockers

Gonadotropin-releasing hormone agonists (GnRHa), known as "puberty blockers" (PBs), are used to prevent or arrest the development of sex characteristics in peripubertal and pubertal children and adolescents with GD. This overview identified nine SRs that assessed the treatment effects of PBs. Among these four were English-

[25] Cass (2024, p. 158).
[26] Dopp et al. (2024); Hall et al. (2024).

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language SRs[27] assessed at low risk of bias. The eligibility criteria and number of included studies varied in these four SRs, and the certainty of evidence is very low regarding the effect of PBs on GD (or gender incongruence), improvement in mental health, and safety. There is high certainty evidence that PBs exert physiological effects (such as sex hormone suppression) and often cause infertility when followed by CSH, depending on the patient's pubertal stage and sex.[28] Low certainty evidence suggests that PBs may compromise bone health.[29] A high proportion of youth proceed to CSH after PBs, though the certainty of evidence regarding any causal role PBs play in this progression is very low.

Important gaps remain in both the range and quality of outcomes assessed across the existing literature. Many primary studies were not adequately designed for measuring or reporting on the outcomes related to PBs. For example, few primary studies included in the SRs assessed the impact of PBs on outcomes such as GD or mental health. Although PBs are frequently described as a "pause button,"[30] no studies have systematically examined their role in the decision-making process or the outcomes of those who discontinue treatment.

When outcomes were assessed, the focus was largely on short-term psychological or physiological changes, or surrogate outcomes—such as suicidal ideation or bone mineral density, rather than on endpoints like suicides or fractures. The evidence is particularly limited regarding long-term outcomes related to fertility, growth, and neurocognitive development.

While studies suggest a high proportion of youth proceed to CSH after puberty suppression,[31] there is minimal evidence on the impact of this combined pathway

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[27] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan et al. (2025); Taylor, Mitchell, Hall, Heathcote et al. (2024).
[28] See subsequent discussion of fertility in Chapter 7.
[29] See subsequent discussion of physiologic mechanisms whereby induced hypogonadotropic hypogonadism negatively impacts bone development.
[30] See, for example, a puberty blocker fact sheet from Cambridge Health Alliance/Harvard Medical School Teaching Hospital (Cambridge Health Alliance, n.d.).
[31] In the systematic reviews that were assessed at low risk of bias, only two studies (Carmichael et al., 2021; Karakılıç Özturan et al., 2023a) reported data on this outcome, each reporting progression rates from PBs to CSH of >95%. Other studies not captured by this overview, cited elsewhere in this Review,

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compared to CSH alone, or on how this pathway affects longer-term outcomes such as undergoing surgery. Furthermore, no studies have clearly examined the physical or psychosocial trajectories of the small minority of those who undergo PBs but do not proceed to CSH. As a result, there is little data on what happens after treatment ends, and the assumption that the effects of PBs are reversible remains largely untested. Another important limitation is that most of the primary studies have not distinguished the effects of PBs on females versus males. Overall, the absence of long-term, high-certainty evidence on these critical outcomes (including suicides, fractures, fertility, growth, and neurocognitive development) leaves substantial uncertainty about the effects of PBs.

5.4 Outcomes of cross-sex hormones

Estrogen for males and testosterone for females are used off-label to induce physical changes in the sex characteristics of youth with GD. This overview identified eight SRs on the treatment effects of CSH, among which four were in English language and assessed at low risk of bias.[32] The certainty of evidence is very low regarding the effect on GD or incongruence, improvement in mental health, and safety metrics including fertility and bone health. There is high certainty evidence that CSH exert physiological effects.

As with PBs, important evidence gaps exist for CSH. Many studies were not specifically designed to capture the full range of long-term outcomes and have primarily concentrated on short-term psychological or physiological changes. Key outcomes such as effects on GD, other mental health outcomes, and quality of life have been inconsistently measured and, when reported, often are derived from small, observational studies with limited follow-up. Critically important long-term outcomes remain poorly understood. Sexual dysfunction, despite being highly relevant to long-

also reported >90% progression rate from PBs to CSH: Brik et al. (2020); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).

[32] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024).

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term well-being, has been infrequently assessed. Although a few studies have reported cardiovascular event rates, long-term follow-up is needed to evaluate cumulative risk.[33]

Evidence on fertility is sparse, with little data on whether reproductive effects vary by age at treatment initiation or whether these effects are reversible. Furthermore, the compounded effects of sequential (and sometimes concurrent, especially among males) treatment with PBs followed by CSH—such as their impact on bone health recovery, final adult height, or the likelihood of requiring surgical interventions—have not been adequately investigated. As with PBs, the lack of methodologically rigorous, long-term studies significantly limits researchers' understanding of the broader health implications of CSH use during adolescence. A lack of primary studies that separately evaluate the effects of estrogen in males and testosterone in females is a significant limitation, as hormone-sex interactions may meaningfully influence outcomes.

5.5 Outcomes of surgery

Masculinizing mastectomy for adolescent females is the most frequently performed surgery in the context of youth with GD. This overview identified three SRs on surgeries for children or adolescents with GD, with most primary studies considering mastectomy only.[34] Two SRs were assessed at low risk of bias.[35] There is high certainty evidence that mastectomy is associated with predictable surgical complications such as necrosis and scarring. The certainty of evidence is very low regarding the effect of surgery on GD or incongruence, improvement in mental health including suicidality and depression, and long-term outcomes such as sexual function, quality of life, and regret.

There are substantial gaps in the evidence on surgeries for adolescents with GD. Most studies are case series or small observational designs, with limited or no comparator groups, and thus are unable to isolate the effects of surgery from prior medical or psychosocial interventions. Outcomes such as effects on GD, mental health, and quality

[33] This is particularly true for pediatric medical transition (due to starting CSH in adolescence, the duration of treatment will be longer than for previously studied populations of adults).
[34] Dopp et al. (2024) included 18 studies; more than half of the included studies were on mastectomy. Miroshnychenko et al. (2024) included 39 studies and only assessed the effects of mastectomy. The other SR included 25 participants receiving surgeries, of which 24 received mastectomy. See Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[35] Dopp et al. (2024); Miroshnychenko et al. (2024).

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of life are inconsistently reported and often lack validated measures. Long-term outcomes, including the durability of psychological benefits, sexual function, need for revision surgeries, as well as satisfaction and well-being into adulthood, remain poorly characterized. Furthermore, while regret is a frequent topic of public discussion, existing studies do not provide robust data on the factors influencing regret. There are also knowledge gaps for other types of surgeries, including genital surgeries.

5.6 Outcomes of psychotherapy

Discussions about the role of psychotherapy in the treatment of youth with GD suffer from internal inconsistencies in the field of gender medicine, whereby psychotherapy is both recognized as an important tool but is also stigmatized if its aim is the resolution of GD (Chapter 14). The overview identified a total of five SRs assessing psychotherapy among children or adolescents with GD. Only two were assessed at low risk of bias.[36]

The evidence on the effects of psychotherapy is limited. A 2024 review conducted by Dopp et al. included one randomized controlled trial (RCT) evaluating the effects of "coping-oriented brief videos" on suicidality, which did not provide direct evidence about the effect of psychotherapy in youth with GD. There are no other RCTs. Both SRs found that psychotherapy interventions were delivered through a range of formats, highlighting considerable heterogeneity in delivery. Formats for both face-to-face and online interventions varied widely, including individual, group, family-based, and combined approaches. Face-to-face interventions took place in diverse settings, such as specialist gender services, community programs, community mental health clinics, a weekend retreat, and an acute residential treatment program. These heterogeneities limit the generalizability of evidence. For mental health outcomes, the certainty of evidence was very low. However, no harms were reported.

The overview found no evidence on the effect of psychotherapy on GD itself. This evidence gap may be due to a conflation of psychotherapy with "conversion therapy." As noted by the Cass Review, "[the] role of psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an

[36] Dopp et al. (2024); Heathcote et al. (2024).

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unhelpfully polarised debate around conversion practices."[37] There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with childhood or adolescent GD,[38] including depression, anxiety, eating disorders, self-harm, and suicidality. Early reports often did not isolate the effects of psychotherapy from those of other concurrent interventions such as social transition, PBs, or CSH, making it difficult to attribute observed outcomes to psychotherapy alone. There is little understanding of which therapeutic approaches may be more or less effective for specific subgroups. The lack of robust research was acknowledged by the Cass Review, which noted that "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[39]

Of note, although the direct evidence for psychotherapy in children and adolescents with GD is limited, there is available evidence to support the role of psychotherapy in treating children and adolescents with other mental health problems, including depression, anxiety, eating disorders, self-harm, and suicidality (See Section 14.5.1).

5.7 Discussion

5.7.1 Findings of this overview

This overview of SRs includes 17 SRs evaluating the effects of interventions for children or adolescents with GD. For social transition, the certainty of benefits and harms is very low due to problems in the study designs. While studies suggest that early social transition is associated with a high rate of persistence of GD and a >90% rate of continuation to PBs and CSH,[40] from a methodological perspective there is uncertainty due to very low-quality evidence about causal explanations/pathways. Specific to medical transition, this overview highlights a consistent pattern across interventions for children or adolescents with GD: while PBs, CSH, and surgeries reliably produce expected physiological changes, there remains substantial uncertainty about their psychological and long-term health impacts. High-quality evidence confirms that PBs suppress pubertal development and CSH induce changes to sex characteristics. There

[37] Cass (2024a, p. 150).
[38] See Chapter 14.
[39] Cass (2024a, p. 155).
[40] Hall et al. (2024).

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is low quality evidence suggesting that PBs compromise bone health.[41] However, the quality of evidence for outcomes such as GD, mental health, quality of life, and regret remains very low across all intervention types. The interpretation of many of the SRs' findings should be approached with caution, particularly given the sources of uncertainty, the robustness of this overview's conclusion, and the methodological limitations inherent in the evidence reviews.

5.7.2 Sources of uncertainty in evidence

Across the included SRs, the quality (certainty) of evidence is predominantly limited by lack of methodologically rigorous studies. For instance, across all primary studies included in the nine SRs on PBs, there were no eligible randomized controlled trials.

The lack of proper controls is another common methodological limitation in the studies. This overview found that across all primary studies in the nine SRs on PBs, only six were observational studies with parallel control groups that compared PBs with no PBs among children or adolescents with GD.[42] However, the overall certainty of evidence was influenced not only by methodological shortcomings, but also by factors such as small sample size and small or no effects, which signify imprecision in GRADE terminology. For instance, the sample sizes of the six comparative observational studies addressing PBs were small, with three studies which each included fewer than 100 participants. One SR downgraded the quality of evidence on the effect of PBs on global function for imprecision, noting that the evidence "suggests both a possibility of a benefit or a harm in the outcome."[43]

Inconsistent study findings are another frequently cited concern that lowers the quality of evidence. For instance, one SR of CSH found "limited or inconsistent evidence regarding GD, body satisfaction, psychosocial and neurocognitive outcomes, fertility, height/growth, bone health and cardiometabolic effects."[44] Similar limitations were

[41] Physiological mechanism for PBs' effect on bone mineralization is discussed in Chapter 7.
[42] Becker-Hebly et al. (2021); Costa et al. (2015); Grimstad et al. (2021); Jensen et al. (2019); McGregor et al. (2024); Tordoff et al. (2022).
[43] Miroshnychenko, Roldan et al. (2025).
[44] Taylor, Mitchell, Hall, Langton et al. (2024).

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observed across studies evaluating other medical and surgical interventions for youth with GD.

Thus, it is important to clarify that the absence of high- or even moderate-quality evidence is not only due to a lack of randomized controlled trials (RCTs). The quality of evidence could have been improved through well-conducted observational studies,[45] which can provide moderate and even high-quality evidence when effects are large, consistent, and clearly attributable to the intervention.

5.7.3 Robustness of this overview's conclusion

Although this overview focused on English-language SRs assessed at low risk of bias, another low risk of bias SR, published in German, reached similar conclusions, reinforcing the overall patterns identified here.[46] As stated earlier, this overview did not include the NHS-commissioned SRs on PBs and CSH in 2020, as they were superseded by the SRs published in 2024 to inform the Cass Review. However, these two earlier SRs also concluded that the evidence was of very low quality,[47] and their inclusion would not have altered the conclusions of this overview.

Furthermore, it is also important to note that while this overview focused on SRs assessed at low risk of bias, this designation does not imply that these SRs were without methodological limitations. The "low risk of bias in the systematic review" in ROBIS allows for some flexibility. The included SRs still had shortcomings, such as limited search strategies, outdated literature searches,[48] or lack of precision in evidence assessments. In contrast, SRs assessed at high risk of bias consistently exhibited serious methodological flaws, including poorly defined eligibility criteria, absence of risk of bias assessments for included studies, and unsystematic synthesis approaches. These SRs were judged to be too biased to inform reliable conclusions. The findings

[45] See the checklist for ways to improve observational research in this field in Ludvigsson et al. (2023).
[46] Zepf, König et al. (2024).
[47] National Institute for Health and Care Excellence (2020b, 2020a).
[48] According to the Cochrane Handbook, reviews should be as up-to-date as possible. However, as recency is not the sole consideration, SRs with outdated search strategies can still be considered at low risk of bias overall (Higgins et al., 2019).

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presented in this overview, therefore, reflect a deliberately cautious approach, drawing only from the most trustworthy sources currently available.

Finally, rather than extending beyond what the evidence can support, this overview is confined to summarizing the conclusions of SRs. As a result, it may not include some of the most recently published studies (due to the timing of the SRs' literature searches). However, a targeted search[49] of recently published studies did not reveal any published or ongoing studies that would significantly change the conclusions, especially those pertaining to benefits. This is due to ongoing problems such as an absence of comparison groups, inadequate sample sizes, and limited follow-up. Should the contemplated U.K. RCT trial of PBs[50] receive ethics approval, it might improve the evidence base for short-term (24 month) effects of PBs on certain outcome measures. However, based on the elements of the study design publicly disclosed to date, it might not provide information about the effect of treatment when PBs are followed by CSH—a clinical trajectory which appears to occur more than 90% of the time.[51] Such combination use would have a different risk/benefit profile than the use of PBs alone, both in terms of possible benefits and possible harms. Finally, the anticipated short-term follow-up will not adequately address the key question of long-term outcomes.

Without a meaningful shift toward more robust research designs—such as RCTs that test each intervention as it is currently provided (i.e., sequential treatment of PBs followed by CSH), prospective cohorts with suitable comparators, or natural experiments—the quality of evidence likely will remain low.[52] Conducting new SRs to answer the same research questions in the near future is unlikely to yield novel insights. This dearth of robust research and evidence has direct implications for clinical guidance

[49] A targeted search in this field identified recent publications based on observational studies from the U.S. (Hidalgo et al., 2024; Olson-Kennedy et al., 2025; Wittlin et al., 2025), Canada (Lawson et al., 2024), the Netherlands (van der Meulen et al. 2025), and the U.K. (Morandini et al., 2023). These studies have similar limitations (including study design, small sample size, short-term follow up, etc.) to the primary studies included in the SRs.
[50] National Institute for Health and Care Research (2024).
[51] Brik et al. (2020); Carmichael et al. (2021); van der Loos, Klink, et al. (2023); Wiepjes et al. (2018).
[52] There is debate about whether high-quality research on effects of PBs/CSH in minors should be pursued. Ethical deliberations factor into this debate. Some have argued that research should focus on patients who already received PBs, CSH or surgery (Ryan, 2024b). The Cass Review called for more robust research into psychotherapeutic approaches to GD, which is a promising treatment approach so-far neglected by research (Cass, 2024a).

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and policy development, where expectations of benefit must be weighed against the persistent uncertainty of the evidence documented in the literature.

5.7.4 Limitations and strengths of this overview

All SRs and overviews of SRs have limitations. SRs aim to capture all relevant research that meets predefined eligibility criteria. However, this objective may be undermined by reporting (or non-reporting) bias — a form of bias that arises when the decision to publish, delay, or selectively report study results is influenced by the statistical significance, size, or direction of the findings.[53]

As discussed in Chapter 6 of this Review, research in the field of PGM suffers from significant publication and reporting bias. The extent of the problem is difficult to quantify due to widespread poor methodology and a lack of consistency in reporting effect sizes.[54] Notably, publication bias has not been considered as a reason for downgrading the certainty of evidence in the included SRs.

Another limitation is that SRs serve to answer well-defined research questions which have prespecified outcomes, but cannot detect signals or generate hypotheses. Many studies in PGM focus on psychological outcomes but only inconsistently track other outcomes that may be signals of the intervention's adverse effects. When outcomes are not reported using rigorous methodological standards—such as being clearly listed in a dedicated outcomes table—but instead are only mentioned in the discussion section, SR methodologies are unlikely to flag the study as relevant to that outcome during the screening process. As a result, important adverse effects may go unnoticed. This issue is discussed at some length in the next chapter.

A key characteristic of SRs and overviews of SRs is their emphasis on population-level epidemiological data,[55] often with limited integration of mechanistic evidence or considerations of biological plausibility. This narrow scope limits the ability of this

[53] Guyatt, Oxman, Montori, Vist et al. (2011).
[54] Publication bias is notoriously hard to measure, and the existing statistical tools have significant limitations (Afonso et al., 2024).
[55] Guyatt et al. (1992, 2015).

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overview to elucidate potential causal pathways or to fully interpret observed associations—or their absence.

This overview of SRs has other limitations. Like all overviews, it is constrained to synthesizing published SRs and does not reanalyze primary studies. The scope of this overview was intentionally narrow, focusing on young patients and excluding indirect evidence from adult populations that may provide insight into long-term effects.

Strengths included systematic evaluation of the risk of bias across SRs using the ROBIS tool. Thus, this overview offers a transparent assessment of the reliability of each SR's conclusions. It also allows for comparison across SRs with overlapping but differently scoped studies, helping to identify consistent findings, methodological gaps, and areas of agreement or divergence.

5.7.5 Conclusion

This overview synthesizes the best available clinical evidence from population-level data, highlighting a consistent pattern across interventions for children and adolescents with GD. The benefits and harms of social transition remain unknown; PBs, CSH, and surgeries consistently produce certain physical and physiological effects; and there is considerable uncertainty regarding their psychological and long-term health outcomes.

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Chapter 6 Limitations of Systematic Reviews

As reported in the overview of systematic reviews (SRs), the quality of evidence for benefits of the interventions used in pediatric medical transition (PMT) is very low. Nevertheless, the practice has continued to expand rapidly. The “very low” quality of evidence for benefits demands additional scrutiny of the potential harms in order to arrive at a proper understanding of the risk/benefit ratio.

It is well-established that SRs are better at detecting benefits than harms.[1] Consequently, the absence of evidence of harms in published studies is not equivalent to evidence of absence of harms. In pediatric gender medicine (PGM), inadequate harm detection is amplified by the following factors:

- Insufficient time has elapsed since the widespread adoption of PMT;
- Short-term before-and-after observational studies that comprise the bulk of the evidence often have high ‘loss to follow up’ rates and do not systematically look for, track, or completely report harms;
- Publication bias impedes the recognition of harms.

The first three sections of this chapter (6.1-6.3) consider how these factors affect the ability of SRs to detect harms, with a summary in Section 6.4.

A comprehensive examination of harms associated with PMT is necessary to inform clinical practice. Harms associated with surgeries that remove healthy body parts are easy to recognize, as are some of the adverse effects of hormonal interventions. The latter are noted both in the Food and Drug Administration (FDA) drug labels[2] and on informed consent or assent forms parents and children sign prior to initiating treatment.[3] Use of these drugs off-label in PGM may add additional risk. It is well-established in adults that for the same drug, off-label uses are associated with considerably higher

[1] Loke et al. (2007); Mayo-Wilson et al. (2023); Qureshi et al. (2022).
[2] Testosterone is one of the most widely used drugs in the field and is classified as a Schedule III controlled substance due to the risk of psychological dependence and abuse.
[3] E.g. Cornell Health (n.d); Fenway Health (2024a, 2024b, 2025).

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rates of adverse effects, especially when strong scientific evidence is lacking.[4] Clinical trials have never been conducted for using puberty blockers (PBs) to stop normally-timed puberty; such use will have a different risk profile than the use of PBs to temporarily stop abnormally early (precocious) puberty.

Additional uncertainty arises from the fact that, in studies, PBs are followed by cross-sex hormones (CSH) over 90% of the time;[5] this de facto combination therapy introduces new and potentially serious risks (e.g., concerning fertility) and has never been subjected to any FDA-regulated clinical trial for any population. Further, research shows that when the evidence supporting a particular off-label use is of very low certainty—as is the case for PMT—the already elevated risk of adverse effects associated with off-label use is increased even further.[6]

6.1 Insufficient elapsed time

Although the Dutch Protocol was first published 20 years ago,[7] it was not until the late 2010s to early 2020s that there were sufficient numbers of patients to allow for studies that can estimate rates of harms and benefits.[8] In addition, because the emergence of harms may be delayed by a decade or longer, SRs conducted relatively early in the field's tenure are more likely to understate these outcomes.[9] The average patient is still quite young—typically in their teens or early twenties—at the time of follow-up. This compounds problems with risk detection, since the effect of hormones on health may be cumulative (e.g., effects of hormones on cardiometabolic disease or malignancies) and may not fully manifest until later in life.

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[4] Eguale et al. (2016).
[5] E.g., Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[6] Eguale et al. (2016).
[7] de Vries et al. (2006); Delemarre-van de Waal & Cohen-Kettenis (2006). See Chapter 3.
[8] Respaut & Terhune (2022).
[9] A study in gender medicine with longer-term follow up found "poorer outcome[s] … [which] might also be explained by longer follow-up period (median 10 years) compared to previous studies. In support of this notion, the survival curve (Figure 1) suggests increased mortality from ten years after sex reassignment and onwards" (Dhejne et al., 2011).

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6.2 Short-term observational studies

The Cass Review recognized continued reliance on poorly-designed observational studies as a "key limitation to identifying … safety of gender-affirming hormones for children and adolescents."[10] A key problem that disadvantages SRs in their detection of harms is the fact that the entire body of evidence in PGM is largely composed of short-term "before and after" observational studies that are particularly prone to bias. Such studies focus on demonstrating benefits while inconsistently reporting harms.[11] Unlike the intended benefits of an intervention, which are hypothesized before the study begins and investigated as primary outcomes,[12] harms are not always expected, surveilled, or reported. Therefore, SRs are limited by being able to identify only those outcomes reported by primary studies.[13]

An example of the difficulty in identifying harms pertains to whether PBs represent a harmless "pause button" providing "time to think"[14] or a powerful intervention that promotes iatrogenic persistence of GD and promotes continuation to CSH. At least five studies indicate >90% rate of progression from PBs to CSH.[15] As the Cass Review noted, "These data suggest that puberty blockers are not buying time to think, given that the vast majority of those who start puberty suppression continue to masculinizing/feminising hormones, particularly if they start earlier in puberty."[16] Because the high rate of persistence from PBs to CSH is often mentioned only in the text of a study (and not delineated in outcome tables or abstracts), SRs may overlook this information at the screening stage. Only one low risk of bias SR assessed the proportion of CSH use after PBs, identifying only two studies.[17]

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[10] Cass (2024a, p. 76).
[11] Loke et al. (2007); Mayo-Wilson et al. (2023); Qureshi et al. (2022).
[12] In the case of prospective studies.
[13] Researchers may want their intervention to lead to beneficial outcomes, and may be reluctant to look for or focus on harms.
[14] See Chapter 4 for discussion of the "time to think" rationale.
[15] Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[16] Cass (2024a, p. 176).
[17] Miroshnychenko, Roldan et al. (2025) was the SR that identified Carmichael et al. (2021) and Karakılıç Özturan et al. (2023a).

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There are other examples of inappropriate reporting of adverse effects.[18] Three notable ones are profiled below.

6.2.1 de Vries et al., 2011, 2014[19]

The pair of seminal Dutch studies that launched PMT worldwide can serve as an example of how harms can go unreported. The 2014 study's conclusion that treatment with PBs, CSH and surgery "leads to improved psychological functioning"[20] did not comment on the finding that at least four of the original 70 young patients experienced adverse effects during treatment. Three adolescents were diagnosed with obesity and diabetes, which disqualified them from continuing to surgery, and one patient died from complications following surgery after early pubertal suppression.[21] These serious adverse events were not reported as formal outcomes,[22] precluding any discussion of whether they were caused by the experimental intervention or occurred incidentally. More recently published evidence suggests that the postsurgical death was likely directly related to the practice of early pubertal suppression.[23] Further, because these adverse effects were noted only in the context of accounting for the reduced postsurgical sample size, the study may not have attempted to detect and report less severe adverse effects that were not disqualifying for further participation.

Inadequate reporting of harms in the Dutch study was compounded when SRs excluded this study due to its unreliable design (e.g. the study comingled the CSH and surgery phases, making it impossible to determine which outcomes were associated with which

[18] This is not atypical in medicine. Researchers who invent innovative treatments are likely to focus on the apparent benefits.
[19] de Vries et al. (2011); de Vries et al. (2014).
[20] de Vries et al. (2014, p. 703).
[21] See Chapter 4 for discussion of the weaknesses in the original Dutch Protocol research.
[22] These outcomes were only discussed in the "methods" section (de Vries et al., 2014).
[23] de Vries et al. (2014) had 15 missing cases from the original cohort of 70 participants. Of these 15 participants, three were disqualified from the study because they developed obesity and/or diabetes. One dropped out of treatment, and one died from a surgical complication that was a likely consequence of pubertal suppression (Biggs, 2023b; Negenborn et al., 2017). Several others failed to return postsurgical questionnaires for unknown reasons.

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intervention).[24] Thus, the serious harms reported incidentally by the study authors were entirely omitted from the SRs due to the study's poor design.

6.2.2 Tordoff et al., 2022[25]

Inadequate reporting of harm is also evident in more recent research. A highly influential 2022 study from Seattle Children's Gender Clinic by Tordoff et al. focused exclusively on psychological outcomes, where benefits had been hypothesized. It did not study or report physical health outcomes, where harms would have been more likely to occur.

The study by Tordoff et al. reported mental health outcome data for adolescents and young adults aged 13-20 years who were treated with PBs or CSH for up to one year. The study claimed to provide "quantitative evidence" of mental health improvements; however, the rates of depression in youth who started PBs or CSH remained unchanged—about 6 in 10 youth were moderately-to-severely depressed both pre- and post-intervention.[26] These data were reported in a supplement which was available only online. The study finding of improved mental health was derived from the odds ratios: 60% lower odds of depression and 73% lower odds of suicidality in patients treated with PBs or CSH as compared to those who were not. However, major methodological issues, including potential selection bias and confounding,[27] inappropriate statistical

[24] de Vries et al. (2014) was excluded from the systematic review of CSH by the SR conducted by the U.K.'s National Institute for Health and Care Excellence (NICE). The stated reason for exclusion was: "Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported" (National Institute for Health and Care Excellence, 2020a, p. 72). This study was also excluded from the SR by Miroshnychenko, Ibrahim et al. (2025) on CSH. Though it was included in the SR by Taylor, Mitchell, Hall, Langton et al. (2024) on CSH, it was classified as a low-quality study and not included in the evidence synthesis.

[25] Tordoff et al. (2022). This research was conducted in the U.S. at Seattle Children's Hospital/Washington State University.

[26] Raw Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) data was not reported, even in the online-only supplement.

[27] Of 104 youth aged 13-20, 62 initiated treatment with PBs or CSH during the 12-month study, and 7 were already on treatment at baseline. Participants who initiated treatment during the study contributed to both "treated" and "untreated" groups at different times, complicating interpretation.

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modeling,[28] missing participant data,[29] and selective reporting[30]—raise serious concerns about the reliability of the reported findings.

The impressive-sounding odds ratios were thus calculated by relying on progressively smaller denominators in the untreated "comparator" group. The supplementary online-only data revealed that only seven cases from the "comparator group" of patients not treated with PBs or CSH remained enrolled in the study by its end.[31] It was also unclear if or to what extent this "comparator" group could be considered representative of all untreated patients. It appears that the "untreated" group comprised youth whose mental health problems and GD issues resolved who dropped out from the gender clinic and the study (representing 80% of the total "untreated group"); the patients who were about to cross-over to the treated group after a short assessment; and the 8 patients (7 of whom provided follow-up data) who continued to attend the gender clinic 12 months later, but for an unknown reason were not starting hormonal interventions.[32]

Two recent systematic reviews have assessed Tordoff et al. for risk of bias, using two different tools (the Newcastle Ottawa Scale and ROBINS-I).[33] While both analyses identified some methodological weaknesses (e.g., short follow-up, high attrition rate), the study's inclusion of untreated youth as a comparison group somewhat boosted its

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[28] Rather than analyzing individual mental health trajectories before and after treatment, the study performed cross-sectional comparisons at various time points, leading to potential bias.
[29] At 12 months, data are missing for 17% of medicalized youth (12 of 69) and an astounding 80% of non-medicalized youth (28 of 35). It is likely that non-medicalized participants without mental health distress, including those whose gender distress resolved, would be least likely to return to the clinic
[30] The authors performed analyses following multiple strategies, reporting in the abstract only the version of the analysis that produced the most dramatic results (strongest aOR [adjusted odds ratio] and smallest p-values), raising concerns about data-dredging.
[31] Based on eTable 3 in the supplementary material, the estimated prevalence of depression in the control group was 59% at baseline, 76% at month 3, 58% at month 6, and 86% at month 12. The substantial fluctuation across time points indicates that the estimates for the control group were unstable and likely influenced by random error.
[32] There was incomplete data for 80% of patients in the untreated group. It is possible that patients whose GD resolved stopped attending appointments. Additionally, the 7 untreated patients with follow-up data at one year may not have been approved for medical transition because they did not have sufficient capacity for consent—the only scenario under which this pediatric gender clinic would not recommend medical transition if desired by the patient, according to the study's lead author ("In practice, the only instances when it would have been appropriate to delay initiation of PB/GAH is if there was a concern that a patient did not have the capacity to provide informed consent … which is exceedingly rare in adolescence" (Tordoff, 2022). Barriers to provision of informed consent can include active psychosis or mania and profound intellectual disability.
[33] Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024b). ROBIS: Risk of bias in non-randomized studies - of interventions.

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quality ratings. Systematic reviews are not always able to capture serious problems with comparison groups of this type.

This study's misrepresentation of its own results, serious confounding, and the exceptionally loss-follow-up for untreated youth have been highlighted by science journalists and discussed in peer-reviewed articles.[34] Despite these well-demonstrated problems, this study, published in the *Journal of the American Medical Association* (JAMA) Open Network, continues to be uncritically described, by authoritative sources, as evidence that PBs and CSH are beneficial to mental health, medically necessary, and lifesaving.[35]

6.2.3 Chen et al., 2023[36]

Similarly, while a National Institutes of Health (NIH)-funded initiative, "The Impact of Early Medical Treatment in Transgender Youth,"[37] registered a study protocol in 2016 that included plans to evaluate the safety of PBs and CSH, researchers committed to a short follow-up of only 24 months.[38] Upon reviewing the protocol of this study, its design appears inadequate to comprehensively assess the safety of PMT. The lack of a parallel control group impairs the ability to attribute observed safety outcomes specifically to the intervention, as it becomes difficult to differentiate treatment effects from normal developmental changes. Moreover, the exclusive reliance on biochemical markers fails to capture other critical safety outcomes such as growth and fertility. Additionally, the small sample size undermines the study's capacity to evaluate rare but clinically significant harms, such as thromboembolic events. The absence of long-term follow-up

[34] E.g., Abbruzzese et al. (2023); Biggs (2023b); Singal (2022a). The university that conducted the research was made aware of the study's problems, but chose not to disrupt the very positive medical narrative that misrepresented the authors' findings Singal (2022b).
[35] E.g., American Psychiatric Association (2023); Boerner (2022); Stringer (2023); U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024). To date, this study has been cited over 300 times in other peer-reviewed publications, and viewed nearly half a million times.
[36] Chen et al. (2023). This was an NIH-funded multi-site study performed in the U.S. at Children's Hospital of Chicago, Boston Children's Hospital, and the Los Angeles Children's Hospital.
[37] The research protocol can be found in the supplementary material in Chen et al. (2023).
[38] The study recruited patients from four pediatric gender clinics: Benioff Children's Hospital, Boston Children's Hospital, Children's Hospital Los Angeles, and Lurie's Children's Hospital of Chicago. Two young patients died by suicide while taking CSH, and "suicidal ideation" was registered as the most common adverse event (Chen et al., 2023). The protocol can be found in supplementary material.

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further limits the detection of delayed or cumulative adverse effects. These methodological limitations weaken the strength of any conclusions that can be drawn regarding the overall safety of the intervention.

The study reported mental health outcome data for 315 adolescents and young adults aged 12-20 who were treated with CSH for a period of 24 months. This study, published in the *New England Journal of Medicine* (NEJM), framed its findings in a positive light: "our findings showed improvements in psychosocial functioning ... which supports the use of [CSH] as effective treatment for transgender and nonbinary youth."[39]

However, two of the study subjects died by suicide within one year of initiating hormones, representing a rate that is 30-50 times higher than expected in adolescents of similar age.[40] The only statistically significant finding was a small improvement on the "transgender congruence scale," which has not been validated in minors.[41] Critically, only four out of 19 mental health outcomes described in the study's pre-registered protocol were reported; in particular, outcomes of GD, self-harm, and suicidality outcomes were not reported, and no explanation was provided for omitting these critical data.[42] The authors claimed that depression symptoms decreased during the study period.[43] However, further subgroup analysis by sex showed that the reported outcomes in females were of questionable clinical significance, while males experienced no statistically significant improvement in the reported measures at all.

According to the study's pre-registered protocol, the authors originally hypothesized that patients would exhibit "decreased symptoms of … gender dysphoria, self-injury, trauma symptoms, and suicidality" (among other changes) over time.[44] Instead, as mentioned,

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[39] Chen et al. (2023, p. 249).
[40] For comparison of the suicide rate in Chen et al. to that of other populations (e.g., other cohorts referred to pediatric gender clinics; patients taking antidepressants) see McDeavitt (2025).
[41] Strauss et al. (2024).
[42] In Chen et al. (2023), life satisfaction/positive affect were measured with the NIH Toolbox Emotion Battery. A recent paper describing this same patient cohort published more information on these life satisfaction/positive affect results along with information on additional measures from the NIH Toolbox Emotion Battery (Olson-Kennedy et al., 2025), but it did not report the gender dysphoria, self-harm, or suicidality outcomes, nor did it reference the two patient suicides.
[43] The mean Beck Depression Inventory score improved from 15.46 to 12.92 on a 63-point scale (Chen et al. 2023).
[44] See pp. 25-26 of the study's pre-registered protocol, which is linked to the article Chen et al. (2023) on the New England Journal of Medicine's website.

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two young patients died by suicide within one year of initiating treatment, and the most frequently occurring adverse event during hormonal treatment was "suicidal ideation."[45] Thus, the findings do not support the original hypothesis.

Although a recent systematic review was able to capture issues like study attrition in its risk of bias assessment for Chen et al., methodological analyses are not able to capture serious concerns that may be more related to research ethics than to methodology (e.g., study hypotheses changing between the protocol and the published article). Peer-reviewed critiques addressing the issues with Chen et al. were eventually published by the journal, but not until nearly a year after the article first appeared.[46]

The study continues to be widely cited and uncritically described as providing evidence of benefit for hormonal transition of minors.[47]

6.3 Publication bias

It is a well-documented problem in biomedical research that positive findings confirming an original hypothesis are much more likely to be published or published expeditiously, as compared to studies with inconclusive or negative results. "Publication bias" is not unique to this field. The U.K.'s national PGM clinic, the Gender Identity Development Service (GIDS), tried to replicate the seminal 2011 Dutch study, launching its own "early intervention" study of PBs in 2011. Although the results were available in 2016-2017, they were only released in 2021 following a complaint to the U.K. Health Research Authority.[48] Once published, the study acknowledged that the outcomes reported by the Dutch were not replicated.[49] The study also found that puberty blockade was associated with impaired bone density accumulation. Subsequent reanalysis of the same data showed that up to one-third of participants experienced a deterioration in mental health while on PBs.[50]

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[45] Chen et al. (2023, p. 241).
[46] E.g., Biggs (2023a); Hare (2023); Jorgensen (2023c); Dutch PMT researchers also published a commentary on Chen et al., which acknowledged the study's many problems (de Vries & Hannema, 2023).
[47] E.g., U.S. v. Skrmetti (No. 23-477*),* Expert Researchers and Physicians*,* Amicus curiae brief (2024).
[48] Biggs (2023b).
[49] Carmichael et al. (2021).
[50] McPherson & Freedman (2023).

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A similar pattern may be unfolding in the United States. The lead investigator of a NIH-funded PB study acknowledged delaying the publication of results—apparently due to fear that the unimpressive findings would undermine the field.[51]

A similar reluctance to report on disappointing findings is evident in other places, too. According to court disclosures, the World Professional Association for Transgender Health (WPATH) suppressed publication of SRs on at least ten of thirteen topics relating to endocrine treatment of adolescents with GD.[52] The unpublished SRs evaluated harms, including the effects of PBs on "clinical outcomes and harms"; the effects of estrogen on the risk of pulmonary embolism, deep-vein thrombosis, stroke, and myocardial infarction; the effects of testosterone on uterine, ovarian, cervical, vaginal, and breast pathology; and the effects of hormone therapy on fertility and metabolic syndrome.[53]

There also are instances of SRs arriving at conclusions that contradict the underlying evidence. One SR commissioned by WPATH found only "low" and "insufficient"[54] strength of evidence regarding the effects of hormonal interventions on mental health. Nevertheless, the SR's authors came to the unsupported conclusion that this treatment pathway "is likely associated with improvements" in quality of life, depression, and anxiety. The authors also asserted that "[t]hese benefits make hormone therapy an essential component of care that promotes ... health and well-being." Notably, there was no attempt to evaluate hormone effects on physical health.[55] The content of this SR was influenced by WPATH leadership, including approving the conclusion as a condition for eventual publication. This may explain the discrepancy between the SR's optimistic conclusion and its more problematic findings. Section 10.3.2 discusses evidence suppression by WPATH in detail.

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[51] As reported in the New York Times (Ghorayshi, 2024c). Of note, the investigator, Johanna Olson-Kennedy, denied having said this in a later deposition (Deposition of J. Olson-Kennedy in LB v Premera Blue Cross NO. 2:23:Cv-00953-TSZ, 2024).
[52] See Chapter 10.
[53] Sharma et al. (2018). See also Society for Evidence-Based Gender Medicine (2024b).
[54] Baker et al. (2021, p. 13).
[55] Appendix 4 includes a ROBIS assessment of Baker et al. (2021).

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Another 2021 SR, conducted by Bustos et al., examined postsurgical regret rates.[56] This SR is often cited as evidence that the regret rate after transition-related surgery is very low, about 1%.[57] But of the 27 studies included in Bustos et al., 23 were rated as "poor" or "fair" in quality. The few higher-rated studies suffered from substantial loss to follow-up and the reported results included deaths from suicide and complications. One included study contributed nearly half the total participants but reported a 36% loss to follow-up. The study authors acknowledged that the short follow-up period was a key limitation. However, the authors failed to address the most serious criticism, namely that their central conclusion of "extremely low regret" was unsupported.[58]

6.4 Summary

The quality of SRs in the field of gender medicine varies widely, but even the highest quality SRs typically find only "low certainty" evidence for most harms. However, there are familiar and plausible explanations for why evidence of harms may not have been sought, detected or reported. Reflecting on the state of evidence in PGM, the Cass Review noted, "it has been evident that there has been a failure to reliably collect even the most basic data and information in a consistent and comprehensive manner; data have often not been shared or have been unavailable."[59]

Unless SRs specifically search for harms (and with the provisos above), they are not well-suited to detect complications or adverse effects. This is due to the relatively recent debut and rapid growth of the field of PGM, the tendency of the predominantly short-term observational studies to focus on benefits and underreport harms, and publication bias. EBM emphasizes the role of best available evidence. To address SRs' limited ability to detect harms, decision-makers must consider other sources of scientific information. That is the topic of the following chapter.

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[56] Bustos et al. (2021) reported regret rates of around 1%. This SR was not included in this Review's overview of SRs as most of the included studies did not focus on the adolescent population.
[57] See examples of such statements in Cohn (2023).
[58] For the criticism, see Expósito-Campos & D'Angelo (2021). The authors provided a reply to the critique (Escandón et al., 2021), which addressed some but not all of the key concerns.
[59] Cass (2024a, p. 39).

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Chapter 7 Evidence from Basic Science and Physiology

When clinical studies provide insufficient information about harms, and therefore systematic reviews (SRs) are unable to reliably collate information about harms, other types of evidence should be integrated. Trustworthy evidence from other sources, including basic sciences, should be considered to arrive at a more informed understanding of the plausible effects of interventions.[1] In the case of pediatric medical transition (PMT), this involves consideration of human physiology, development, and the well-established mechanisms of action of the drugs used. The consideration of such evidence aligns with the core requirement of evidence-based medicine (EBM): the judicious use of the "best available" evidence.

The following sections explain: normal pubertal development and the mechanisms of action of PMT interventions (Section 7.1); treatment of central precocious puberty with puberty blockers (PBs) (Section 7.2); biologically plausible implications of using PBs to arrest normally timed puberty and cross-sex hormones (CSH) (Sections 7.3 and 7.4); surgical implications, particularly when pubertal development has been arrested (Section 7.5); and psychological risks of undergoing PMT interventions given what is known about child and adolescent development (Section 7.6). Mortality is discussed in Section 7.7.

7.1 Puberty

This section overviews physiology and the implications of disrupting normally-timed puberty. Of note, there are three distinct waves of hypothalamic-pituitary-gonadal (HPG) axis activity over an individual's lifespan: in utero, during the first month after birth, and in late childhood-early adolescence.[2] Only the latter is referred to as "puberty."[3] Medications can be given to suppress the HPG axis.

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[1] Sackett et al. (1996).
[2] Rohayem et al. (2024).
[3] The discussion in this section focuses on normal pubertal development. Individuals with disorders (differences) of sex development (DSDs) are not a focus of this chapter because the vast majority of adolescents with gender dysphoria do not have a DSD. Among those with DSDs, approximately 5% experience identity changes (Kreukels et al., 2018). As noted in the Cass Review, "Studies of children with DSD suggest that a complex interplay between testosterone levels, external genitalia, sex of rearing and socio-cultural environment all play a part in eventual gender identity" (Cass, 2024a, p. 102).

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7.1.1 Overview of normal pubertal development

In mammals, puberty is defined as the period of time during which immature juveniles reach adult sexual maturity and become capable of reproduction. It is a transitional phase between childhood and adulthood. In humans, pubertal onset typically occurs between ages eight and 13 in females and nine and 14 in males. It is driven by increasing levels of sex steroid hormones—primarily estrogen and progesterone in females, and testosterone in males.[4]

During puberty, sex steroid hormones promote skeletal growth, muscular development, and neurologic development. In females, estrogen initiates breast development, menarche, ovulation, and changes in body composition and skeletal morphology.[5] In males, the androgenic surge results in testicular enlargement, penile growth, spermatogenesis, deepening of the voice, and the emergence of secondary sexual characteristics such as facial and body hair. Spermatogenesis in males and ovulatory cycles in females mark the attainment of fertility.

7.1.2 Tanner Stages of puberty

Physicians use a system known as Tanner Staging to document the physical progression of puberty based on a physical examination.[6] This framework delineates five stages of maturation, from a prepubertal baseline (Stage 1) to full adult development (Stage 5). Intermediate stages capture transitional morphological and physiological characteristics.

In females, Tanner Stage 2 commences with the growth of breast tissue (thelarche), followed by hair growth (pubarche), and then the first period (menarche), typically by Tanner Stage 3 or 4. Menarche typically occurs one to two years after thelarche, at an average age of 12-13 years. The first egg release (ovulation) generally occurs within the first year following menarche, typically at Tanner Stage 4. Ovulatory function stabilizes approximately one year after menarche. Female pubertal development is accompanied by bone growth, body hair growth, widening of the hips, redistribution of fat to the hips

[4] Breehl & Caban (2025).
[5] Kuohung & Hornstein (2024).
[6] Tanner (1962).

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and breasts, and enlargement of both internal reproductive organs (i.e., uterus, ovaries) and external genitalia (i.e., labia, clitoris).[7]

In males, the initiation of Tanner Stage 2 is typically identified by increased testicular volume, followed by growth of the penis, emergence of pubic and later facial hair, and a rapid increase in lean body mass and skeletal size driven by androgens. There are significant increases in bone and muscle mass and thickening and elongation of the vocal cords results in voice deepening. First ejaculations (spermarche) generally occur about one year after the onset of puberty, with full gamete maturation following approximately one year later.[8] Spermatogenesis generally occurs during Tanner Stage 4.[9]

7.1.3 Neuroendocrine regulation of puberty

Puberty is initiated and sustained by complex endocrine signaling. In the brain, the anterior pituitary, in response to pulsatile gonadotropin-releasing hormone (GnRH) release from the hypothalamus, secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Collectively termed gonadotropins, LH and FSH act on the gonads (ovaries and testes) to stimulate the synthesis of sex steroids and promote gametogenesis.[10]

7.2 Puberty blockers and central precocious puberty

In central precocious puberty (CPP) — a condition occurring in one out of 5,000 to one out of 10,000 children, more often in girls[11]—the pituitary gland is activated prematurely, sometimes even during infancy or early childhood.[12] This leads to early-onset, or precocious, pubertal development. CPP is associated with several potential negative

[7] Breehl & Caban (2025).
[8] Breehl & Caban (2025); Kota & Ejaz (2023).
[9] Emmanuel & Bokor (2022).
[10] In males, LH stimulates Leydig cells to produce testosterone while FSH targets Sertoli cells to facilitate spermatogenesis. In females, LH and FSH coordinate estrogen production and follicular development in the ovaries.
[11] Eugster (2019). Although there are some genetic causes of CPP, it is usually idiopathic, meaning the cause is unclear. Females are generally treated for CPP with PBs if puberty occurs at age six or younger, males are generally treated if puberty occurs at age eight or younger (Ergun-Longmire et al., 2023).
[12] E.g., Nienaber & Van Der Walt (1991); Yoon & Kim (2016).

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health outcomes, including decreased adult height due to early presence of sex hormones causing premature epiphyseal fusion.

GnRHa (puberty blockers or PBs) have been approved by the Food and Drug Administration (FDA) for use in the treatment of CPP. The evidence to date comparing large populations of untreated patients to treated patients suggests that, at least for appropriately chosen female patients, treatment of CPP with PBs is associated with increased height attainment and lower body mass index (BMI).[13]

When PBs are used for CPP, the medication is discontinued when the child reaches a more typical age for pubertal onset, allowing normal puberty to resume. The goals include facilitating normal timing of puberty, so that the patient goes through puberty alongside peers (as opposed to significantly before). Although FDA-approved for this indication, PBs—like all medications—are associated with risks and side effects, even when used for CPP.

7.3 Puberty blockers and gender dysphoria

The use of PBs to arrest normally timed puberty is the central element and original contribution of the Dutch Protocol. PBs act directly on the pituitary gland to significantly reduce the release of LH and FSH. Continuous administration of these agents desensitizes GnRH receptors, suppressing LH and FSH secretion, and consequently arresting the production of endogenous sex steroid hormones. In females, this causes the cessation of normal menstrual function, if it has begun. In males, sperm production is halted or forestalled. PBs have not been approved by the FDA for the indication of gender dysphoria (GD); they are used “off-label” in pediatric gender medicine (PGM).[14] Unlike in CPP, use of PBs for PMT is not FDA-approved and safety data are lacking.

Using PBs to stop normally timed puberty effectively induces hypogonadotropic hypogonadism (HH), a condition characterized by the failure of the pituitary to

[13] Luo et al. (2021).
[14] GnRHas have been approved by the U.S. Food and Drug Administration (FDA) for various indications, with effects that can differ significantly depending on their application. For instance, the GnRHa leuprolide (commonly marketed as Lupron) is FDA-approved for androgen deprivation therapy in adult males with prostate cancer and for estrogen deprivation in adult females with endometriosis. It has also been FDA-approved to treat central precocious puberty (CPP).

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appropriately release gonadotropins. As a result, the gonads are unable to produce the sex-specific hormones testosterone or estrogen. Pubertal development is disrupted, halting the progression of physical and reproductive maturity. Left untreated, clinical research shows HH is associated with a range of risks including infertility and decreased bone mineral density, elevating the risk of osteoporosis and fractures.[15]

Although PBs for GD are typically indicated for short-term use (about two years), this time range may be considerably longer for some patients.[16] The reasons for the apparent deviation from the original Dutch Protocol in regard to the length of PB use remain unstudied, but may include increasingly younger social transition ages which 'necessitate' pubertal blockade at increasingly younger ages to allow young patients to continue living in "stealth,"[17] as well as the medical treatment of youth who identify as nonbinary and wish to maintain a sex-ambiguous appearance for an extended period of time.[18]

7.3.1 Developmental risks of blocking normal puberty

One of the key rationales for using PBs in CPP is to allow the child to experience normative psychosocial development alongside same-age peers. By contrast, in PMT, patients are maintained in a prepubertal or early pubertal stage while their peers developmentally progress. This has potential sequelae for the adolescent's psychosocial development.[19]

7.3.2 Bone mineral density and skeletal development

Puberty is recognized as providing a critical window for the accrual of peak bone mass. Sex steroid hormones play an essential role in the mineralization of the skeleton.[20] Failure to reach peak bone density may lead to increased risk of osteopenia,

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[15] Zhu & Chan (2015).
[16] A Cambridge Health Alliance fact sheet, for example, discusses using puberty blockers for up to four years (Cambridge Health Alliance, n.d.).
[17] The Cass Review's qualitative research program found that for prepubertal children who underwent full social transition "living in stealth appears to increase a child's level of stress and anxiety with resultant behaviour and mental health problems. These included social withdrawal, with children becoming increasingly isolated, including resorting to home-schooling or tutoring and even rarely leaving their house" (Cass, 2024a, p.159).
[18] Notini et al. (2020).
[19] This is noted in Vrouenraets et al. (2022), for example.
[20] Elhakeem et al. (2019).

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osteoporosis, and fractures later in life, including debilitating fractures of the spine and hip. In older adults, hip fractures are particularly concerning, as they significantly elevate the risks of morbidity and mortality.[21]

Because of the known physiological role of sex steroid hormones in skeletal development, the original Dutch research acknowledged the possibility of negative effect on bone mineralization. Researchers measured 'Z-scores,' a measure comparing individual bone density to age- and sex-matched population norms, and these scores decreased after PBs in the original Dutch cohort.[22] Since then, multiple longitudinal, observational studies on pediatric patients undergoing medical transition have consistently demonstrated decreases in Z-scores with PB use.[23] In addition to decreases in the *average* scores, a re-analysis of the United Kingdom (U.K.) data found that one third of the puberty-blocked patients had a Z-score of below -2 (indicating osteoporosis) for hip, and more than one quarter of patients had low Z-scores for spine.[24] Fracture rates have not been reported alongside Z-scores in this literature.[25]

When PBs are followed by CSH, as has occurred in studies over 90% of the time, bone mineralization will increase, but a critical developmental window for bone density accrual during adolescence may have been missed or foreshortened, as bone density accrual slows during the 20s and then begins to decline. These patients may never reach the peak bone density they otherwise would have achieved. Research on medium and long-term outcomes is limited.[26] Due to the novel nature of PMT no studies have yet followed patients into middle age or late adulthood.

7.3.3 Neurocognitive and psychosocial development

The human brain undergoes substantial reorganization during adolescence, including synaptic pruning and myelination, processes that are influenced by sex steroid

[21] Bentler et al. (2009).
[22] Delemarre-van de Waal & Cohen-Kettenis (2006).
[23] E.g., Boogers et al. (2023); Carmichael et al. (2021); Ciancia et al. (2024); Delemarre-van de Waal & Cohen-Kettenis (2006); Joseph et al. (2019); Klink et al. (2015); Navabi et al. (2021); Schagen et al. (2020); Stoffers et al. (2019); Van der Loos, Vlot et al. (2023); Vlot et al. (2017).
[24] Biggs (2021).
[25] E.g., Roy et al. (2024).
[26] Two longer-term studies (Schagen et al., 2020; van der Loos et al., 2023) found Z-scores returned to pre-treatment baseline after 3-11 years of subsequent CSH treatment in females, but not in males.

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hormones. Research suggests that sex steroid hormones impact brain regions associated with executive function, emotion regulation, and social cognition.[27] The precise neurocognitive effects of puberty suppression remain understudied,[28] and researchers in this field have recognized the limitations of the evidence in this area.[29] A recent literature review concluded that the effect of PBs on neurocognitive development is unknown, but that "there is some evidence of a detrimental impact of pubertal suppression on IQ [intelligence quotient] in children."[30] However, a 2022 Dutch study found that in patients treated with PBs the associations between pretreatment IQ and eventual education achievement were similar to population norms (the study did not longitudinally measure IQ).[31] The Cass Review has raised concern over the potential harm and unknown effects of pubertal suppression on the developing brain,[32] noting that "[t]here is increasing evidence that the changes in brain maturation described above are driven by a combination of chronological age and sex hormones released through puberty."[33]

7.3.4 Reproductive maturation

By halting the development of sex characteristics, PBs interrupt the maturation of reproductive anatomy and function. Suppression of the HPG axis can impair gametogenesis, potentially resulting in permanent infertility if CSH are started thereafter, particularly when gonadal maturation is not completed prior to the interruption of normally-timed puberty.

In adult males initiating estrogen for medical transition, testicular atrophy results, leading to impaired fertility or infertility that may be irreversible (even if estrogen were to

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[27] Cservenka et al. (2015); Gonnabathula & Yakubu (2023); Macoveanu et al. (2016); Pillerová et al. (2022).
[28] One cross-sectional study (which cannot methodologically suggest causation) found poor executive functioning in patients taking PBs >1 year, but their baseline functioning before PBs was unknown (Strang et al., 2022). Another cross-sectional study reported similar executive functioning between patients on PBs and patients not on PBs (Staphorsius et al., 2015). Arnoldussen et al. (2022), another study, is discussed in the text.
[29] Chen et al. (2020).
[30] Baxendale (2024).
[31] Arnoldussen et al. (2022).
[32] Cass (2024a, p. 115).
[33] Cass (2024b, p. 104).

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be discontinued).[34] However, adult males may choose to cryopreserve sperm prior to initiation of estrogen. This is not the case with children or early adolescents.[35] Spermatogenesis generally occurs in Tanner Stage 4 of puberty.[36] In PMT, if PBs are started in Tanner Stage 2, prior to gamete maturation, and estrogen is started thereafter (as is likely), cryopreservation of sperm cannot be completed beforehand.[37] Additionally, fertility may be affected in females initiated on PBs who proceed to take testosterone.[38] Effect of testosterone on the reproductive tract makes the likelihood of conception, pregnancy, and birth uncertain.[39] Maternal and fetal outcomes under these circumstances are also poorly studied.

It is possible that CSH use after pubertal arrest could permanently damage the immature gonadal tissues, leading to sterilization.[40] If the gonads are arrested in an immature state due to prolonged use of PBs, and this is followed by administration of CSH, there is no proven physiological mechanism by which fertility can reliably be re-established. The likelihood of permanent infertility will be substantially increased.[41,42]

With respect to fertility preservation (FP), techniques can range from relatively simple to technically challenging to not currently viable, depending on the patient's sex and Tanner Stage of development. For example, males who have undergone spermarche can produce a semen sample for long-term storage. However, males who have puberty

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[34] Cheng et al. (2019); Deutsch (2020a).
[35] Fertility preservation for natal males in early puberty remains a theoretical and experimental undertaking, with no clinically validated protocol currently available (Laidlaw et al., 2025).
[36] See above, Section 7.1.2.
[37] The original Dutch research acknowledged that infertility would result for males initiated on PBs in Tanner Stage 2 and on estrogen thereafter: "In early pubertal boys, the hypogonadotrophic state will block the development of fertility" (Delemarre van de Waal & Cohen-Kettenis, 2006, p. S134).
[38] Cheng et al. (2019). Although pregnancies can occur in adult females taking testosterone, less is known about pregnancy in females who underwent PMT in childhood/adolescence.
[39] Laidlaw et al. (2025).
[40] See the subsequent section for specific effects of CSH.
[41] It should be noted that PBs for CPP does not negatively impact fertility. In pediatric medical transition, because PBs are generally the first part of a continuum including CSH, infertility is a likely result of treatment (depending on sex and Tanner Stage of patient).
[42] There is controversy regarding minors' capacity to provide informed consent to potential loss of fertility with respect to PMT. E.g., "Can these minors make adequately autonomous decisions in the present that may impact their opportunities in the future? This is less a question of decision-making capacity…than a matter of sufficient life experience to know their future desires … How to maintain an "open future" for transgender youth is a common concern of parents and healthcare professionals" (Harris et al., 2020, p. 2459). See also Jorgensen & Masson (2024). In a study of patients in their early 30's who had begun hormonal interventions at age 15, 23% expressed regret about infertility (de Nie et al., 2024).

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blocked at Tanner Stage 2 will have immature testicles; FP necessitates testicular tissue cryopreservation, which currently remains entirely experimental.[43] For the mature female patient, oocyte preservation involves an invasive procedure (and is costly). For females in early Tanner Stages, techniques such as ovarian tissue cryopreservation, although technically possible,[44] have yet to be shown to result in viable pregnancies in patients who have undergone PMT.

Most studies on FP in adolescents with GD undergoing PMT have shown very low rates, between 0% and 4.7% of patients who underwent FP.[45] One study in which male patients were able to access fertility preservation via testicular biopsy reported that 10 out of 23 patients (43%) were able to have gametes cryopreserved prior to PB initiation (Tanner Stages were not reported).[46]

7.3.5 Risks of sexual dysfunction

Concerns have been raised about the potential consequences of PMT on sexual function, particularly with regard to the ability to experience sexual pleasure and orgasm. In 2021, Marci Bowers—a leading vaginoplasty surgeon and then-president-elect of the World Professional Association for Transgender Health (WPATH)—voiced concerns that male patients who commenced PBs at Tanner Stage 2 and subsequently received CSH were physiologically anorgasmic, prior to and following vaginoplasty surgery.

Many of these patients reported no history of genital sexual sensation before undergoing vaginoplasty. After vaginoplasty, the constructed clitoris provided no meaningful tactile or erogenous response. Bowers suggested that this issue had not been adequately addressed in discussions of informed consent for youth undergoing puberty suppression.[47]

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[43] Klipstein et al. (2020).
[44] Practice Committee of the American Society for Reproductive Medicine (2019).
[45] Chen et al. (2017); Chiniara et al. (2019); de Nie et al. (2024); Nahata et al. (2017).
[46] Pang, Peri, et al. (2020).
[47] Shrier (2021b). It has been questioned "whether even highly intelligent children who have not had sexual experiences can meaningfully comprehend the loss of future sexual function and reproductive abilities" (Levine et al., 2022a, p. 720).

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Despite these concerning clinical observations, there is a striking paucity of research on sexual function outcomes in this population.[48] The potential for anorgasmia and sensory dysfunction merits serious consideration, especially given the irreversible nature of some interventions and the centrality of sexual health to overall quality of life.

There is a lack of published research regarding sexual function outcomes in females who underwent PMT with PBs followed by CSH.

7.4 Cross-sex hormones and gender dysphoria

Testosterone for females and estrogen for males are routinely used in PGM to induce changes in the secondary sex characteristics that resemble those typical of the opposite sex. In males, estrogen is frequently used alongside a testosterone blocker or PB to enhance estrogen's effects.

7.4.1 Physical effects of cross-sex hormones

As described above, puberty involves the maturation of primary sex characteristics—the male and female genitalia—and the entire reproductive system, enabling the production of mature gametes: sperm in males and ova in females. The ES guidelines for PMT describe titration of testosterone for females and estrogen for males as the "Induction of Puberty," a term that is misleading.[49] Under the influence of high doses of testosterone, females may develop facial and body hair, cystic acne, male pattern scalp hair distribution, clitoral growth, changes in musculature, thickening of vocal cords leading to voice deepening, and alterations in fat deposition. Similarly, males receiving high doses of estrogen may experience significant breast tissue growth (gynecomastia), reduced muscle mass, change in skin texture, and may develop a more typically female pattern of fat distribution. These physical changes reflect the body's response to unusually high levels of sex steroids, not actual opposite-sex pubertal development. In fact, development of reproductive capacity—definitionally, the purpose of puberty—may be

[48] Two Dutch studies have published data from one small patient cohort: Bungener et al. (2020); van der Meulen et al. (2025). Although the researchers found that for the males, sexual function outcomes after vaginoplasty were similar regardless of which Tanner Stage of puberty PBs had been started in, experts pointed out that the small study was methodologically limited due to sample size (therefore unable to reliably compare different subgroups) and that the patients frequently reported serious sexual difficulties/dysfunction (orgasm difficulties, pain, shame about genitalia) (Clayton et al., 2025).

[49] Hembree et al. (2017, p. 3884), for example. See also Coleman et al. (2022, p. S115), and Chapter 2.

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hindered. The physiological end point of puberty—sexual maturation that makes possible reproduction—is not and cannot be obtained via PMT.

7.4.2 Dosing of cross-sex hormones

In WPATH and ES guidelines, the principal goal of CSH administration is to induce physical characteristics typical of the opposite sex. When hormone levels rise beyond the typical reference range for a person's sex, they are considered supraphysiologic. ES guidelines suggest that the sex an individual identifies as—as opposed to their biological sex—should determine the target reference range for hormonal concentrations.[50] Critics have argued that perceived identity does not alter physiological processes and that such a belief can result in inappropriate and potentially dangerous hormone dosing.[51]

7.4.3 Hyperandrogenism in females

Hyperandrogenism refers to the condition of abnormally elevated androgen levels—most commonly testosterone—in the bloodstream. Among adult females, typical serum testosterone levels range between 2–45 ng/dL. In certain pathological conditions, testosterone may rise well above this range.

ES guidelines for cross-sex hormone administration in females recommend testosterone between 320–1000 ng/dL, comparable to, or exceeding levels found in endocrine disorders.[52] These concentrations represent a six to 100-fold increase above physiologic norms for females, inducing hyperandrogenism. Hyperandrogenism is also associated with health risks, discussed below.

7.4.4 Hyperestrogenemia in males

Hyperestrogenemia is defined as elevated blood levels of estrogens, such as estradiol, above the normal physiological range. In males, the standard reference range for estradiol is approximately 60–190 pg/mL. Certain disease states are known to cause

[50] Rosenthal et al. (2019).
[51] Laidlaw et al. (2021).
[52] Hembree et al. (2017).

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excess estrogen. For instance, certain adrenal tumors can elevate estrogen levels by a factor of 3 to 10.[53]

In PMT, supraphysiologic estrogen levels are intentionally induced through the off-label use of high doses of estrogen. ES guidelines advise titration of estradiol to levels between two and 43 times higher than the typical male range to induce the development of female-typical secondary sex characteristics such as breast tissue.[54]

7.4.5 Effects of testosterone on the female reproductive system

Testosterone use causes histopathological changes in the female reproductive tract.[55] Given the potential—though not well-defined—risk of cancer in the female reproductive tract, ES guidelines recommend that "health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer."[56] WPATH's clinical practice guideline[57] has not adopted the same recommendation, but there is limited reliable evidence regarding the long-term cancer risks associated with testosterone use in the female reproductive tract. Testosterone can cause reproductive organ atrophy, including thinning and atrophy of vaginal epithelium,[58] persistent pelvic pain and discomfort,[59] and pelvic floor dysfunction.[60]

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[53] Cavlan et al. (2010).
[54] Hembree et al. (2017).
[55] A review of 11 histopathologic studies of resected ovaries found that 34.9% exhibited polycystic-appearing ovaries, and 0.7% had benign ovarian neoplasms (Toland et al., 2023). In another study of females aged 18-56, 57% of 35 ovariectomy cases showed multiple bilateral cystic follicles, and 80% of 40 uterine resections displayed endometrial stromal fibrosis. Abnormal tissue growth was also noted in the vagina and cervix following hysterectomy and vaginectomy. The most common findings included transitional cell metaplasia and the development of prostatic-type glands (Lin et al., 2022). A separate study found that 100% of vaginectomy specimens contained abnormal prostatic tissue growth (Xu et al., 2022).
[56] Hembree et al. (2017).
[57] Coleman et al. (2022).
[58] In 2020, a whistleblower from Washington University in St. Louis clinic described a case in which a female minor taking testosterone called the clinic due to vaginal bleeding: "In less than an hour she had soaked through an extra heavy pad, her jeans, and a towel she had wrapped around her waist … We found out later this girl had had intercourse, and because testosterone thins the vaginal tissues, her vaginal canal had ripped open. She had to be sedated and given surgery to repair the damage" (Reed, 2023a). Reportedly, multiple patients at this clinic had problems with vaginal lacerations.
[59] Patients have sought hysterectomies due to these symptoms; e.g., Zwickl et al. (2023).
[60] Da Silva et al. (2024); Tordoff et al. (2023); Zwickl et al. (2023).

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7.4.6 Effects of estrogen on the male reproductive system

Testicles have two primary functions: producing testosterone and generating sperm capable of fertilizing an ovum. The use of estrogen in accordance with the ES and WPATH guidelines results in impairment of normal testosterone production and significant abnormal histologic changes to the male reproductive system.[61] These findings point to widespread structural reconfiguration of testicular tissue in response to prolonged exposure to the high levels of estrogen used in medical transition.

7.4.7 Cardiovascular and metabolic risks

Among the most significant long-term risks associated with CSH is an increase in cardiovascular risk factors. A 2018 review found that patients taking CSH had an elevated risk of heart attack and CV mortality compared to controls.[62]

Several studies and reviews have found increased risk of CV events like heart attacks and strokes in females taking testosterone.[63] This is thought to result from testosterone's effects on underlying metabolic factors related to CV risk. In females, testosterone can cause elevated blood pressure, polycythemia, and atherogenic

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[61] In one study of 99 testicle specimens, Leydig cells (crucial for producing testosterone) were completely absent or extremely diminished in 80% of cases. There was a significant average decrease in the diameter of the seminiferous tubules (site of spermatogenesis) when compared with controls, with 82% showing peritubular fibrosis, which interferes with tubular function (Matoso et al., 2018). In another study, 74% of specimens had abnormal basement membrane thickening (Riva-Morales et al., 2025). This mimics findings seen in conditions like cryptorchidism (undescended testes), which are associated with infertility (Mittal et al., 2017). In one of the abovementioned studies, all 125 testicular specimens showed atrophic changes and decreased spermatogenesis, with 71.2% having no sperm production at all (Riva-Morales et al., 2025). In another study, 80% of testicular tissue samples from males on estrogen showed maturation arrest, meaning that although the early stages of the sperm development may have begun, maturation to fully functioning spermatozoan did not occur (Matoso et al., 2018). These findings point to widespread structural reconfiguration of testicular tissue in response to prolonged exposure to high levels of estrogen used in medical transition. Other structures affected by estrogen (and/or androgen deprivation) include the epididymis, rete testes, and prostate (Crowley et al., 2023; Matoso et al., 2018). A long-term analysis involving 86 patients who underwent orchiectomies after a median duration of 7.5 years on estrogen therapy found a clear correlation between the length of hormonal treatment and the degree of tissue abnormality (Marins et al., 2024). This study discussed "[c]ompromise in integrity of blood-testis-barrier with *increased vulnerability to cytotoxic and immune damage*; impaired adhesion with premature detachment of spermatids from Sertoli cells, causing altered shaping in spermatids; germ cells phagocitation" as theoretical mechanisms of impaired spermatogenesis (emphasis added).

[62] Irwig (2018).

[63] E.g., Nota et al. (2019). A systematic review found moderate and high certainty evidence of some incidence of cardiovascular events in young females under 26 years old (Miroshnychenko, Ibrahim et al., 2025).

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changes in the lipid profile.[64] Longitudinal studies of PMT have reported increases in BMI (and/or fat mass) after initiation of CSH[65] and PBs.[66] Atherogenic changes to the lipid profile have also been reported.[67]

With respect to polycythemia, elevated hematocrit levels are known to increase blood viscosity, raising the risk of thromboembolic and CV complications. Among females, even modest elevations in hematocrit levels have been independently associated with heightened risks of CV disease, coronary events, and CV-related mortality.[68]

In males taking estrogen, studies have shown increased risk of CV events like venous thromboembolism and stroke.[69]

7.4.8 Other risks associated with cross-sex hormones

In both sexes, CSH use may be associated with early mortality.[70] In females taking testosterone, breast tissue undergoes structural remodeling, often with increased fibrous connective tissue and decreased glandular volume.[71] There is also some concern about possible increased risk of breast and ovarian cancer.[72] In males, some studies suggest that estrogen may increase risk of developing multiple sclerosis[73] and thyroid cancer,[74] and that it may lead to a decrease in brain volume.[75] However, research in these areas is still preliminary. While breast cancer is uncommon in natal males, data suggest that high-dose estrogen therapy increases this risk.[76] Other effects

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[64] Glintborg et al. (2024); Safer & Tangpricha (2019).
[65] Boogers et al. (2024); Jarin et al. (2017); Klaver et al. (2018, 2020).
[66] Carmichael et al. (2021); Ciancia et al. (2024); Delemarre-van de Waal & Cohen-Kettenis (2006); Fisher et al. (2024).
[67] Klaver et al. (2020); Olson-Kennedy, Okonta, et al. (2018). Millington et al. (2021) found atherogenic changes only in females, not in males.
[68] Gagnon et al. (1994). In a longitudinal cohort study of 1,073 adult females taking testosterone (Madsen et al., 2021), approximately 24% of participants developed hematocrit values ≥50%, a threshold commonly used to define severe erythrocytosis. While the study did not report prevalence in the intermediate range (hematocrit levels between 45% and 50%) it is reasonable to infer that a similar or greater proportion of individuals would fall within this bracket.
[69] Nota et al. (2019) reported a nearly five-fold (4.6x) elevation in risk of venous thromboembolism, and Getahun et al. (2018) reported a nearly ten-fold (9.9x) elevation in risk of stroke.
[70] C. J. de Blok et al. (2021).
[71] Grynberg et al. (2010).
[72] Hembree et al. (2017).
[73] Papkoor et al. (2016); White et al. (2022).
[74] Derwahl & Nicula (2014).
[75] Pol et al. (2006); Seiger et al. (2016); Zubiaurre-Elorza et al. (2014).
[76] C. J. M. de Blok et al. (2019).

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of estrogen may include diminished libido, erectile dysfunction, and loss of spontaneous erections.[77]

7.5 Surgery and gender dysphoria

WPATH provides an extensive list of surgeries it considers appropriate treatments for GD.[78] All surgeries carry risks,[79] some of which are amplified when surgery follows PBs and CSH. Further, surgeries to remove healthy and functioning organs introduce a unique set of iatrogenic harms not encountered in other areas of medicine.

7.5.1 Surgical problems related to early pubertal blockade

Males who initiate PBs at Tanner Stage 2 and then proceed to estrogen have narrowed options for future genital surgery, should this be desired. PBs arrest development of male genitalia. If PBs are started in Tanner Stage 2 and estrogen is started some time thereafter, the male genitalia will never develop beyond the prepubertal or early-pubertal state. For patients who proceed with vaginoplasty later in life, this may foreclose the surgical option of penile inversion vaginoplasty due to lack of sufficient genital tissue for this procedure. This issue was recognized in the original Dutch papers,[80] but over subsequent decades almost no research has been published on this topic. A single Dutch study found greatly increased odds of receiving intestinal vaginoplasty (compared to penile inversion) in male patients with history of pubertal blockade.[81] Intestinal vaginoplasty is a more technically complex and risky procedure.[82] One notable and tragic case involved a member of the original Dutch Protocol research cohort who died

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[77] Hembree et al. (2017). Of note, some or all of these effects on sexual function (diminished erections, for example) may be desired by certain patients.
[78] According to WPATH's SOC-8, even highly unusual surgeries such as non-binary mastectomies (where female breasts are reshaped to resemble gynecomastia in males), penis-preserving vaginoplasty, and vagina-preserving phalloplasty (to provide patients with both sets of genitals), and genital nullification procedures (involving genital removal) are considered medically-necessary procedures for some patients. Only phalloplasty for females has a minimum recommended age of 18 (Coleman et al., 2022). In 2024, a Canadian patient successfully sued a provincial health insurer, who had declined to cover "penile-preserving vaginoplasty" surgery, considering it experimental. Media coverage noted that "…the court decided that [this] procedure…[was] consistent with the World Professional Association for Transgender Health (WPATH) Standards of Care, the leading authority on gender-affirming medical and surgical care, especially as it recommends individualized treatment plans" (Arsenych, 2024).
[79] E.g., bleeding, infection, scarring, and risks related to anesthesia.
[80] Delemarre-van de Waal & Cohen-Kettenis (2006).
[81] van de Grift et al. (2020).
[82] Lee et al. (2023).

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from necrotizing fasciitis at age 18 following an intestinal vaginoplasty conducted because of inadequate genital tissue.[83]

7.6 Other risks associated with hormonal interventions or surgeries

The use of endocrine interventions affects multiple organ systems beyond the reproductive tract. In addition, there are psychological risks associated with PMT.

7.6.1 Adverse psychiatric effects

The FDA-mandated labeling for testosterone cautions about abuse potential, noting: "Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication ... Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions." These effects have been reported in males and females, including adolescents.[84]

Research on anabolic steroid misuse has demonstrated associations with severe psychiatric problems, including mood instability, psychosis,[85] and dependence.[86] The most frequently observed symptoms include irritability, aggression, euphoria, inflated self-perception, impulsivity, and risk-taking behaviors. Additional manifestations may include acute psychotic episodes, worsening of tic disorders or depression, and delirium-like states. One study assessing medium (300–1000 mg/week) and high (>1000 mg/week) anabolic steroid use found that 23% of users met diagnostic criteria for a major mood disorder, including mania, hypomania, or depression, while 3.4-12% developed psychotic features.[87]

In an analysis of the FDA's Event Reporting System (FAERS) database for people using CSH for medical transition, 88% of adverse drug reactions were classified as serious.[88] Without an idea of denominators, individual risks are not possible to quantify. Among the 83 reports regarding females using testosterone, 87.8% of the events were deemed

[83] Negenborn et al. (2017).
[84] Actavis Pharma, Inc. (2018).
[85] R. C. W. Hall et al. (2005).
[86] Skauen et al. (2023).
[87] R. C. W. Hall et al. (2005).
[88] Gomez-Lumbreras & Villa-Zapata (2024).

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serious, with two reported deaths (2.4%) and 25 hospitalizations (30.5%).[89] Reported psychological harms included anxiety, depression, mood swings, suicidal ideation and behavior, aggression, dissociation, and self-harm. More extreme symptoms, such as antisocial behavior and homicidal ideation, were also documented.[90]

A separate study from Sweden found an elevated rate of criminal convictions in natal females who had taken testosterone and undergone gender-transition surgery, compared to age-matched controls. This study also found that adults who had undergone medical and surgical transition had 19 times the rate of suicide deaths and nearly three times the rate of all-cause mortality and inpatient psychiatric care compared to age and sex-matched controls.[91] Elevated suicide rates (compared to the general population) have also been reported in other studies.[92] It is impossible to determine causation based on this data, in part due to presence of confounders like co-occurring mental health conditions.

7.6.2 Detransition and regret

In males, estrogen causes breast growth and infertility that may be irreversible even with cessation of CSH.[93] In females, irreversible virilizing effects of testosterone include face and body hair growth, deepening of the voice, clitoral growth, and male-pattern baldness.[94] Patients of any age may experience regret regarding the permanent physical and physiologic effects of CSH, regardless of how they identify. For example, stably transgender-identified patients may regret loss of fertility. Developing baldness, or chafing/discomfort caused by clitoromegaly, may lead a patient who identifies as a transgender man to regret taking testosterone.

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[89] Laidlaw & Jorgensen (2024).
[90] Laidlaw & Jorgensen (2024).
[91] Dhejne et al. (2011).
[92] C. J. de Blok et al. (2021) found that the standardized mortality ratio for suicide among transgender adults was 3.1 compared to the general population of the Netherlands. In Van Cauwenberg et al. (2021), five out of 177 adolescent patients died by suicide. All suicide deaths were in patients who had been started on CSH (Society for Evidence-Based Gender Medicine, 2024a). Biggs (2022) reported that four out of 15,032 patients referred to the U.K.'s pediatric gender medicine (PGM) clinic died by suicide over a ten-year period. Two of the suicides were in waitlisted patients (i.e., probably not taking CSH). A recent U.S. study reported a suicide rate of two out of 315 patients taking CSH over a two-year period (Chen et al. 2023).
[93] Cheng et al. (2019); Deutsch (2020a).
[94] Deutsch (2020b).

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If patients do detransition,[95] they may experience regret,[96] but some patients may integrate the physical changes into their self-concept and not experience regret.[97] Even proponents of PMT acknowledge that regret is a risk (e.g., the phrase "Some adolescents may regret the steps they have taken" in WPATH's guidelines).[98]

This serious issue has been minimized with the claim that detransition and regret rates are vanishingly low. In fact, the detransition rate is unknown.[99] The ubiquitous claim that the detransition and regret rates are vanishingly low is unsupported by the evidence.[100] A U.K. population-based study not focused on minors found that about one-fifth of patients discontinued hormonal interventions within five years, with more than half of them reporting experiences of detransition and/or regret.[101] Reasons for detransition are complex[102] and can be related to external[103] or internal[104] factors. With respect to

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[95] Detransition refers to reverting back to living as one's sex after having medically and/or surgically transitioned. For discussion of detransition as a phenomenon see Butler & Hutchinson (2020); Irwig (2022); MacKinnon, Expósito-Campos et al. (2023). For research based on survey data from detransitioners or their parents, see Bailey & Diaz (2023); Littman (2018), (2021); Vandenbussche (2022).

[96] Some detransitioners have described adverse experiences with CSH as well as regret; e.g., in a recent court case (DH v. Snyder Case: 21-15668, 07/07/2021, ID: 12164749, DktEntry: 22, n.d.) one patient described that testosterone "exacerbated her anxiety and depression" in addition to prompting increased aggression, risk-taking, and suicidal ideation (p. 22); another patient experiencing depression after several months of euphoria, (p. 24) and another described ongoing regret and distress due to a permanently deepened voice from testosterone and numb scars and absent breasts from mastectomy surgery (p. 18).

[97] MacKinnon et al. (2022).

[98] Coleman et al. (2022, p. S47).

[99] Cohn (2023).

[100] The detransition rate after PBs and CSH has been described as very low, but this is backed by little evidence. A few sources are frequently cited. One is an SR of surgery studies with limited (if any) relevance to PMT, which reported a regret rate of around 1% (Bustos et al., 2021). This SR had methodological problems, calculation errors, and included mostly studies of poor or moderate quality, many with follow-up times that were inadequate for capturing regret (Cohn, 2023; Expósito-Campos & D'Angelo, 2021). Additionally, there were issues with the ways included studies defined regret; in Wiepjes et al. (2018), for example, patients needed to report regret to their clinician and ask to start natal sex hormones. Another study was based on survey research of individuals who identified as transgender *at the time of survey completion*. Some respondents had detransitioned in the past (usually due to factors like stigma or other external difficulty) before re-identifying as transgender (Turban et al., 2021). A survey of surgeons found respondents had rarely been asked to perform reversals (Narayan et al., 2021); Cohn (2023) noted that these findings were hard to interpret because of "unclear follow-up time, loss to follow-up, and even measurement instrument (Were questions about regret routinely asked and was there a consistent definition of regret in use?)" (p. 1944). Another study of surgical regret partly quantified regret via request for surgical reversals (Jedrzejewski et al., 2023), which Cohn pointed out would have excluded patients who do not return to their surgeons.

[101] Boyd et al. (2022).

[102] MacKinnon, Gould et al. (2023).

[103] Turban et al. (2021).

[104] Littman (2021); Littman et al. (2024).

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clinical research studies of children and adolescents, one study reported a 7.1% regret rate,[105] two found low rates of CSH discontinuation or reidentification with birth sex (<5%),[106] and one found a higher rate of CSH discontinuation (25%).[107]

7.7 Mortality risk

Four population-based cohort studies have found that transgender individuals appear to have higher mortality risk when compared to members of the general population of similar age and sex. In the U.S., private insurance data from 2011 to 2019 indicated that transgender persons were nearly twice as likely to die as age- and sex-matched controls.[108] A Dutch cohort study that included five decades of data found that compared to their natal sex peers, transgender people had an elevated standardized mortality ratio (higher risk of death).[109] A 2023 cohort study from the U.K. found that compared to their natal sex peers, transgender people had higher risk of mortality (34 % higher for females, 60% higher for males).[110] Finally, a Swedish study that included three decades of data found that the mortality risk for transgender persons was 2.8 times that of age and natal sex matched population controls.[111]

This Review does not assess the methodological quality of these epidemiological studies or quantitatively synthesize their findings. The magnitude of the mortality risk for maintaining a transgender identity remains uncertain, as do the underlying causal factors (causes of death found to be elevated among transgender persons included suicide, cardiovascular disease, and HIV[112]). Moreover, in light of ongoing epidemiological shifts (see Section 4.3.1.1), it is unclear whether these findings extend to children and adolescents with gender dysphoria (GD). These studies further support a cautionary stance toward PMT, however, especially insofar as the Dutch cohort study

[105] Crabtree et al. (2024).
[106] Cavve et al. (2024); van der Loos et al. (2022).
[107] Roberts et al. (2022).
[108] Hughes et al. (2022).
[109] de Blok et al. (2021).
[110] Jackson et al. (2023).
[111] Dhejne et al. (2011).
[112] See de Blok et al., 2021; Dhejne et al., 2011; Hughes et al., 2022; Jackson et al. 2023.

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found that despite changes in care of the transgender population over five decades, the elevated mortality risk has persisted, not declined.[113]

[113] de Blok et al. (2021).

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Chapter 8 Summary and Implications of Evidence Review

Medical and surgical interventions for children and adolescents with gender dysphoria (GD) are widely promoted as essential and even lifesaving, yet the evidence base does not support strong conclusions about their effectiveness in improving mental health or reducing GD. Analysis of the biological plausibility of harms is necessary, and suggests that some short- and long-term harms are likely (in some cases expected) sequelae of treatment.

The Food and Drug Administration (FDA) also looks at risks in this manner when making a risk/benefit determination:

> Benefit-risk planning is most valuable in cases where a challenging benefit-risk assessment can be reasonably anticipated, either because the extent of benefit is expected to be modest or is highly uncertain, or when serious adverse events of the drug can be anticipated (e.g., based on a suspected class effect, understanding of the mechanism of action, and/or early-phase or non-clinical safety findings).[1]

The FDA states that with respect to risks, it is important to understand suspected class effects, meaning the types of predicted effects that are known to occur within the same class of medications. For example, the class of diuretics called thiazides are known to cause hypokalemia (low potassium), and so this potential adverse effect must be taken into account when making a risk/benefit determination regarding thiazides.

The FDA also emphasizes the importance of understanding the physiological mechanism of action, meaning the known way in which a drug affects the body. For example, medications called beta blockers affect the beta-adrenergic receptor and by their known mechanism of action cause effects such as slowed heart rate and decreased cardiac contractility. These physiological mechanisms—and the potential adverse effects of bradycardia (slow heart rate) and reduced cardiac output (amount of

[1] Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) (2023).

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blood pumped by the heart)—must be taken into account when making a risk/benefit determination regarding beta blockers.

Similarly, risk/benefit determinations regarding PMT must take into account both class effects and known mechanism of action for these interventions. Moreover, as the FDA also emphasizes, when the risks of a treatment are serious, anticipated effects must be proportionate:

> In cases where serious risks are anticipated, it is important to consider whether the risk can be outweighed by a benefit of sufficient certainty, magnitude, and clinical relevance to patients.[2]

Some of the plausible harms of PMT are serious. The likelihood of infertility when puberty blockers (PBs) are provided at the early stage of puberty and followed by cross-sex hormones (CSH) does not have to be demonstrated in a clinical trial. This is because the mechanism is well-understood and conducting a trial would amount to an unethical "parachute test."[3]

Analysis of all available data described in this section of the Review suggests that the risk/benefit profile of medical and surgical interventions for children and adolescents with GD is unfavorable.

This has implications for decision-makers—ranging from individual clinical care to guideline development, health policy, and regulation.[4] The findings of this evidence review also underscore the importance of clearly distinguishing how values and preferences are incorporated at different levels of decision-making.

At the individual level, shared decision-making must be grounded in transparency. This means that patients and their families need to be fully informed—not just about available interventions, but also about their potential benefits, harms, alternative

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[2] Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) (2023). See Chapter 13 for discussion of ethical implications.
[3] Smith & Pell (2003). The paper highlights the limitations of "gold-standard" research designs such as randomized controlled trials (RCTs) by pointing out that no RCTs have been done on the effects of jumping from a plane without a parachute. Narrow (mis)application of EBM would conclude that there is "very low certainty evidence" of death, given the dearth of high quality studies.
[4] Zeng et al. (2023); Zhang et al. (2017).

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options, and the certainty or uncertainty of the supporting evidence. When this information is missing or inaccurate, the values and preferences people express may be influenced by incomplete understandings.[5]

At the level of clinical practice guidelines and health policy, values and preferences should reflect those of a population well-informed about the strength of evidence. Weak or uncertain evidence for benefits requires greater caution and flexibility, not stronger recommendations.[6]

At the regulatory level, because decisions must prioritize public health and safety, the strength of the evidence is especially important. When evidence for benefit is lacking or of very low certainty, regulatory frameworks should focus on ongoing evaluation, risk mitigation, and the collection of more robust data before allowing broad implementation. At all levels, responsible decision-making requires a clear grasp of what is known, what remains uncertain, and how this understanding informs ethical obligations of clinicians. Several of the other chapters in this Review explore these issues in greater depth.

[5] Zhang, Alonso-Coello, et al. (2019); Zhang, Coello, et al. (2019).
[6] Guyatt et al. (2008).

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PART 3

CLINICAL REALITIES

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Chapter 9 Review of International Guidelines

Like in other areas of medicine, clinical care for gender dysphoric (GD) youth is typically guided by clinical practice guidelines (CPGs). The aim of such guidelines is to promote practices that are proven to improve patient outcomes and reduce unwarranted variation in care. Although guidelines are not mandates and clinicians must still exercise professional judgment, they serve as important reference points that influence treatment decisions, institutional protocols, insurance coverage policies, and broader standards of medical practice.

This chapter provides an overview of CPGs that address care for youth with GD. Section 9.1 is a primer on the purpose and characteristics of trustworthy evidence-based guidelines. Section 9.2 provides an overview of the quality of the existing guidelines in the area of pediatric gender medicine as assessed by two systematic reviews (SRs). It also discusses the newest guidelines not included in the extant SRs. Section 9.3 profiles the clinical recommendations set out in the only two guidelines rated as trustworthy (both from Nordic countries).

9.1 The role and process of clinical practice guidelines

Clinical practice guidelines are a set of clinical care recommendations intended to optimize patient care.[1] While used primarily by healthcare providers, CPGs also guide hospitals in standardizing care, informing insurance coverage decisions, shaping health policy, and supporting medical education. Researchers use them to identify knowledge gaps, and legal professionals may cite them in malpractice cases. Informed patients and caregivers may also rely on CPGs to participate in shared decision-making and advocate for appropriate care.

The field of evidence-based medicine (EBM) provides several sources describing the characteristics of a trustworthy guideline.[2] According to the National Academy of Medicine (NAM),[3] trustworthy CPGs:

[1] Brignardello-Petersen et al. (2021).
[2] Brignardello-Petersen et al. (2021); Brouwers et al. (2010); Lima, Mirza et al. (2023).
[3] Formerly the Institute of Medicine.

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> should be *based on a systematic review of the existing evidence*; be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups; consider important patient subgroups and patient preferences, as appropriate; be based on an explicit and transparent process that *minimizes distortions, biases, and conflicts of interest*; provide a clear explanation of the logical relationships between *alternative care options* and health outcomes, *provide ratings of both the quality [certainty] of evidence and the strength of the recommendations*; and be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.[4]

Most guideline users will focus on two core elements of guidelines: the content of the recommendations, and their strength. One of the most widely accepted approaches to rating the strength of recommendations is the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. GRADE classifies recommendations according to their direction and strength into four categories: 1) strong recommendation for an intervention; 2) conditional or weak recommendation for an intervention; 3) conditional recommendation against an intervention; and 4) strong recommendation against an intervention.[5]

In addition, there is a GRADE recommendation known as "only in research."[6] It is used sparingly in situations in which an intervention may be promising but lacks sufficient evidence to support its general use. The "only-in-research" recommendation is appropriate when three conditions are met: 1) the available evidence is of low or very low certainty, making it unclear whether the intervention provides meaningful benefit; 2) further research has a large potential to reduce this uncertainty and produce more definitive evidence; and 3) conducting such research is deemed valuable given anticipated costs and risks. This recommendation may be accompanied by a second strong recommendation not to use the intervention outside the research context.[7]

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[4] Graham et al. (2011, p. 5, emphasis added).
[5] Andrews, Schünemann et al. (2013).
[6] Agarwal et al. (2020).
[7] Andrews, Guyatt et al. (2013, p. 724); Guyatt, Oxman, Kunz et al. (2008, p. 1051).

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In addition to interpreting evidence of benefits and harms, guideline panels that develop CPGs also must "trade off the benefits and risks, burden, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and values and preferences" to make their final recommendations and GRADE them for strength.[8] Guideline development groups must be free from or carefully manage financial, intellectual, and personal conflicts of interest, and should represent diverse and balanced views.

The credibility of guidelines should be assessed before their recommendations are accepted as trustworthy. A guideline's trustworthiness and authority depend on how closely the development group adhered to best practices for guideline development.[9] The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument is one of the most well-established validated tools for assessing the quality and methodological rigor of CPGs. The AGREE II instrument evaluates guidelines across six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Each domain is rated on a standardized 7-point scale, with higher scores indicating greater methodological quality and trustworthiness. AGREE II further provides two overall assessments, one summarizing the guideline's overall quality and another evaluating whether the guideline should be recommended for implementation in clinical practice. By promoting transparency and consistency in guideline appraisal, AGREE II helps healthcare providers, policymakers, and patients identify guidelines most likely to improve patient outcomes and quality of clinical decision-making. Other approaches for evaluating the trustworthiness of CPGs emphasize related but distinct dimensions.[10]

9.2 Summary of systematic appraisals of clinical guidelines and guidance documents

At least two SRs have evaluated the quality (trustworthiness) of CPGs addressing the care of patients with GD. One focused on guidelines applying to all age groups,[11] and

[8] Guyatt et al. (2015).
[9] Graham et al. (2011).
[10] Brignardello-Petersen et al. (2021); Lima, Mirza et al. (2023).
[11] Dahlen et al. (2021).

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the other on guidelines devoted specifically to the care of youth.[12] Both relied on AGREE II.[13] This section focusses on the SR that assessed guidelines for pediatric GD, which was conducted by researchers at the University of York to inform the development of the Cass Review.[14]

The York analysis identified 23 and appraised 21 clinical guidelines and clinical guidance documents for their methodological rigor and quality. York's analysis revealed three main findings: 1) all the guidelines, with the exception of two (from Sweden and Finland), were found to be untrustworthy due to serious deviations from the methodological standards for trustworthy guideline development; 2) most international guidance documents have relied heavily on WPATH and Endocrine Society (ES) guidelines,[15] which were themselves closely linked through overlapping authors and with WPATH acting as a sponsor for the development of ES guidelines; and 3) none of the three guidance documents that have shaped the United States's approach to pediatric GD are trustworthy due to serious problems in their development methodology.[16]

9.2.1 Methodological quality of existing guidelines and guidance documents

All guidelines and guidance documents appraised by the York SRs were evaluated across AGREE II's six domains. The SR authors also provided two assessments, one on quality of the guideline overall, and the other on whether the guideline can be recommended for clinical implementation.

The reviewers noted that while generally most guidelines scored well in the domain of "clarity of scope and purpose," most scored poorly in the domains of "rigour of development," "editorial independence," and "applicability," the domains that tend to

[12] Taylor, Hall, Heathcote et al. (2024a, 2024b).
[13] Brouwers et al. (2010).
[14] Taylor, Hall, Heathcote et al. (2024a, 2024b). In this chapter, as in this two-part systematic review (SR), the word "guidelines" will be used to refer to the various documents that were appraised, some of which were not formal clinical practice guidelines (CPGs). The reviewers included "published articles or documents that [provided] at least one specific recommendation for the assessment and/or care of children and/or adolescents (age 0–18) experiencing gender dysphoria/incongruence, and which were developed by or for a professional, healthcare or government organisation or from a research study" (Taylor, Hall, Heathcote et al., 2024a, p. s66).
[15] Coleman et al. (2012); Hembree et al. (2009); Hembree et al. (2017).
[16] See Taylor, Hall, Heathcote et al. (2024a).

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most strongly influence the overall rating and the recommendation for use in clinical practice.[17]

Only the Swedish and the Finnish guidelines were rated as "recommended for implementation" by all reviewers; they also received the highest overall quality score, with Sweden rated as 6 and Finland rated as 5 (out of 7).[18] The Swedish and Finnish guidelines were the only guidelines that described how the evidence base was reviewed and that linked the evidence to clinical recommendations. All other guidelines and guidance documents scored between two and four and were not recommended for implementation by one or more reviewers.[19]

Overall, the reviewers described existing guidance documents that recommend pediatric medical transition (PMT) as "[lacking] an independent and evidence-based approach," noting that it was difficult to detect what evidence had been reviewed and how this informed development of recommendations. Moreover, they reported that the links between specific recommendations and evidence were often unclear or missing.

[17] Hoffmann-Eßer et al. (2018).
[18] See Figure 9.1 below.
[19] Taylor, Hall, Heathcote et al. (2024a, p. s65).

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Figure 9.1[20]

Guideline ID	OQA1	R1	OQA2	R2	OQA3	R3
AACAP 2012	3	No	3	No	4	Yes (mod)
American Academy of Paediatrics 2018	2	No	3	No	1	No
American Psychological Association 2015	3	No	2	No	3	No
Council for Choices in Healthcare Finland 2020	5	Yes (mod)	5	Yes	5	Yes (mod)
de Vries 2006	2	No	3	No	2	No
Endocrine Society 2009	3	No	4	No	4	Yes (mod)
Endocrine Society 2017	4	Yes (mod)	4	No	4	Yes (mod)
European Society for Sexual Medicine 2020	3	Yes (mod)	2	No	3	No
Fisher 2014	2	No	3	No	1	No
Health Policy Project 2015	2	No	1	No	2	No
Norwegian Directorate of Health 2020	3	No	3	Yes (mod)	4	Yes (mod)
Oliphant 2018	2	No	3	No	1	No
Pan American Health Organisation 2014	2	No	2	No	1	No
Royal Children's Hospital Melbourne 2018	3	No	3	No	2	No
Society for Adolescent Health and Medicine 2020	2	No	2	No	1	No
South African HIV Clinicians Society 2021	3	No	3	No	2	No
Strang 2018	3	Yes (mod)	2	No	2	No
Swedish National Board of Health & Welfare 2022	6	Yes (mod)	6	Yes	6	Yes
University California San Francisco 2016	3	No	2	No	3	No
WPATH 2012	3	Yes (mod)	3	No	2	No
WPATH 2022	3	Yes (mod)	3	No	3	No

OQA: Overall quality assessment - 1-7 where 1 is lowest possible score and 7 is the highest possible score

R: Recommend guideline for use - Possible responses are Yes, Yes with modifications (Yes (mod)), No

The numbers 1-3 refer to the three reviewers who appraised the guidelines

Abbreviations
AACAP – American Academy of Child & Adolescent Psychiatry
WPATH – World Professional Association for Transgender Health

[20] Supplementary Table S3 in Taylor, Hall, Heathcote et al. (2024a).

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Figure 9.2[21]

Table 1 Critical appraisal domain scores

Guideline ID	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence
AACAP 2012	65	39	44	63	7	31
American Academy of Paediatrics 2018	70	26	12	30	6	69
American Psychological Association 2015	74	74	24	50	18	14
Council for Choices in Healthcare Finland 2020	91	69	51	72	56	0
de Vries 2006	63	31	10	74	17	6
Endocrine Society 2009	65	33	44	70	22	31
Endocrine Society 2017	63	33	42	72	21	92
European Society for Sexual Medicine 2020	63	52	39	70	7	58
Fisher 2014	65	20	12	35	17	44
Health Policy Project 2015	63	63	16	24	33	6
Norwegian Directorate of Health 2020	76	81	30	57	47	17
Oliphant 2018	44	39	12	33	21	0
Pan American Health Organisation 2014	52	44	13	31	21	0
Royal Children's Hospital Melbourne 2018	81	59	19	41	19	14
Society for Adolescent Health and Medicine 2020	41	24	17	41	7	0
South African HIV Clinicians Society 2021	59	59	21	43	24	69
Strang 2018	87	31	18	37	15	19
Swedish National Board of Health & Welfare 2022	91	87	71	83	25	36
UCSF 2016	70	41	23	37	26	0
WPATH 2012	85	61	26	56	17	17
WPATH 2022	83	63	35	56	24	39

≥70%, 31%–69%, ≤30%.
AACAP, American Academy of Child & Adolescent Psychiatry; UCSF, University of California, San Francisco; WPATH, World Professional Association for Transgender Health.

9.2.2 Interdependence of the existing guidelines and guidance documents

The SR authors noted an unusual interdependence between much of the published guidance supporting the management of children and adolescents with GD.[22] There was a marked pattern of "circular referencing and mutual endorsements"[23] between guidelines recommending PMT for routine care, with WPATH and the ES guidelines influencing all other guidelines and guidance documents.

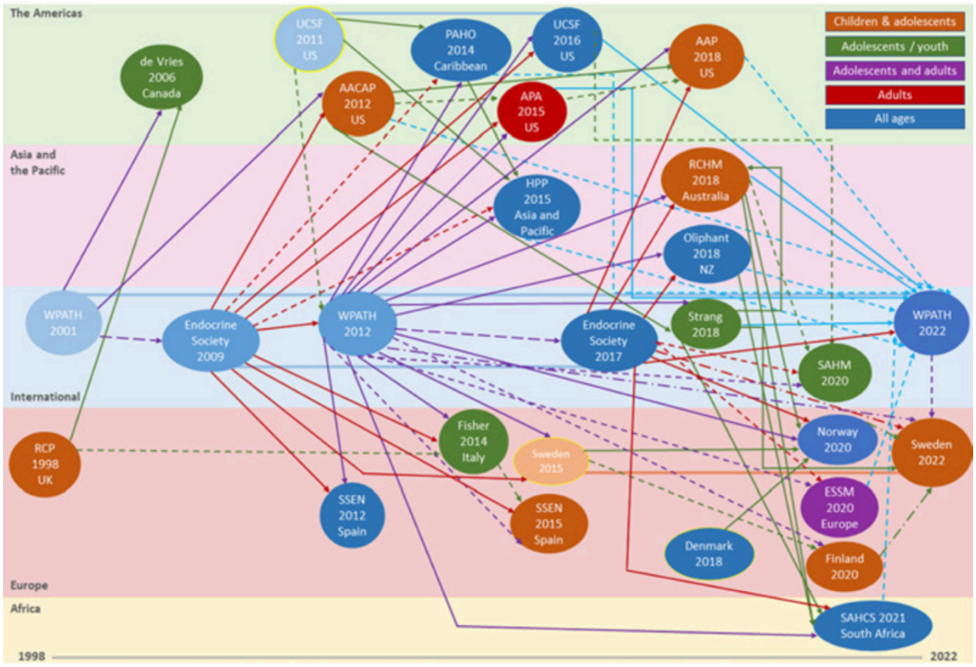
The pattern of "links and influences between guidelines"[24] had been established early in the field's tenure with the ES 2009 and WPATH 2012 guideline versions.[25] The pattern persisted as both ES and WPATH updated their guidelines in 2017 and 2022 respectively.[26] Moreover, the 2009 and 2017 ES guidelines state that WPATH was a guideline sponsor.[27] The University of York reviewers noted that this represents

[21] Taylor, Hall, Heathcote et al. (2024a, Table 1).
[22] Taylor, Hall, Heathcote et al. (2024a, pp. s69-s70).
[23] Donkin et al. (2025, p. 3).
[24] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[25] Coleman et al. (2012); Hembree et al. (2009).
[26] Coleman et al. (2022); Hembree et al. (2017).
[27] Hembree et al. (2009); Hembree et al. (2017).

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problematic circularity, "with WPATH adopting Endocrine Society recommendations in its own guideline and acting as a cosponsor for and providing input on drafts of the Endocrine Society guideline."[28]

Figure 9.3[29]



The Cass Review emphasized the interdependence and circularity of the guidance documents:

> The circularity of this approach may explain why there has been an apparent consensus on key areas of practice despite the evidence being poor … the guideline appraisal raises serious questions about the reliability of current guidelines.[30]

9.2.3 WPATH, Endocrine Society, and the American Academy of Pediatrics (AAP) guidelines and practice statements

The most influential sources of clinical guidance for treating pediatric GD in the U.S. are the WPATH and ES CPGs and the American Academy of Pediatrics' (AAP) guidance

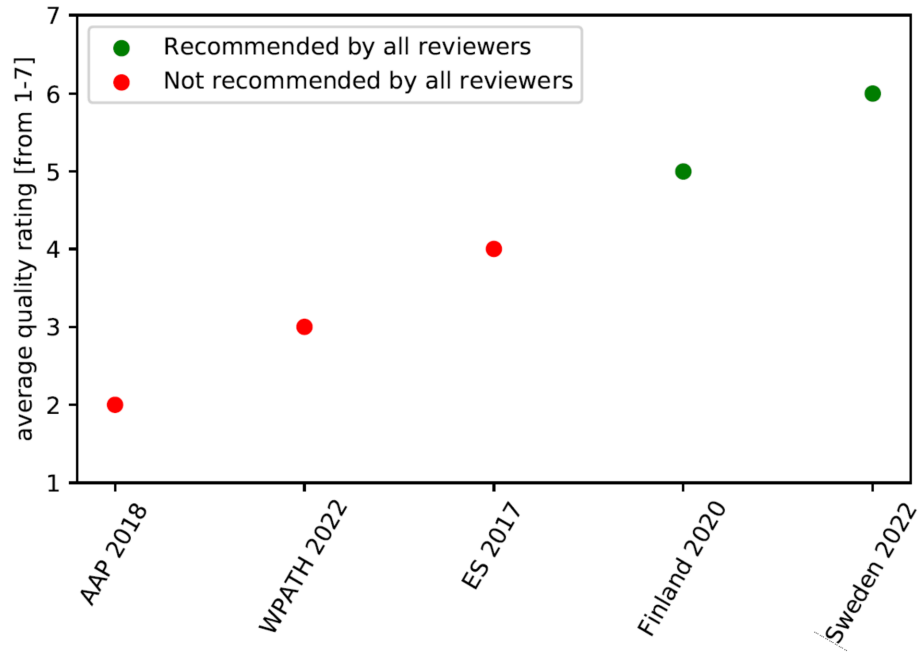
[28] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[29] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[30] Cass (2024a, pp. 129-130).

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document.[31] The York SR assessed all three documents as very low quality and did not recommend them for implementation.

Figure 9.4 plots the overall rating of the quality of these three guidance documents relative to the only two guidelines that have been recommended for implementation by the York SRs.[32]

Figure 9.4[33]



Legend**:** AAP: American Academy of Pediatrics; WPATH: World Professional Association for Transgender Health; ES: The Endocrine Society

The York appraisals found that WPATH's guideline, *Standards of Care*, Version 8 (SOC-8) and the ES guidelines were both "[lacking] in developmental rigour." SOC-8 was given an overall score of 3 out of 7; the ES guideline scored 4 out of 7. The extensive problems in the SOC-8 development process, which included the failure to base recommendations on SRs and numerous other serious limitations in the process,

[31] The American Academy of Pediatrics' (AAP) 2018 Policy Statement was reaffirmed in 2023 (Rafferty et al., 2018); the Endocrine Society's (ES) published in 2017 represents the most recent published version (Hembree et al., 2017); the World Professional Association for Transgender Health's (WPATH) most recent clinical practice guideline is *Standards of Care*, Version 8 (SOC-8) (Coleman et al., 2022).
[32] Taylor, Hall, Heathcote et al. (2024a).
[33] Figure 9.4 plots data from Supplementary Table S3 in Taylor, Hall, Heathcote et al. (2024a).

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ultimately led to this low rating and the status of "not recommended for implementation." These problems are discussed in more detail in Chapter 10.

The ES 2017 guideline, which used the GRADE framework, has been criticized for making strong recommendations for hormonal interventions in the setting of a weak evidence base.[34] Notably, none of the systematic reviews that supported the ES guidelines were based on outcomes for children or adolescents.[35] The ES recommendation to initiate puberty blockade using GnRH as was derived by putting a higher value on achieving a "satisfactory physical appearance" while putting the lowest value on avoiding physical harms.[36] The ES recommendation for the initiation of cross-sex hormones no earlier than age 16 was justified by placing a higher value on adolescent's purported ability to meaningfully consent to cross-sex hormones (CSH) and placing a lower value on avoiding harm from potentially prolonged pubertal suppression.[37]

The AAP 2018 policy statement is not technically a CPG but has been widely cited in the U.S. as influential in establishing how pediatricians respond to children and

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[34] E.g. Block (2023c). If such recommendations are made, which the GRADE framework allows in specific circumstances, the reasoning for this must be clear. The ES guidelines did not do this.
[35] Maraka et al. (2017); Singh-Ospina et al. (2017); Of note, the only study of adolescents included in these systematic reviews, Klink et al. (2015), concluded that puberty blockers impede the development of bone mass density (BMD) and cross-sex hormones fail to bring up BMD to its pretreatment potential: "Between the start of GnRHa and age 22 years the lumbar areal BMD z score (for natal sex) in transwomen decreased significantly from 0.8 to 1.4 and in transmen there was a trend for decrease from 0.2 to 0.3. This suggests that the BMD was below their pretreatment potential and either attainment of peak bone mass has been delayed or peak bone mass itself is attenuated" (Klink et al., 2015, p. E270).
[36] Full quotation: "These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression" (Hembree et al., 2017, p. 13). Published gender-affirming care literature has also described a prioritization of aesthetic outcomes, e.g., a research paper noted gender-affirming care can be beneficial because (among other reasons) "The combination of pubertal suppression and cross-sex hormones] may … increase the concordance of youths' appearance with cisgender norms …" (McGregor et al., 2024, p. 5).
[37] Full quotation: ""The recommendation to initiate pubertal induction [cross-sex hormones] only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/ harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers" (Hembree et al., 2017, p. 3885).

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adolescents with GD.[38] Because the document offers extensive clinical recommendations regarding every step of PMT—from social transition to PBs, CSH, and surgery—the York team assessed the trustworthiness of the AAP guidance using the same criteria they applied to CPGs. Using the AGREE II criteria, the AAP policy statement received the second-lowest average score among all international guidelines: 2 out of 7.

As noted in Chapter 2, the AAP's policy statement's use of "gender diverse" casts a very wide net regarding which patients the organization considers eligible for medical intervention. The statement has been heavily criticized in peer-reviewed articles, which have pointed out that it is rife with referencing errors and inaccurate citations.[39] Despite persistent advocacy among its members, who have petitioned the organization to release updated, evidence-based guidance for treating pediatric GD,[40] the organization chose to reaffirm their policy statement in 2023.[41]

9.2.4 More recent international guidelines

Since the publication of the York reviews, several new European guidelines have been issued in final or draft form, including those from the German AWMF, the French Society of Pediatric Endocrinology and Diabetology, the Polish Sexological Association, the European Society for Paediatric Endocrinology (ESPE), and the forthcoming final version of the French National Authority for Health (HAS) guidelines.[42] These reviews have been developed amid growing international awareness of the weaknesses of WPATH's SOC-8 and the outdated nature of the Endocrine Society's guidelines,

[38] Rafferty et al. (2018).
[39] E.g., Cantor (2020); McDeavitt (2025).
[40] See description of efforts led by pediatrician Julia Mason in Block (2023c).
[41] Block (2023c).
[42] The AWMF German guidelines (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy [DGKJP], 2025) are comprehensive; the guidelines by the French Society of Pediatric Endocrinology and Diabetology (SFEDP; Brezin et al., 2024) are limited to hormonal interventions and is currently available only as a preprint; the Polish guidelines, supported by the Polish Sexological Association, the Polish Psychiatric Association, and the Polish Society of Paediatric Endocrinology and Diabetology cover most aspects of PMT but are almost entirely derivative (Gawlik-Starzyk et al., 2025); the ESPE guidelines (Hannema et al., 2024) primarily focus on endocrine (medical/hormonal) interventions; the draft French national HAS guidelines became publicly available when a French newspaper published a draft in November 2024 (Sugy, 2024); the final version has not yet been released.

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reflecting the need to have defensible, localized, up-to-date guidelines that set the standards of care for youth with GD.

Unfortunately, these recently-published (or as yet to be finalized) guidelines suffer from the same or similar methodological weaknesses that have rendered the WPATH and the Endocrine Society's guidelines not trustworthy and not recommended for implementation. All suffer from non-evidence-based approaches to guideline development and exhibit one or more of the following problems: 1) guideline development groups are composed of individuals with unmanaged conflicts of interest relating to the provision of pediatric gender transition services; 2) the guideline takes an a priori WPATH-aligned position that medicalized pathway of hormones (and surgery) is the recommended treatment approach;[43] 3) the recommendations are not based on rigorously-conducted systematic reviews of evidence[44] 4) individual studies that drive treatment recommendations are not appraised for quality, and their conclusions are accepted at face value; 5) the recommendations are not graded for strength, resulting in ambiguity in clinical decision-making.

While some guidelines, in response to criticism of the draft version, have added references to systematic reviews of evidence, it is apparent that SRs were not utilized to make treatment recommendations, with apparent and unreconciled contradictions between the findings of the SRs and the treatment recommendations. [45] Alternatives such as psychological support are in nearly all cases marginalized or even entirely absent. Ongoing reliance on the "consensus-based" non-evidence-based process

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[43] For example, the German AWMF guidelines state that the members of the guideline development group adhere to the WPATH positions (Society for Evidence-Based Medicine, 2025).The Polish guideline explicitly bases itself on WPATH SOC-8, without independent review, stating, "This document is based on the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (2022) [1] and an Endocrine Society Clinical Practice Guideline … The person conducting psychological or sexological assessment and care should be familiar with the content of the current standards of care of the World Professional Association for Transgender Health and comply with them" (Gawlik-Starzyk et al., 2025, pp. 4, 8).

[44] The German guidelines methodological report explicitly states that no evidence-based recommendations were developed (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP), 2025, p. 6).

[45] Society for Evidence-Based Gender Medicine (2025).

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underlines the trustworthiness of these guidelines, raising questions about the rigor of guideline development in pediatric gender medicine not just in the U.S., but worldwide.

9.3 Overview of recommendations in the high-quality guidelines

Of the 23 guidelines that were appraised in the systematic evidence review, only two were recommended for practice by all three reviewers: the guidelines from Finland (which were scored five out of seven), and those from Sweden[46] (which were scored six out of seven). Both guidelines recommend that psychotherapy—not hormones or surgeries—should be the standard of care for youth with GD, and that any use of hormones should be limited to nationally overseen research or exceptional circumstances. As described in the systematic review, the two Scandinavian guidelines were the only ones that based their treatment recommendations on systematic evidence reviews, a key element of trustworthy clinical practice guidelines.

9.3.1 Finland

In 2020, Finland's Council for Choices in Health Care (PALKO/COHERE) issued national guidelines for treating gender dysphoria in minors, representing a major shift away from the model endorsed by WPATH's *Standards of Care* Version 7.[47] Finland's guidelines emphasize that the first-line treatment for adolescents experiencing gender distress should be psychosocial support and psychotherapy, not early medical intervention.[48]

Following an SR, Finnish authorities concluded that the body of evidence supporting puberty blockers and cross-sex hormones for youth is inconclusive. Importantly, the guidelines explicitly state that "in light of available evidence, gender reassignment of minors is an experimental practice."[49] While medical transition remains possible, it is restricted to highly select cases—specifically, adolescents with persistent, childhood-

[46] In 2022, Sweden's healthcare authority, Socialstyrelsen, issued guidelines recommending that "Psychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures" (Socialstyrelsen, 2022b, p. 45).
[47] Council for Choices in Health Care Finland (2020a). There is an official English-language summary (Council for Choices in Health Care Finland, 2020c), as well as an unofficial English translation of the complete guideline document (Council for Choices in Healthcare Finland, 2020b).
[48] Council for Choices in Healthcare Finland (2020a).
[49] Council for Choices in Healthcare Finland (2020b, p. 8).

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onset gender dysphoria, no major psychiatric comorbidities, and stable identity development through adolescence.

Surgery is not offered to minors in Finland. Furthermore, the guidelines stress that psychiatric conditions must be treated and stabilized before considering hormonal interventions. Special caution is placed on the use of puberty blockers, given emerging evidence about their potential impact on brain maturation and long-term decision-making capacity.

Adherence to this strict protocol is assured because Finland has only two centres that provide assessments and approve treatment indications for youth with GD, with highly coordinated clinical teams that adhere to the Finnish strict protocol.

Since the publication of the Finnish guidelines, two major register studies have provided additional support for their cautious approach. One explored psychiatric needs among gender-referred individuals, finding high rates of psychiatric comorbidities and suggesting that the rising number of referrals includes increasingly complex clinical cases.[50] The second examined suicide mortality among individuals under 23 and found that, after adjusting for psychiatric needs, there was no statistically significant difference in suicide rates between gender-referred youth and matched controls from the general population.[51]

Finland's cautious, evidence-focused guidelines stand in stark contrast to the WPATH model. Rather than expanding access amid uncertain outcomes, Finland has re-centered pediatric care around rigorous assessment, psychotherapeutic exploration, and prioritizing long-term health.

9.3.2 Sweden

In 2022, Sweden's National Board of Health and Welfare (Socialstyrelsen) issued an update to its national guidelines for the treatment of children and adolescents with

[50] Kaltiala et al. (2023).
[51] Ruuska et al. (2024).

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gender dysphoria.[52] This update was motivated in part by shifts in epidemiology and uncertainty about the recent rise in cases, and limited data regarding rates of detransition or regret among young adults. Grounded in a systematic review of the evidence,[53] the new framework departs sharply from the SOC-8. Unlike WPATH's affirmation-based model, Sweden's guidelines conclude that the risks associated with puberty blockers and gender-affirming treatments likely outweigh the expected benefits for young people. As with Finland, such interventions are now restricted to research settings, with exceptions permitted under strict clinical oversight.

The Swedish guidelines prioritize a comprehensive psychosocial evaluation and support. Clinicians are instructed to conduct thorough assessments of psychological, psychosocial, and psychiatric factors, utilizing validated instruments, investigative interviews, and detailed life histories from both the young person and their guardians.[54] Rather than presuming a fixed outcome, the guidelines emphasize the importance of supporting the open-ended exploration of gender identity.[55] Systematic screening for neurodevelopmental conditions, including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), is required early in the evaluation process, with full neuropsychiatric assessments initiated when indicated.[56] Moreover, concurrent psychiatric conditions must be identified and addressed as early as possible, ensuring that psychosocial support and psychiatric interventions are available to bolster overall mental health throughout the evaluation.

Medical and surgical interventions are subject to equally rigorous restrictions. Treatment with puberty blockers (GnRH analogues) is confined to the context of clinical research. Until such research protocols receive ethics board approval, puberty blockers may be administered only in exceptional cases under the updated guidelines.[57] Similarly, the use of cross-sex hormones—testosterone or estrogen—is permitted solely within

[52] The official Swedish-language guidelines are Socialstyrelsen (2022c). Page numbers in this section refer to a certified, complete, unofficial translation that was submitted as evidence in a U.S. court case (Socialstyrelsen, 2022b). There is also an official English-language summary (Socialstyrelsen, 2022a).
[53] Swedish Agency for Health Technology Assessment and Assessment of Social Services (2022).
[54] Socialstyrelsen (2022b, p. 63).
[55] Socialstyrelsen (2022b, p. 66).
[56] Socialstyrelsen (2022b, p. 69).
[57] Socialstyrelsen (2022b, p. 85).

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research studies, with narrowly defined exceptional cases allowed.[58] Only adolescents who meet stringent eligibility criteria for gender-affirming hormone therapy may be considered for surgery, again under exceptional circumstances.[59] Across all interventions, the emphasis is on minimizing risk and ensuring that treatment decisions are based on the best available evidence.

Sweden's 2022 guidelines represent a marked shift away from affirmation-driven PMT model. Anchored in a systematic review of the literature, they embody a precautionary approach grounded in the principles of evidence-based medicine. Sweden's approach signals an important recalibration in gender medicine, reinforcing that interventions involving youth must be guided by systematic evidence appraisal, ethical responsibility, and a focus on long-term health trajectories.

9.3.3 United Kingdom

Currently, there is no finalized clinical practice guideline for pediatric gender medicine available from the National Institute for Health and Care Excellence (NICE) for England and Wales, or the Scottish Intercollegiate Guidelines Network (SIGN) for Scotland.[60]

NICE was commissioned by NHS (National Health Service) England[61] to perform a systematic evidence review evaluating treatments for gender dysphoria among children and adolescents. NICE's evidence reviews identified significant limitations in existing research, concluding that the available evidence was of very low quality (as assessed by the GRADE methodology) [62] and therefore insufficient to support the development of a formal clinical guideline.

These two SRs were cited as part of the Terms of Reference for an independent review that NHS England commissioned, led by Dr. Hilary Cass.[63] Released in 2024, the Cass Review aimed to thoroughly evaluate pediatric gender medicine services in the U.K. and provide clear recommendations on clinical practices and service delivery. Rather than

[58] Socialstyrelsen (2022b, p. 90).
[59] Socialstyrelsen (2022b, p. 95).
[60] Silver et al. (2025, p. 2).
[61] On March 13, 2025 it was announced that NHS England would be merged with the Department of Health and Social Care (DHSC).
[62] National Institute for Health and Care Excellence (2020b, 2020a).
[63] Cass (2024a, Appendix 1).

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providing explicit clinical guidelines, the Cass Review is a detailed, independent, investigative assessment based on multiple, commissioned, peer-reviewed systematic reviews.[64]

The Cass Review identified critical issues within the existing pediatric gender services, such as inadequate clinical assessments, insufficient long-term outcome data, and significant concerns over rapidly increasing referrals of young people with gender incongruence. Overall, it identified a significant gap between the available evidence and the clinical justifications for medical interventions for gender dysphoria in young people[65] and emphasized the necessity for comprehensive psychological support and thorough, individualized assessments.

In response to the Cass Review, NHS England introduced major policy changes. Puberty blockers are no longer routinely commissioned due to insufficient evidence regarding their long-term safety and effectiveness. Instead, they will only be accessible through structured clinical research trial, which is currently being designed. Additionally, CSH (masculinizing or feminizing hormones) are available to young people around the age of 16, contingent upon strict eligibility criteria and detailed assessment protocols by specialist multi-disciplinary teams and a new national Multi-Disciplinary Team (MDT) review process.[66] As reported most recently, no adolescent was prescribed cross-sex hormones in the last year. The NHS recently revealed that since the Cass Review was published, no minor has been found eligible to receive CSH according to the updated policy.[67]

Without a finalized clinical practice guideline, clinicians must follow the current policies directly informed by the Cass Review. These interim standards prioritize patient safety, rigorous clinical evaluation, ongoing research, and holistic care approaches, significantly revising the clinical pathways for young individuals experiencing gender incongruence.

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[64] Archives of Disease in Childhood (2024).
[65] Cass (2024a, pp. 22, 29, 32-35).
[66] National Health Service England (2024a); a review of adult services was also announced (National Health Service England, 2024b).
[67] Spencer (2025).

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9.4 Conclusion

The current landscape of CPGs for treating youth with GD underscores significant variability in methodological rigor and trustworthiness. Rigorous appraisals consistently demonstrate that only a select few guidelines, notably those from Finland and Sweden, meet high standards for evidence-based clinical decision-making. These Scandinavian guidelines emphasize cautious approaches grounded firmly in systematic evidence reviews, advocating psychotherapy and psychosocial interventions as first-line treatments, and restricting medical interventions to carefully monitored research settings or exceptional circumstances.

In contrast, many internationally influential guidelines, including those from WPATH, the Endocrine Society, and the American Academy of Pediatrics, have been criticized for substantial methodological shortcomings and conflicts of interest, resulting in recommendations not reliably supported by rigorous evidence. This pattern of circular referencing and mutual endorsement among these guidelines further compromises their credibility and has likely perpetuated a perceived consensus in pediatric gender medicine that belies the actual paucity of high-quality evidence.

Given the ethical implications and lifelong consequences of medical interventions in youth, it is imperative that future guidelines in pediatric gender medicine adhere strictly to established standards of evidence-based medicine. Guideline developers must prioritize transparency, methodological rigor, independence from vested interests, and systematic evidence appraisal. Only through such disciplined approaches can clinical practice guidelines fulfill their intended role of safeguarding the health and well-being of youth with GD, promoting informed decision-making among clinicians, families, and policymakers alike.

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Chapter 10 WPATH's *Standards of Care* 8

As shown in Chapter 9, the guidelines issued by the World Professional Association for Transgender Health (WPATH) have been rated among the lowest in quality and have not been recommended for implementation by systematic reviews of guidelines. Despite their lack of trustworthiness, for more than a decade WPATH guidelines have served as the foundation of the healthcare infrastructure for gender dysphoric (GD) youth in the United States. The WPATH *Standards of Care* guidelines are embedded in nearly all aspects of healthcare including clinical education, delivery of care, and reimbursement decisions by private and public insurers.

This chapter focuses on the current Version 8 of the WPATH *Standards of Care* guidelines (SOC-8),[1] published in 2022.[2] Section 10.1 describes WPATH's central role in shaping the treatment of youth with GD in U.S. healthcare settings. Section 10.2 provides a brief overview of the rationale for the development of SOC-8, highlighting how it differs significantly from earlier guideline versions with particular emphasis on the new Adolescent chapter. Section 10.3 examines the development process of SOC-8, considering both internal dynamics and external pressures, and analyzes its multipurpose role as a clinical guideline, a tool to secure insurance coverage, and a legal instrument aimed at promoting broad access to pediatric medical transition (PMT). Section 10.4 highlights one critical downstream consequence of the guideline's flawed development process: the elimination of all minimum age requirements for endocrine and surgical interventions (except phalloplasty) in minors. Section 10.5 discusses the implications of continued reliance on WPATH.

10.1 Influence of WPATH in the United States

There is no accredited subspecialty in "gender medicine" in the U.S. Instead, the practice of PMT typically involves a series of handoffs among different providers: a pediatrician or an adolescent medicine specialist[3] first assesses whether PMT may be

[1] Coleman et al. (2022).
[2] Portions of this evaluation necessarily rely on internal WPATH communications made publicly available through subpoena. See Boe v. Marshall, No. 2:22-cv-00184, (M.D. Ala.). Some material from Boe v. Marshall was previously released in Voe v. Mansfield, No. 1:23-Cv-00864: 100-1 (M.D.N.C.).
[3] American Board of Pediatrics (2024).

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warranted; mental health professionals diagnose GD or a related condition and recommend PMT; endocrinologists prescribe hormonal interventions (i.e., puberty blockers and cross-sex hormones); and various surgical specialties including plastic surgeons, urologists, and gynecologists perform a range of surgical procedures to alter the adolescent's sex-specific physical characteristics.

The multidisciplinary nature of PMT combined with the absence of a single medical specialty responsible for overseeing patient care has resulted in an oversight gap WPATH has filled. WPATH has successfully positioned itself as the leading authority in the field of gender medicine, including pediatric gender medicine. The first version of WPATH's Standards of Care was published in 1979. Subsequent updates followed in 1980, 1981, 1990, 1998, 2001, and 2012.[4] The most recent version, SOC-8, was published in 2022.[5] Chapter 3 provides a brief history of gender medicine and the role of WPATH, which was originally formed (under a different name, the "Harry Benjamin International Gender Dysphoria Association") to focus on the gender transition wishes of mature adults, but after pediatric transitions were pioneered in the Netherlands, increasingly shifted its attention to children and adolescents.

10.1.1 WPATH's role in clinical practice

Although some medical societies involved in providing PMT have issued guidance documents on specific aspects of care for youth with GD,[6] no professional society has published a comprehensive, up-to-date, evidence-based clinical guideline covering the full PMT pathway. Instead, medical societies have largely deferred to WPATH, adapting their own clinical positions to WPATH's most recent recommendations.[7] Unlike the U.K., Sweden, Finland, and other countries with centralized medical policymaking bodies that

[4] SOC-7 was released in 2011 and published in 2012.
[5] Coleman et al. (2022).
[6] The most notable documents are discussed in Chapter 9 and include the Endocrine Society's guidelines (Hembree et al., 2017) and the American Academy of Pediatrics position statement (Rafferty et al., 2018). Both are significantly outdated.
[7] In August 2024, WPATH was presented in a court case as "the leading association of medical professionals treating transgender individuals." It was further asserted that "[t]he Nation's leading medical and mental health organizations recognize [SOC-8] as reflecting the accepted standard of care for treating gender dysphoria." See U.S. v. Skrmetti (No. 23-477), Brief for the petitioner (2024, p. 3).

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issue independent, authoritative clinical care guidelines,[8] in the United States, WPATH's influence has been outsized and largely uncontested—primarily due to the fragmented healthcare system and the complexity of the U.S. regulatory environment.[9] WPATH's influence on clinical protocols for the care of youth with GD is pervasive within U.S. medicine. Its *Standards of Care* have become the primary framework embedded in clinical protocols and hospital operating procedures for the diagnosis and treatment of youth with GD.[10]

10.1.2 WPATH's role in medical education and training

WPATH has become the dominant influence shaping the education and training of U.S. healthcare providers who treat youth with GD. Indeed, it is virtually coterminous with the field itself. Because there is no officially accredited medical subspecialty in gender medicine in the U.S., and no formal board certification process as exists in fields like adolescent medicine, endocrinology, or psychiatry, training in PMT remains informal, variable, and largely organized through WPATH-affiliated medical education efforts.

WPATH's Global Education Initiative (GEI) offers certified courses that serve as the core curriculum for clinical training in the U.S. and worldwide. WPATH GEI's official collaborators include pediatric gender clinics and hospitals, the American Medical Student Association, and the World Health Organization (WHO).[11] Major U.S. hospitals and medical schools have embedded WPATH-aligned standards into their residency, fellowship, and continuing medical education programs.[12] Gender clinics reference

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[8] When NHS England moved to remove puberty blockers for GD from clinical practice, it received complaints that the decision was "not consistent … with the WPATH standards of care for trans children." NHS England responded: "The policy proposition has been developed following a review of peer reviewed published evidence as per NHS England Policy Development Methods. NHS England does not commission based upon guidelines or treatment protocols e.g. WPATH 8.0 [SOC-8] or practices in other countries. The not for routine commissioning position has been concluded based on 'insufficient clinical benefit to the patient of which evidence of harm is one aspect'" (National Health Service England, 2023, p. 4).

[9] The U.S. lacks a centralized medical policy-making body, resulting in what has been described as a "bewildering regulatory maze" (Field, 2008, p. 607).

[10] For an example, see Seattle Children's Hospital (n.d.). Note: it appears some pediatric gender clinics have recently removed public references to WPATH and have also removed the backups of the websites, making them inaccessible to citation.

[11] See World Professional Association for Transgender Health (n.d.).

[12] For example, Mt. Sinai's transgender psychiatry fellowship: "Fellows are provided time and financial compensation to attend the U.S. Professional Association for Transgender Health or World Professional

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WPATH's *Standards of Care* in clinical protocols and physician training.[13] WPATH-certified trainers further extend WPATH's reach into professional training at institutional and community levels.[14] WPATH certification not only is encouraged but also in some cases mandated.[15] This widespread integration has effectively established WPATH as the de facto authority for defining clinical competency, treatment eligibility criteria, and ethical frameworks across much of U.S. medicine.

10.1.3 WPATH's role in insurance reimbursement

Many U.S. public and private health insurers and regulatory bodies rely on SOC-8 when making coverage determinations. Requirements for credentialing, assessing medical necessity, and making coverage decisions almost universally reference WPATH's *Standards of Care*. Major U.S. private insurers, including Anthem,[16] Kaiser,[17] Aetna,[18] Cigna,[19] and UnitedHealthcare,[20] explicitly reference SOC-8 to define medical necessity, eligibility criteria, and coverage decisions.

Association for Transgender Health bi-annual conferences" (Icahn School of Medicine at Mt. Sinai, n.d.-b). Mt. Sinai's transgender surgery fellowship attending faculty includes Marci Bowers, the former president of WPATH (Icahn School of Medicine at Mt. Sinai, n.d.-a). Oregon Health and Sciences University's gender surgery fellowship program director is "the surgical lead for the World Professional Association for Transgender Health (WPATH) and the United States Professional Association for Transgender Health (USPATH) meetings" (OHSU School of Medicine Surgery, n.d.).

[13] For example, the Stanford Medicine Children's gender clinic website states, "the expert members of the Gender Clinic team consists [sic] of providers from pediatric endocrinology, adolescent medicine, pediatric urology and social services, supporting each child's or adolescent's gender identity. All our providers are members of the World Professional Association for Transgender Health (WPATH)" (Stanford Medicine Children's Health, n.d.). Fenway Health references WPATH as the authority in the field: "The World Professional Association of Transgender Health (WPATH) monitors current research and new knowledge about evidence-based medicine for transgender people. It publishes Standards of Care and Ethical Guidelines for health care providers, which 'articulate a professional consensus about the psychiatric, psychological, medical, and surgical management of gender dysphoria' to guide clinicians in providing quality care for transgender and gender diverse people, including children and adolescents" (Fenway Health, n.d.).

[14] See Harvard Medical School's continuing medical education (Harvard Medical School, n.d.), led by senior WPATH leaders involved in the production of SOC-8 (e.g., Sari Reisner, WPATH board member). Also see the following training initiatives: Gender Health Training Institute (n.d.); Silver Hill Hospital/World Professional Association for Transgender Health (n.d.).

[15] For example, the Washington State Department of Corrections mandates that physicians providing "gender-affirming care" must be WPATH-certified or obtain certification within two years (Washington State Department of Corrections, 2025). The Oregon Health Authority is another example (see following section).

[16] Anthem (2023). WPATH is referenced 35 times as the basis for all recommendations.

[17] Kaiser Permanente (2023). Transition and detransition policies require "WPATH letters."

[18] Aetna (2024). Adolescents are to meet "WPATH criteria" for hormonal interventions.

[19] Cigna (2025).

[20] Stroumsa & Kirkland (2020).

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Government payers, such as Medicaid programs, also commonly rely on WPATH guidelines as the primary basis for developing their medical policies. In 2024, Oregon became the first state to officially adopt SOC-8 as its standard of care, committing the Oregon Health Authority to cover treatments based entirely on WPATH guidelines. Oregon additionally requires that if a patient is denied coverage for medical or surgical intervention related to gender transition, the clinicians reviewing the patient appeal must complete WPATH-aligned training:

> health care providers reviewing adverse benefit determinations denying or limiting access to gender-affirming treatment complete the "WPATH SOC-8 Health Plan Providers Training," which is specifically designed for providers responsible for such reviews, or an equivalent training.[21]

This is notable as WPATH SOC-8 lists a wide range of procedures that should be provided to patients wishing to receive them. These include, in addition to puberty blockers, cross-sex hormones, mastectomy, and male-to-female or female-to-male genital surgeries, procedures such as vaginoplasty with a "retention of penis and/or testicle" (also known as penis-preserving vaginoplasty), removal of genitals entirely to create a "flat front" appearance, and uterine transplantation for male patients. Procedures listed as potentially necessary also include body contouring, liposuction/lipofilling, facelift, blepharoplasty, various implants, hair transplantation, vocal cord surgery, and a wide range of other appearance-modifying surgical procedures.[22]

10.2 The development of SOC-8 and the Adolescent chapter

Unlike most professional medical associations, WPATH does not require its members to be medical professionals. Full professional membership with voting privileges is also available to professionals in such fields as law, family studies, anthropology, and other areas. Reflecting the diverse aims of its broad membership, WPATH treatment

[21] Oregon Department of Consumer and Business Services (2024a). This position was further strengthened in the final ruling in Oregon Department of Consumer and Business Services (2024b).
[22] Coleman et al. (2022, p. S136).

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guidelines are designed to serve multiple purposes, ranging from clinical care to political advocacy.

Published in 2022, SOC-8 marked WPATH's first attempt to develop guidelines that were "evidence-based" and aimed to meet higher methodological standards through reliance on systematic reviews (SRs) of evidence.[23] The previous version, SOC-7, published in 2011 and described in Chapter 4, under which PMT began rapidly to accelerate, did not rely on SRs. Instead, its recommendations were based on "cultural shifts" and other factors.[24]

In pursuit of its goal to develop an evidence-based guideline, WPATH entered into a contractual agreement with the Evidence-Based Practice Center (EPC) at Johns Hopkins University (JHU), tasking JHU experts with conducting SRs and serving as methodological advisors to ensure a trustworthy guideline development process.[25] Given the sharp increase in the numbers of adolescents seeking PMT, and the rapid growth of pediatric gender clinics and PMT providers in the U.S., WPATH recognized the need to develop a robust adolescent section, acknowledging that "the Adolescent chapter is going to be one of the most scrutinized chapters in the entire standards of care."[26]

As the process of guideline development began, WPATH focused on two cornerstone issues for PMT: the evidence regarding the effectiveness of endocrine interventions in treating GD, and the evidence that adolescents have the capacity to consent to such treatments.

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[23] See Sinai (2022): "The World Professional Association for Transgender Health (WPATH) Standards of Care Version 7 (SOC7) are not evidence-based. The WPATH website clearly states that SOC8 is the first version being developed using an evidence-based approach."
[24] The prior version, SOC-7, stated that its recommendations were "based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender nonconforming people beyond hormone therapy and surgery" (Coleman et al., 2012, p. 166).
[25] Coleman et al. (2022, pp. S248-S249); Karen Robinson is named as the EPC lead and listed as a member of the SOC-8 Guideline Steering Committee.
[26] Boe v. Marshall, No. 2:22-cv-00184: 560-18 (2024, p. 42).

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10.2.1 Hope for evidence of effectiveness

At the outset of its collaboration with JHU's EPC team, WPATH leadership expressed confidence that an SR would yield "evidence-based statements" supporting both the benefits of PMT interventions and the capacity of adolescents to consent to them. SOC-8 Adolescent chapter co-chair Scott Leibowitz wrote:

> We are a unique chapter when it comes to the evidence based review because we do feel that there is a justification to do a literature review on what we postulate will be evidence based statements about the interventions (even though we expect the evidence to be graded low). Essentially the literature reviews on some of our statements—as we plan on submitting once I edit them to incorporate the feedback from our workgroup—are important for the following reasons:
>
> - Studies that demonstrate the psychological effectiveness of some of the interventions (blockers, hormones) in adolescence all included cohorts who went through a rather rigorous psychological assessment. We would like to talk this through as a group because it's a very important point.
> - There is also literature on adolescent decision making and capacity to make informed decisions that carry lifelong ramifications. Since our chapter is a new chapter for the standards of care, and it focuses in on a developmental age group/assessment, (as opposed to other chapters that are more intervention specific), we are going to want to justify certain statements with graded evidence in terms of looking at the literature on *decision making in the developmental cohort (adolescence)* in general.[27]

The JHU evidence evaluation team was presented with the expectation that their appraisal would support the "gender-affirming" medical approach WPATH had been advancing for over a decade. The original plan was for SOC-8 recommendations—asserting that treatment effects are beneficial and that adolescents possess sufficient capacity to consent to medical interventions—to be labeled "evidence-based," even if

[27] Boe v. Marshall, No. 2:22-cv-00184: 560-18 (2024, pp. 43-44).

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the quality of the evidence was low.[28] However, the evidence evaluation challenged WPATH's expectations on both fronts: adolescent capacity to consent, and the benefits of PMT overall.

10.2.2 Adolescent capacity to consent

In response to a request from JHU, Annelou de Vries, the leading Dutch developer of PMT and a co-chair of SOC-8's Adolescent chapter section, supplied the JHU team with publications she believed demonstrate adolescent competence to consent to PMT.[29] Upon reviewing these publications, however, the JHU team informed WPATH that they provided, at best, "limited indirect evidence" and were insufficient to support a statement asserting that adolescents possess the capacity to consent.[30]

Following the JHU team's findings, WPATH abandoned its original plan to base its claim about adolescent capacity to consent on evidence. Instead, the Adolescent chapter of SOC-8 features a section on consent that stresses the importance of careful assessment but cites the same studies that JHU had deemed insufficient to answer the question of competence. The section also features a discussion about the "unique situations in which an adolescent minor is consenting for their own treatment without parental permission."[31]

The section fails to acknowledge the dearth of reliable information about whether adolescents in a state of clinical distress can meaningfully consent to drastic interventions—with many known and some unknown risks—in the absence of

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[28] From a WPATH internal email exchange related to SOC-8: "Adolescent medical decision making literature is something that the Johns Hopkins team is able to help out in terms of a literature review and grading" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 116); for discussion of grading recommendations, see Chapter 9.

[29] The primary investigator of the Dutch Protocol and WPATH Adolescent chapter co-lead (de Vries) provided the relevant literature on adolescent consent for JHU evaluation, writing: "some articles on decision making in teens; these are review articles, but show that there is some evidence. I think we need this sort of evidence base on decision making capacity in adolescents, regarding medical affirming treatment" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 106).

[30] The JHU response to WPATH regarding the literature on adolescent consent to PMT stated, "The articles forwarded provide limited indirect evidence for this question. Please let me know if I missed something" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 106).

[31] Coleman et al. (2022, pp. S61, Section 6.12.c).

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demonstrable physical disease and without credible knowledge of their likely future identity trajectory.

The ethical challenges of obtaining informed consent from adolescents regarding the procedures that are expected to threaten their fertility is illustrated by a candid comment from a WPATH physician, who observed, “it’s always a good theory that you talk about fertility preservation with a 14-year-old, but I know I’m talking to a blank wall,” adding, “they’d be like, ew, kids, babies, gross.”[32]

10.2.3 Treatment effects

In contrast to WPATH’s early abandonment of efforts to evaluate minors' capacity to consent, SRs assessing the treatment effects of puberty blockers (PBs), cross-sex hormones (CSH), and surgeries were completed by the JHU team. As the following sections in this chapter detail, WPATH perceived the JHU evidence appraisals as unfavorable to its goals of promoting broad access to these interventions for minors. In response, WPATH leadership moved to suppress the findings, barring the JHU evidence evaluation team from publishing its results.

The Adolescent chapter does not disclose that the SR regarding the effects of PMT had, in fact, been conducted. Instead, the chapter claims that SRs are not feasible:

> Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible.[33]

Ultimately, SOC-8 recommended that adolescents wishing to undergo PMT be provided with PBs, CSH, and surgery. The recommendations are couched in cautious-sounding language, stating that GD should be “sustained over time,” particularly before administering CSH. However, no clear standard is set; the only guidance offered is the vague and clinically meaningless phrase “several years, leaving critical decisions open to broad and subjective interpretation”:

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[32] Hughes (2024, p. 12).
[33] Coleman et al. (2022, p. S46).

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> Given potential shifts in gender-related experiences and needs during adolescence, it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones or surgeries.[34]

As the following sections describe, the recommendations were deliberately crafted to allow any "willing" medical provider to prescribe hormones or perform surgeries on minors, even those with significant co-occurring mental health conditions.

10.3 The process of creating SOC-8

The creation of trustworthy, evidence-based guidelines requires first assembling a guideline development group (GDG) that is free from conflicts of interest (COI) or, at minimum, where COIs are transparently disclosed and rigorously managed. Only after this foundation is established should SRs proceed, addressing pre-specified guideline questions. Finally, recommendations should be based on SRs of evidence and should consider additional factors, with the aim of improving healthcare quality for individual patients and improving public health and access to care.

Although WPATH originally embarked on an evidence-based guideline development process, internal documents reveal significant deviations from internationally recognized clinical guideline development standards established by organizations such as the National Academy of Medicine[35] (NAM) and the World Health Organization (WHO).[36] These serious deviations from established standards meant that the GDG could not fulfill its promise of producing credible, evidence-based guidelines.

[34] Coleman et al. (2022, p. S60).
[35] Graham et al. (2011), published under its previous name, Institute of Medicine (IOM).
[36] SOC-8's reference to WHO's International Classification of Diseases (ICD) appears to have intended to be WHO's *Handbook for Guideline Development*, 2nd Edition. See Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 204).

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10.3.1 Conflicts of interest management

Managing COIs—both financial[37] and intellectual[38]—is essential for producing trustworthy clinical practice guidelines. Intellectual conflicts may even surpass financial ones in their influence,[39] especially when guidelines rely heavily on expert consensus. The selection of the GDG[40] chair plays a pivotal role in ensuring the integrity of clinical guideline development.[41] WHO recommends selecting a guideline chair who is free of significant conflicts and neutral between differing perspectives.[42] NAM advises using "unconflicted methodologists"[43] to lead recommendation development, working alongside clinical experts as advisors rather than panel members.[44] Both NAM and WHO stress that conflicted members should constitute no more than a minority of any GDG, emphasizing ongoing COI management throughout the entire guideline development process.[45] In 2022, the Endocrine Society adopted NAM's recommendations, prioritizing reduced conflicts even if it limits expert involvement.[46]

When the principal investigator of the JHU EPC team became involved in the SOC-8 process, she observed that they "would expect many, if not most, SOC8 members to have competing interests."[47] SOC-8's final COI statement reads as follows:

> Conflict of interests [sic] were reviewed as part of the selection process for committee members and at the end of the process before publication. No conflicts of interest were deemed significant or consequential.[48]

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[37] The WHO defines financial COI as any "paid work, consulting income or honoraria and travel stipends; support for research, including direct monetary contributions or donations of equipment, laboratory space, etc.;" "that is related to, or could be affected by, the outcome" of the guideline development process (World Health Organization, 2014, p. 63).
[38] NAM and WHO define intellectual COIs relevant to clinical practice guideline development as "academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation" (Guyatt, 2010, p. 739).
[39] Guyatt et al. (2015, p. 540).
[40] SOC-8's GDG comprised a guidelines steering committee with a chair and two co-chairs, who in turn appointed 26 chapter leads, 77 chapter members, and 16 stakeholders.
[41] Graham et al. (2011, p. 87).
[42] World Health Organization (2014, p. 61).
[43] Graham et al. (2011, pp. 81-82).
[44] World Health Organization (2014, p. 82).
[45] Graham et al. (2011, p. 7).
[46] McCartney et al. (2022).
[47] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 2).
[48] Coleman et al. (2022, p. S177).

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Based in part on correspondence between WPATH and the EPC team during the development of SOC-8, there are serious questions regarding the accuracy of this statement.

SOC-8 GDG members, including Chair Eli Coleman, had unmanaged financial and/or non-financial COIs that were plausibly "significant or consequential." Coleman had both financial and non-financial interests in the topic. He was the lead author of SOC-7[49] and had coauthored academic publications in support of expanded access to medical transition.[50] Using WHO criteria, his professional activities and academic profile, which were closely aligned with advancing medical transition, likely constitute both intellectual and financial COIs.[51]

Additionally, Coleman's academic work was supported with funding from the Tawani Foundation, chaired by Jennifer Pritzker, a philanthropist and advocate for transgender issues.[52] The foundation funded a research center at the University of Minnesota, and Coleman played a significant role in its development. Public statements confirm that the Tawani Foundation also funded the majority of the out-of-pocket costs associated with SOC-8's development.[53]

With Coleman as chair of the GDG, the importance of managing COIs appears to have been consistently misunderstood or undervalued. Coleman admitted under deposition that disclosure statements were not presented until at least six months *after* members had already been selected.[54] In a December 21 (2018) email sent to the SOC-8 education committee, EPC's Karen Robinson stated, "Disclosure, and any necessary

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[49] Coleman et al. (2012).
[50] Eisenberg et al. (2020); Rider et al. (2018).
[51] "Financial and nonfinancial interests can overlap. For example, intellectual interests related to career advancement obviously have a monetary component. Examples of roles or positions that might interfere with the objective assessment of a body of evidence include: prior publication of a study or SR that is part of the evidence base under consideration in the guideline; prior public declaration of a firm opinion or position, as in public testimony during a regulatory or judicial process, or in an editorial in a journal; or professional or personal affiliation with an organization advocating for products or services related to the subject of the guideline" (World Health Organization, 2014, p. 63).
[52] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 239).
[53] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 239).
[54] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, pp. 219-222).

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management of potential conflicts, should take place prior to the selection of guideline members. Unfortunately, this was not done here."[55]

For former WPATH president Marci Bowers, who played an influential role in shaping SOC-8, the idea of appointing an unconflicted professional to lead the project was outright nonsensical.[56] Another SOC-8 member wrote to the EPC to explain that "unlike other medical guidelines, trans health care is a socially and politically charged issue," and strongly recommended that the JHU team therefore rewrite their COI forms for this particular guideline.[57] Part of the justification for different treatment was that COIs were so prevalent within the GDG that it would be "impossible" for the group to be free of them.[58] One submitted COI form, on the question of non-financial interests, recorded that "everyone involved in the SOC process has a non-financial interest."[59]

Although WPATH later claimed that none of the SOC-8 members' COIs were significant or consequential, several members clearly met the internationally recognized definitions of COIs established by the NAM and WHO—the kind of conflicts known to bias clinical practice guidelines and erode their trustworthiness. For instance, SOC-8 chapter leaders Dan Karasic and Loren Schechter were paid expert witnesses in legal cases directly related to medical transition before and during the SOC-8 development process,[60] a role NAM explicitly identifies as a COI.[61] Schechter, co-chair of the surgery chapter and a plastic surgeon who derives part of his livelihood from performing gender

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[55] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 2).
[56] Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024, p. 121).
[57] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 3).
[58] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 3).
[59] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 8).
[60] Schechter provided testimony for Dekker v. Weida, No. 4:22-cv-00325 (N.D. Fla. filed Sept. 7, 2022); Willis v. Flagg, No. 17-cv-02754 (N.D. Ill. filed Apr. 10, 2017); Bruce v. South Dakota, No. 3:17-cv-03023-RAL (D.S.D. filed Oct. 5, 2017); Boyden v. Conlin, No. 17-cv-00264-WMC (W.D. Wis. filed Apr. 6, 2017); Kadel v. Folwell, No. 1:19-cv-00272 (M.D.N.C. filed Mar. 11, 2019); Toomey v. State of Arizona, No. 4:19-cv-00035-RM-LAB (D. Ariz. filed Jan. 23, 2019); and Fain v. Crouch, No. 3:20-cv-00740 (S.D.W. Va. filed Nov. 12, 2020).

Karasic provided testimony for C.P. v. Blue Cross Blue Shield of Illinois, No. 3:20-cv-06145 (W.D. Wash. filed Nov. 24, 2020); Kadel v. Folwell, No. 1:19-cv-00272 (M.D.N.C. filed Mar. 11, 2019); Fain v. Crouch, No. 3:20-cv-00740 (S.D.W. Va. filed Nov. 12, 2020); Brandt v. Rutledge, No. 4:21-cv-00450 (E.D. Ark. filed May 25, 2021); K.C. v. Individual Members of the Indiana Medical Licensing Board, No. 1:23-cv-00595-JPH-KMB (S.D. Ind. filed Apr. 5, 2023); Dekker v. Weida, No. 4:22-cv-00325-RH-MAF (N.D. Fla. filed Sept. 7, 2022); and Doe v. Ladapo, No. 4:23-cv-00114-RH-MAF (N.D. Fla. filed Mar. 23, 2023).
[61] Graham et al. (2011, p. 79).

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transition surgeries, voiced concerns to fellow GDG members about openly acknowledging insufficient evidence, noting the potential impact this would have on two federal court cases in which he was serving as a paid expert witness.[62] Despite this clear overlap of financial interest and guideline content, SOC-8 chair Eli Coleman considered it "ethically justifiable" for members involved in active litigation to advocate for guideline changes that could strengthen their legal positions.[63]

WPATH's process not only permitted significant financial and intellectual COIs among GDG members. It also allowed the creation of substantial panel composition bias—a phenomenon known as "panel stacking." This occurs when GDGs predominantly consist of members sharing similar viewpoints or vested interests, thereby threatening the validity and trustworthiness of clinical guidelines. Experts in evidence-based medicine describe panel stacking as a major threat, emphasizing that it can profoundly reduce the credibility of recommendations, particularly when, as in pediatric gender medicine, the evidence is limited, contentious, or unsystematically reviewed.[64]

Kepp et al. note that "recruitment specifically because of expressed viewpoints and allegiance is a recognized major problem for guideline development." In their own example from an appraisal of a consensus statement on COVID-19 recommendations, the authors characterized a panel with a "35% (or more) prevalence" of advocates of COVID-19 elimination ("Zero-COVID") as "extreme."[65] For SOC-8, WPATH required that all members of the GDG be "WPATH Full Members in good standing."[66] Marci Bowers explicitly stated that it was important for participants to be "advocates" for WPATH's "gender-affirming" approach to be considered for the GDG,[67] further underscoring the GDG's bias.

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[62] Boe v. Marshall, No. 2:22-cv-00184: 700-13 (2024, p. 56).
[63] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 158).
[64] Kepp et al. (2024, p. 5).
[65] Kepp et al. (2024, p. 6).
[66] Coleman et al. (2022, p. 248).
[67] Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024, pp. 119-120). This response came after it was pointed out to Bowers that selecting GDG members based on their "advocacy" for medical treatment was in "tension" with selecting GDG members who could be "impartial arbiters" on the evidence for those treatments.

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Internal documents revealed that WPATH actively monitored SOC-8 members and disciplined those who publicly questioned WPATH's "gender-affirming" approach, creating an environment that discouraged critical dialogue. Psychologist Laura Edwards-Leeper, chair of WPATH's Child and Adolescent Committee and a member of both the child and adolescent SOC-8 committees, co-authored a *Washington Post* opinion piece with Erica Anderson,[68] a psychologist and then-president of WPATH's U.S. chapter, arguing that WPATH "largely seems to be a dangerous echo chamber" resistant to constructive criticism. Edwards-Leeper privately warned WPATH leaders that their intolerance for dissent and attempts to "muzzle clinicians" risked damaging the organization's credibility among professionals, patients, and educated parents.[69] Anderson faced a formal reprimand[70] after criticizing (with Bowers) the quality and consistency of care provided under the SOC framework.[71]

This combination of poorly managed COIs and restrictive membership practices significantly undermines the credibility and scientific integrity of SOC-8 as a clinical practice guideline. The GDG's handling of the SRs of evidence WPATH commissioned for development of SOC-8 further highlights the serious threat to clinical integrity that plagued the guideline development process.

10.3.2 Suppression of evidence

NAM stipulates that trustworthy guidelines must be based on SRs of existing evidence. SOC-8 was promoted as the first to be "evidence-based,"[72] with its chair claiming it followed "the most rigorous protocol in the world to ensure these standards reflect scientific evidence."[73] The Methodology section states that SOC-8 "incorporated the recommendations on clinical practice guideline development set forth by the National

[68] Edwards-Leeper & Anderson (2021).
[69] Boe v. Marshall, No. 2:22-cv-00184: 560-26 (2024, p. 153).
[70] Boe v. Marshall, No. 2:22-cv-00184: 560-26 (2024, pp. 114-115).
[71] Shrier (2021b).
[72] "This version of the Standards of Care is the first to be developed using an evidence-based approach" (Radix, n.d., p. 13).
[73] Coleman (2023).

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Academies of Medicine and the World Health Organization, which addressed transparency, conflict-of-interest policy, committee composition, and group process."[74]

In 2018, as part of its development of a new clinical guideline, WPATH commissioned more than a dozen SRs from the EPC at JHU. SRs were completed and handed over to WPATH for its chapters on assessment, primary care, endocrinology, surgery, reproductive medicine, and voice therapy.[75]

These expert reviews had the potential to advance current understanding of the state of the evidence, but their usefulness cannot be evaluated because WPATH successfully suppressed them. In an email exchange from August 2020, a senior author from EPC, writing to the Agency for Healthcare Research and Quality (AHRQ),[76] stated that their SRs "found little to no evidence about children and adolescents" and that WPATH had been "trying to restrict our [JHU's] ability to publish."[77]

In a memo to all SOC-8 working group members, WPATH leadership reported that they "were caught on the wrong foot" when they learned that JHU wanted to publish reviews that would likely undermine WPATH's "gender-affirming" approach.[78] Despite their initial resistance, the JHU researchers ultimately capitulated to WPATH's new terms, allowing SOC-8's chair, co-chairs, a handpicked chapter member, and WPATH's Board of Directors to pre-approve manuscript content before any independent drafting could occur. Under WPATH's imposed process, researchers were required to submit a proposal form outlining the planned results and conclusions before drafting even began—and again once the manuscript was ready for publication—ensuring that leadership could steer findings to align with predetermined agendas rather than allowing an independent, evidence-driven process.[79]

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[74] Coleman et al. (2022, p. S247).
[75] Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 38).
[76] A unit of the U.S. Department of Health and Human Services.
[77] Boe v. Marshall, No. 2:22-cv-00184: 560-23 (2024, p. 23) The AHRQ official acknowledged the message: "Knowing that there is little/no evidence about children and adolescents is helpful." Nevertheless, two years later HHS released a memo in which it asserted that "[r]esearch demonstrates that gender-affirming care improves the mental health and overall well-being of gender diverse children and adolescents" (OPA: Office of Population Affairs, n.d.).
[78] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, p. 14).
[79] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, p. 8).

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Figure 10.1 WPATH approval process for manuscripts

1. The lead author submits a proposal of the publication to WPATH with the following headings: Background; Aim(s); Method; Results;

WPATH Policy Use of Data for SOC8 – Version 2
Approved by WPATH Board of Directors – August 2020

JHU_000003198

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Conclusion (Maximum 1 page and states which SOC8 chapter the publication is linked to);

2. It is WPATH's responsibility that the proposal is shared with the Chair and Co-Chairs of the SOC8, the members of the WPATH Board of Directors and all members of the SOC8 chapter linked to the proposed publication within 14 days after receipt of the proposal. The aim will be to identify an individual (s) from the chapter (maximum 2 individuals if a publication concerns more than one chapter) who will work with the lead author(s) of the proposed publication (unless the lead author is already working with one or more Working Group members); it is the responsibility of the Working Group as a whole to identify and to nominate one of their members, either by vote or general consensus within the Working Group.
3. WPATH will keep a record of the possible proposals with deadlines for draft submissions - in order to avoid the development of multiple papers with the same aims using the same data;
4. It is WPATH Executive Committee's responsibility to ensure that a vote is held within 30 days after the dissemination of the proposal.
5. It will be a blind vote and approval to write the paper is granted to the author(s) by majority vote. In case of a tie, the WPATH President will have the deciding vote.
6. It is the President's responsibility to respond to the author(s) with approval or disapproval within fifty-six (56) days of submission of the proposal to WPATH.
7. Once the manuscript draft is ready for publication, the lead author will submit the publication to WPATH
8. It is WPATH Executive Committee's responsibility to ensure that the manuscript is disseminated to the Chair of the SOC8, the Co-Chairs of the SOC8, and the members of the WPATH Board of Directors within 7 days after receipt of the manuscript.
9. It is WPATH Executive Committee's responsibility to ensure that a vote is held within 14 days after the dissemination of the manuscript to the Chair and Co-Chairs of the SOC8 and Board members.
10. It will be a blind vote and approval is granted to author(s) for publication by majority vote. The Chair and Co-Chairs of the SOC8 and Board members all have one equal vote. In case of a tie, the WPATH President will have the deciding vote.

Among the terms required for gaining WPATH approval was ensuring that the SRs' findings supported, or at least did not undermine, WPATH's goal of promoting greater access to medical interventions. Additionally, the SOC-8 chapter's working group leader or an appointed representative or the SOC-8 chair/co-chairs and at least one person

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who identified as transgender were required to oversee and approve the manuscript's design, drafting, and final content.[80]

Despite this close involvement and editorial control, all final documents were required to include a statement to the effect that "the authors are solely responsible for the content of the manuscript, and the manuscript does not necessarily reflect the view of WPATH."[81]

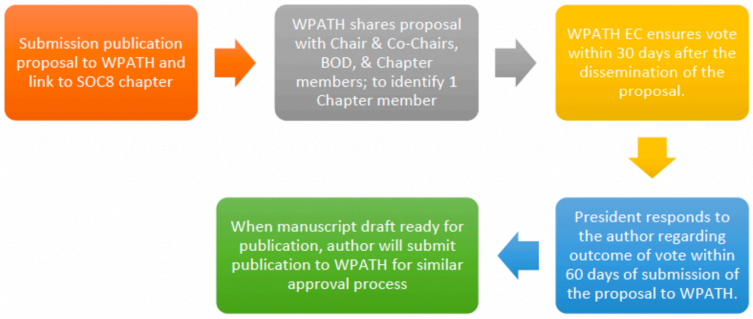
Figure 10.2 Pathway to manuscript approval

Pathway to approval for use of WPATH Data

WPATH grants approval to use the Data for publication to any interested party, when:

a. the directives outlined under the aim of this policy have been fulfilled and;
b. the author(s) have acknowledged that WPATH has sponsored the acquisition of the data in the publication and;
c. the author(s) have acknowledged that the authors are solely responsible for the content of the manuscript, and the manuscript does not necessarily reflect the view of WPATH in the publication and;
d. The publication ("manuscript") has been approved by WPATH via a designated approval process.

Designated approval process for publication of Data (see Figure 1)



WPATH's stated goal was to "ensure that publication does not negatively affect the provision of transgender healthcare in the broadest sense."[82] Following this

[80] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, pp. 5-6).
[81] Boe v. Marshall, No. 2:22-cv-00184: 523-1 Exhibit 1 (n.d., p. 8)
[82] Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 92).

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renegotiation, only one SR was published.[83] Internal WPATH documents reveal that Baker et al. complied with all the mandatory steps of WPATH's updated approval policy—from approving the conclusions before the manuscript was drafted to ensuring extensive WPATH engagement in the process and obtaining the final approvals. The Baker et al. SR was published with the mandatory disclaimer that "WPATH had no role in study design, data collection, analysis, interpretation, or drafting" of the SR, despite the checklist clearly recording that WPATH had engaged in the design, drafting, and final approval of the article.[84]

[83] Baker et al. (2021). Of note, only one other systematic review was published (Wilson et al., 2020), but its publication predates WPATH's updated policy.

[84] Wilson et al. (2020) includes the same statement but was published prior to the new agreement, so it is not possible to determine the degree to which WPATH influenced its drafting and design.

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Figure 10.3 Checklist for Baker et al.[85]

Checklist for JHU SOC8 systematic review papers

Title of Paper: Hormone Therapy, Mental Health, and Quality of Life among Transgender People: A Systematic Review

Supporting Chapter: initial question part of questions from Hormone Chapter

Proposed Authors: Kellan E. Baker, MPH, Lisa M. Wilson, ScM, Ritu Sharma, BSc, Vadim Dukhanin, MD, MHS, Kristen McArthur, BA, Karen A. Robinson, PhD

Acknowledged Authors: None

Yes or No	This paper provides data that advances the knowledge in the field of transgender health in a positive way
Yes or No	This paper will be published in a reputable, academic, peer-reviewed journal
	Journal proposed for first submission The Lancet Diabetes & Endocrinology
Yes or No	Involves the work group leader of the chapter or alternatively a designated representative of that specific SOC8 Chapter in the design, drafting of the article and final approval of the article
	Name of persons involved *chapter members provided original list of questions for reviews*
Yes or No	Involves at least one member of the transgender community in the design, drafting of the article and final approval of the article *chapter members provided original list of questions for reviews*
	Name of person if not open about trans status, if not open about trans status then enter N/A
Yes or No	Adheres to the WPATH language policy

WPATH's policy appears to have effectively blocked the planned[86] and completed[87] research—including critical evidence appraisals—from being developed into publishable manuscripts. As a result, important SRs addressing the safety of PBs, CSH, and surgery for adolescents were suppressed, keeping key findings out of the scientific record and shielding them from professional scrutiny.[88]

[85] Source: Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 41).
[86] Robinson, Sharma, Baker, et al. (2019); Robinson, Sharma, Wilson, et al. (2019); Sharma et al. (2018).
[87] In total, only 2 systematic reviews were published, and only one (Baker et al., 2021) followed the policy update.
[88] See Chapter 7 for a more extensive discussion.

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As established in Section 10.3.1, members of the GDG were committed to PMT and believed their positions to be grounded in evidence. Indeed, a central goal for SOC-8 was to deliver an updated version explicitly supported by robust evidence. However, once the GDG began working with methodological experts and applying evidence-based medicine (EBM) standards, it quickly became clear that their understanding of what constituted "strong evidence" was fundamentally at odds with established scientific criteria. Evidence that the GDG previously regarded as strong or compelling was frequently downgraded under EBM standards to low or very low quality, revealing a troubling gap between WPATH members' beliefs about evidence and the actual rigor of the underlying research. This process is clearly articulated by SOC-8 Chair Eli Coleman under points 6 ("Expert Consultation in Guideline Development") and 7 ("Research Agenda") of a 12-point draft following SOC-8's publication:

> As we faced challenges of developing and revising the methodology of SOC 8, we had to rely on Johns Hopkins, which while some degree helpful, was very constraining. We were able to consult with other experts and was [sic] able to learn that there were other ways of developing guidelines that were probably more appropriate for the state of our science. As a result, our methodology evolved and was improved—however, we were not able to be as systematic as we could have been … Now that we have reviewed the evidence, we are painfully aware of the gaps in the literature and the kinds of research that are needed to support our recommendations and strengthened [sic] the level of evidence in support of them.[89]

When confronted with SRs that did not adequately support its positions—particularly given their stated legal and advocacy concerns (see next section)—the GDG chose not to adjust its views but to find an alternative methodology to support its recommendations. As SOC-8 GDG Co-Chair Jon Arcelus explained in an email to other GDG members, "[t]here are many recommendations in the SOC that don't have direct

[89] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, pp. 8-9).

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evidence (most of the direct evidence is in the hormone chapter) but they have background evidence. This is why we have Delphi."[90]

A consensus-building process, Delphi is not a substitute for evidence-based recommendations but rather a method for GDGs to reconcile disagreement in the interpretation of SRs, or in deciding how evidence should inform treatment recommendations.[91] Guidelines that are not based on SRs inadvertently risk promoting suboptimal or even harmful care. This is why guidelines that rely only on consensus are not considered trustworthy.[92]

10.3.3 Redefinition of medical necessity

SOC-8 makes a strong recommendation that PBs, CSH, and surgery be considered "medically necessary" for eligible adolescents:

> We recommend health care systems should provide medically necessary gender affirming psychological, medical and surgical treatments for trans and gender diverse children, adolescents, and adults."[93]

The development of the "medical necessity" statement in SOC-8 starkly illustrates how many WPATH contributors prioritized goals other than ensuring the highest-quality care for adolescents with GD. A good example is WPATH's rewording of patient "wishes" as patient "needs" with the intent to frame them as "medically necessary." At first, the statement described the desired interventions as "wishes":

> There is strong evidence demonstrating the benefits in quality of life and wellbeing of gender affirming treatments, including endocrine and surgical procedures, properly indicated and performed as outlined by the Standards of Care (Version 8), in TGD people *wishing these treatments.*[94]

However, the final SOC-8 statement reads:

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[90] Boe v. Marshall, No. 2:22-cv-00184: 560-37 (2024, p. 101). Delphi is a structured consensus-building method in which a GDG iteratively reviews and rates statements to achieve agreement; SOC-8 utilized a 75% threshold for consensus.
[91] Djulbegovic & Guyatt (2019).
[92] Lima, Tangamornsuksan et al. (2023).
[93] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 32).
[94] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 38).

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> There is strong evidence demonstrating the benefits in quality of life and well-being of gender-affirming treatments, including endocrine and surgical procedures, properly indicated and performed as outlined by the Standards of Care (Version 8), in TGD people *in need of these treatments*.[95]

This consequential textual change was the result of WPATH members recognizing the implications of their word choice for insurance and legal contexts. The change was made based on the following request during the drafting phase:

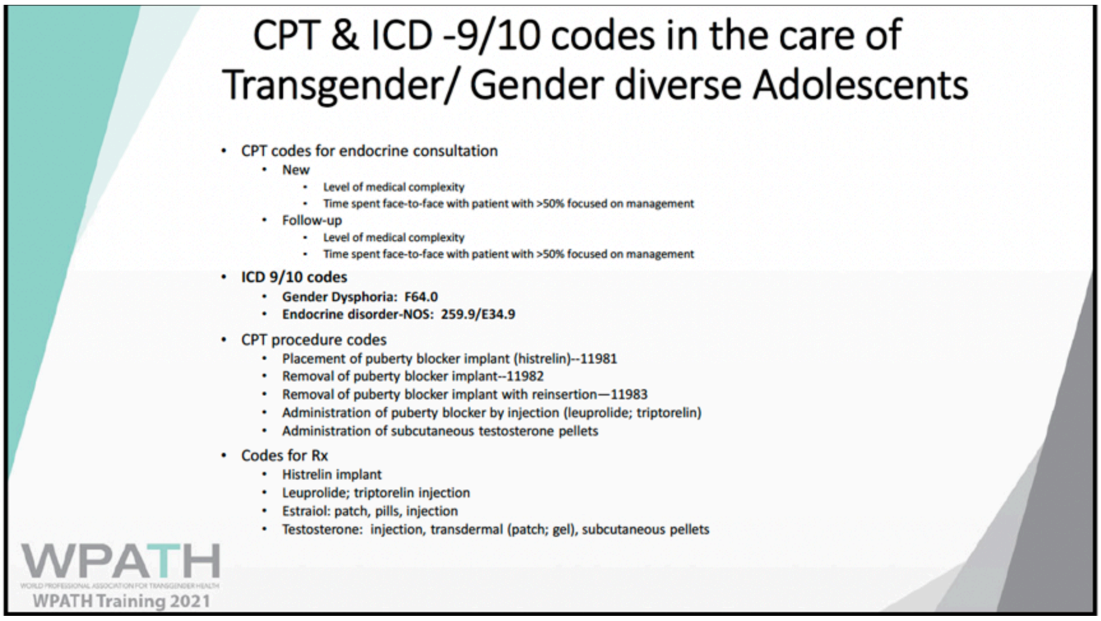
> Thank you, I also very much like this statement and the supporting write-up. There is one word, though, in the middle (on the right side of the page) of the last paragraph on the first page of the document: “wishing.” This word gives me pause, and perhaps I am being too sensitive, but one of the biggest obstacles trans people experience in getting support for coverage of our care is that we are told “you can't always get what you want" and “wishing does not make it so." Wishing makes the needed care seem optional, and we are often told we are imagining that we are not who we are and we should just suck it up. Would it be possible or advisable or prudent to replace “wishing” with “in need of” here? Thanks for your consideration, and for your great work on this.[96]

This was accompanied by WPATH’s explicit instruction to providers to use the “Endocrine Disorder” diagnosis as an alternative for the mental health diagnosis of GD[97]:

[95] Coleman et al. (2022, p. 18, emphasis added).
[96] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 28).
[97] Rosenthal (2021b, Slide 11).

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Figure 10.4 ICD codes for TGD adolescents



Together, these internal WPATH communications reveal that the "medical necessity" framing in SOC-8 was constructed to remove key safeguarding criteria and make patient desires central to treatment decisions. This was confirmed by another GDG member who candidly observed that the guidelines exist to allow any “goodwilling” clinician to meet patients’ wishes—however medically inappropriate they may be.

> I think it is clear as hell that the SOC8 refers to the necessity of treatment (in its broadest sense) of TGD people who pursue treatment (in its broadest sense) for their gender dysphoria (small "d": because it refers to the symptom of distress - which is a very broad category and one that any 'goodwilling' clinician can use for this purpose (or: in the unescapable medical lingo we, as physicians arc stuck with: those who fulfil a diagnosis of Gender Dysphoria and Gender Incongruence as per APA/WHO).[98]

The request to substitute “wish” for “need” and emphasize "medical necessity” was welcomed by WPATH leaders, who responded that the assertion of medical necessity

[98] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 37).

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would influence the “obtuse and unhealthy” U.S. healthcare system by compelling insurance coverage through the courts:

> Thank you for putting this together; you've done a great job with this. Indeed, it is important that such a statement is part of the actual SOC. And, indeed, the original Medical Necessity Statement was specific to the U.S. because this was where we were experiencing the problem with our obtuse and unhealthy system of healthcare "coverage" and we needed a tool for our attorneys to use in defending access to care here. I have long wanted this (and many of our other policy statements) to become part of the SOC because that gives them greater force.[99]

GDG Chair Eli Coleman stated that while WPATH had no definition of “medically necessary,” he understood this to be primarily a term used by insurance companies to determine which conditions or procedures to cover.[100] The SOC-8 legal and political goals are discussed in the next section.

10.3.4 Legal and political considerations

Internal documents reveal that SOC-8 authors manipulated guideline language with the explicit aim of shaping court rulings, legislative actions, and insurance coverage decisions, revealing a clear departure from the principles of unbiased, evidence-driven clinical guideline development. For example, contributors to the “Institutional Environments” chapter disclosed that “social justice lawyers” had advised them against rigorous evidence reviews, stating that such reviews might reveal limited or insufficient evidence, placing them “in an untenable position in terms of affecting policy or winning lawsuits.”[101] As discussed above, a key motivation for including a “medical necessity” statement in the guidelines was described as a strategic move to provide “a tool for our attorneys to use in defending access to care” within the U.S. legal context.[102]

[99] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, pp. 33-34)
[100] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 166).
[101] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 3).
[102] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, pp. 33-34).

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Schechter also expressed concerns about language, cautioning colleagues that terms such as “insufficient evidence” and “limited data” could strengthen legal arguments claiming medical interventions are experimental, and noting his own role as an expert witness in related federal cases.[103] Karasic, chair of the SOC-8 Mental Health chapter, highlighted the critical legal implications of defining treatments for adolescents as “medically necessary,” stating that this determination affects court cases, policy decisions, and insurance coverage.[104] Elsewhere, Karasic emphasized the urgency of addressing this issue clearly in SOC-8 given multiple ongoing lawsuits—some potentially reaching the Supreme Court of the United States—concerning whether medical gender interventions are “medically necessary” or “experimental or cosmetic.”[105]

One internal communication explicitly advised against using specific numerical age guidelines for treatments, stating, “I would avoid absolute numbers [for ages] that can be taken out of context or used in court” because they would disadvantage the people “we are trying to advocate for.”[106] Elsewhere, editorial input was provided specifically to help “Chase” [presumably a reference to Chase Strangio, Deputy Director for Transgender Justice with the ACLU’s LGBT & HIV Project].[107] GDG Chair Coleman urged the group to adopt a stronger defensive stance, stating, “we need a more detailed defense that we can use ... in the many court cases that will be coming up … especially around adolescence.”[108] One contributor even acknowledged prioritizing political advocacy goals explicitly over scientific accuracy, stating that SOC-8 should “land in such a way as to have serious effect in the law and policy settings...even if the wording isn’t quite correct for people who have the background you and I have.”[109]

Further, the U.S. healthcare context was clearly a specific focus of the SOC-8 authors. Karasic (SOC-8 Mental Health chapter chair) wrote:

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[103] Boe v. Marshall, No. 2:22-cv-00184: 700-13 (2024, p. 56).
[104] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 43).
[105] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 44).
[106] Boe v. Marshall, No. 2:22-cv-00184: 560-34 (2024, p. 25).
[107] Boe v. Marshall, No. 2:22-cv-00184: 591-24 (2024, p. 9).
[108] Boe v. Marshall, No. 2:22-cv-00184: 700-8 (2024, p. 40).
[109] Boe v. Marshall, No. 2:22-cv-00184: 560-34 (2024, p. 25).

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> But there are elements of the Medical Necessity statement that are critical to insurance reimbursement and access to care in the U.S., though not so in every country, and these should have a place somewhere in SOC 8. If WPATH SOC 8 fails to adequately support access to trans care in the U.S. by overgeneralizing wording, it may be globally applicable, but it is not globally useful, insofar as the U.S. is part of the globe. There should be room in SOC 8 to address concerns of national health systems, or other non-reimbursement focused systems without making SOC 8 less useful to U.S. trans care … Medical necessity is at the center of dozens of lawsuits in the U.S. right now over state actions to make trans care inaccessible, as well as being at the center of all reimbursement for trans care in the U.S. … it is critical that WPATH SOC 8 gets this right, which I think it does, currently."[110]

Incorporation of legal advocacy goals into guideline language, explicitly for purposes of influencing policy and litigation outcomes, conflicts sharply with accepted international standards emphasizing scientific rigor and impartiality.

Internal documents reveal that WPATH leadership was aware that the guidelines would be criticized due to the "continuing pressure in healthcare to provide evidence-based care." Coleman noted ongoing resistance from "academics and scientists who are naturally skeptical," "parents of youth who are caught in the middle of this controversy," and pressures arising from the "increasing number of regret cases and individuals who are vocal in their retransition process who are quick to blame clinicians for allowing themselves to transition despite an informed consent process."[111]

In response to anticipated criticism of SOC-8, Coleman drafted a "12-point strategic plan to advance gender-affirming care."[112] The plan acknowledged that all members of the GDG were "painfully aware that there are many gaps in research to back up our recommendations," and emphasized the importance of building consensus among

[110] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 65).
[111] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, p. 5).
[112] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, p. 6).

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medical groups in support of SOC-8. Coleman observed that the endorsement of medical organizations "has been an extremely powerful argument" in "legal battles":[113]

> As we are facing so many legal battles over trans health care and rights, the statement that the SOC has so many endorsements has been an extremely powerful argument. We need to be able to get the support of these important organizations and know how to indicate their support accurately or this argument in these court cases could be challenged.[114]

10.4 Elimination of age minimums

The handling of minimum age recommendations for clinical interventions for adolescents in SOC-8 exemplifies what happens when guideline development is compromised by ideological beliefs, COIs, and disregard for established evidence standards.

Initially, SOC-8 included age minimums for certain interventions: 14 years for cross-sex hormones; 15 years for mastectomy; 16 years for breast augmentation and facial surgery; 17 years for metoidioplasty, orchiectomy, vaginoplasty, hysterectomy, and fronto-orbital remodeling; and 18 years for phalloplasty. In July 2022, WPATH faced significant pressure from Admiral Rachel Levine, the U.S. assistant secretary for health, whose office communicated concern that listing specific, minor ages would trigger restrictive legislative actions. Internally, some SOC-8 members expressed discomfort about acceding to pressures from the federal government. "I don't know how I feel about allowing U.S. politics to dictate international professional clinical guidelines that went through Delphi," said one SOC-8 co-chair.[115] Another complained that it "is not appropriate to take any feedback from a nonmedical professional seriously."[116] Despite these reservations, WPATH's apparent investment in securing endorsement from the

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[113] Boe v. Marshall, No. 2:22-cv-00184: 560-40 (2024, pp. 6-8). Of note, although SOC-7 is now outdated, it was SOC-7 that was responsible for establishing the "gender-affirming" medical approach in the U.S. and internationally. The email from the lead author of both SOC-7 and SOC-8, Coleman, discloses that despite the widespread narrative that SOC-7 had been endorsed by all medical organizations, no such endorsements ever occurred. Coleman said he had "no idea how it was ever said that so many medical organizations … endorsed SOC 7" (Boe v. Marshall, No. 2:22-cv-00184: 700-3, 2024, pp. 262-264).
[114] Boe v. Marshall, No. 2:22-cv-00184: 560-40 (2024, p. 8).
[115] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 33).
[116] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 27).

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Biden administration led it to agree to downgrade age guidelines from "recommendations" to "suggestions," thereby circumventing the original consensus process by making these changes without conducting a new round of validation.[117]

The issue of minimum ages resurfaced when the American Academy of Pediatrics (AAP) threatened to publicly oppose SOC-8 unless all age thresholds were eliminated—further exposing how political pressure, rather than scientific evidence or clinical judgment, dictated the final content of the guidelines.[118] Under pressure and facing open opposition from a key ally, WPATH leaders capitulated and agreed to eliminate minimum age criteria for all hormonal and surgical procedures (except phalloplasty). They did so despite acknowledging privately that the individuals within the AAP who were issuing the demand were very junior and lacked the authority or expertise to credibly dictate clinical standards.[119]

In the process of removing minimum ages, WPATH's president wrote that it was "disappointing that politics always trumps common sense and what is best for patients."[120] Another WPATH leader confided that the deletion of age minimums "is a balancing act between what I feel to be true and what we need to say."[121] SOC-8 Co-Chair Jon Arcelus said that removing ages would "make a joke of our methodology."[122]

The rushed, 11th-hour changes—made outside any formal or transparent guideline development process—resulted in SOC-8 initially being published with its original age recommendations still intact. Only after publication did WPATH scramble to issue a correction via an erratum in their official journal, the *International Journal of Transgender Health*, quietly removing age restrictions to align with political demands rather than clinical evidence.[123] The current, published version of SOC-8 states that all

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[117] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, pp. 292-295); Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 33). SOC-8's final round of Delphi processing was in January 2022 (Coleman et al., 2022, p. S251).
[118] Coleman explains that removing ages "led to them [i.e. AAP] formally not opposing the SOC. Yes this is highly confidential" (Boe v. Marshall, No. 2:22-cv-00184: 700-17, 2024, p. 153).
[119] Boe v. Marshall, No. 2:22-cv-00184: 700-16 (2024, p. 201).
[120] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 26).
[121] Boe v. Marshall, No. 2:22-cv-00184: 700-6 (2024, p. 103).
[122] Boe v. Marshall, No. 2:22-cv-00184: 700-16 (2024, p. 110).
[123] Correction (2022).

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recommendations went through the Delphi process. However, Coleman later acknowledged that removal of age minimums did not go through Delphi.[124]

10.5 Continued reliance on SOC-8

It remains concerning that SOC-8 continues to exert substantial influence over U.S. healthcare. WPATH's misconduct during the development of SOC-8 was covered by major news outlets including the *New York Times*,[125] *Economist*,[126] *Boston Globe*,[127] *Fox News,*[128] and *National Review,*[129] as well as by the *BMJ*, a leading medical journal.[130] Despite these reports, with the exception of the American Society of Plastic Surgeons,[131] major American medical associations have not issued public statements addressing the concerns detailed in this chapter.

In an amicus brief submitted to the Supreme Court of the United States for the upcoming case *U.S. v. Skrmetti*,[132] the AAP and 21 other medical organizations describe SOC-8 as an "established, evidence-based clinical guideline." The brief does not address any of the concerns or revelations regarding the guidelines' development outlined in this chapter. Similarly, a group of 11 prominent "adolescent medicine specialists, pediatricians, clinicians, methodologists, professors, and researchers"—including professionals affiliated with the medical schools of Harvard University, Stanford University, and the University of Pennsylvania—asserts in a separate brief that SOC-8 has "all" the National Academy of Medicine's "hallmarks of reliability."[133]

The U.S. Department of Justice (DOJ) intervened in 2022 to challenge Alabama's age limit law in *Boe v. Marshall*, thereby becoming familiar with the subpoenaed documents from WPATH. Nevertheless, in August 2024—two months after the documents were unsealed—the DOJ in a merits brief filed in *U.S. v. Skrmetti* described WPATH as "the

[124] Boe v. Marshall, No. 2:22-Cv-00184: 700-3 (2024, pp. 294-295).
[125] Ghorayshi (2024b).
[126] The Economist (2024).
[127] Selin Davis (2024b).
[128] Joseph (2024).
[129] Whelan (2024a).
[130] Block (2024a).
[131] Sapir (2024c).
[132] U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024, p. 8).
[133] U.S. v. Skrmetti (No. 23-477), Clinical Practice Guideline Experts, Amicus curiae brief (2024, p. 22).

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leading association of medical professionals treating transgender individuals" and asserted that "[t]he Nation's leading medical and mental health organizations recognize [SOC-8] as reflecting the accepted standard of care for treating gender dysphoria."[134]

[134] U.S. v. Skrmetti (No. 23-477), Brief for the petitioner (2024, p. 3).

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Chapter 11 Collapse of Medical Safeguarding

When children or adolescents develop feelings of severe discomfort with their sexed bodies, parents understandably worry and consult pediatricians or therapists for advice. These frontline clinicians in turn refer them to specialists, believing that this requires special expertise. Both parents and the clinicians they initially consult likely expect that those with expertise in "gender" will conduct a comprehensive evaluation to rule out other, perhaps more common causes of such feelings. They may further assume that puberty blockers (PBs), cross-sex hormones (CSH), and surgery are offered only in rare cases, when less invasive alternatives are ineffective, and after careful consideration of the patient's unique developmental needs as well as the profound uncertainties and risks of the treatments.

This chapter documents how the original Dutch Protocol that underpins pediatric medical transition (PMT) has undergone transformation in the U.S. to become a "child led" process in which the patient's personal "embodiment goals" form the basis for the determination of "medical necessity." Section 11.1 revisits the Dutch Protocol (critically assessed in earlier chapters) and explores how the original safeguards on the practice of pediatric medical transition (PMT) have been systematically dismantled in the U.S. Section 11.2 evaluates the frequent assertion that PMT is "rare," questioning whether this claimed infrequency genuinely indicates rigorous assessment standards. Section 11.3 discusses a deeper shift in PMT objectives, highlighting how the concept and role of "assessment" have fundamentally changed. Section 11.4 introduces whistleblowers with direct experience in PMT who, similarly to their counterparts in the U.K.,[1] have revealed practices they consider unsafe and inconsistent with established clinical standards, providing additional evidence of expedited pathways to medical interventions in leading pediatric gender clinics across the U.S.

11.1 The Dutch Protocol and the relaxation of its criteria in the U.S.

According to WPATH SOC-8, the Dutch studies associated with the Dutch Protocol provide "[t]he most robust longitudinal evidence supporting the benefits of gender-

[1] Barnes (2023).

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affirming medical and surgical treatments in adolescence …"[2] In his testimony before the Florida Boards of Medicine and Osteopathic Medicine, Aron Janssen, vice chair of clinical affairs at Lurie's Pritzker Department of Child and Adolescent Psychiatry, who also serves as chair of the American Academy of Child and Adolescent Psychiatry's Sexual Orientation and Gender Identity Issues Committee, said that "the best longitudinal data we have on transgender youth comes primarily out of the Dutch clinic … The Dutch model of care [is] the prevailing model of care that most of the American clinics have based their care upon."[3] SOC-8 seems to acknowledge the guardrails recommended in the Dutch Protocol, contrasting the "detailed comprehensive diagnostic assessment process" of that Protocol with treatment based on "limited or no assessment." According to WPATH, the latter approach "has no empirical support and therefore carries the risk that the decision to start gender-affirming medical interventions may not be in the long-term best interest of the young person at that time."[4]

11.1.1 U.S. gender clinics' departure from the Dutch Protocol

In 2022, investigative reporters from Reuters interviewed "doctors and other staff at 18 gender clinics across the country" and found that "[n]one described anything like the months-long assessments [the Dutch clinicians] adopted in their research." Seven of the 18 clinics said they were comfortable prescribing hormones on an adolescent's first visit, provided clinicians saw no "red flags."[5]

The Dutch clinicians themselves recognized the divergence of the American model from their approach.[6] Noting the shift in age-of-onset, sex ratio, and mental health profile in the pediatric clinical population, Annelou de Vries wrote in 2020 that "[t]hese youth did not yet participate in the early evaluation studies. This raises the question of whether the positive outcomes of early medical interventions also apply to adolescents who more recently present in overwhelming large numbers for transgender care, including

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[2] WPATH is referring to de Vries et al. (2011) and de Vries et al. (2014), discussed in several earlier chapters.
[3] Florida Boards of Medicine and Osteopathic Medicine Joint Rules/Legislative Committee (2022), 47:45-48:03.
[4] Coleman et al. (2022).
[5] Terhune et al. (2022).
[6] For a study on how different countries have responded to the Dutch Protocol see Kozlowska et al. (2024).

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those that come at an older age, possibly without a childhood history of [gender incongruence]."[7] In 2021, Thomas Steensma complained that "the rest of the world is blindly adopting our research …"[8] Steensma reiterated this position in 2023, explicitly distancing his work from the child-led model prevalent in the United States, stating, "That's not our approach."

Of note, the Dutch Protocol did not recommend surgeries prior to legal adulthood, but according to WPATH guidelines, which are followed in the United States,[9] most surgeries, including most genital surgeries, may be deemed medically necessary for certain adolescents with GD.[10] Accordingly, adolescents with GD do undergo mastectomies[11] and (much less commonly) genital surgeries.[12] In the published research on mastectomies in adolescent females with GD,[13] some participants were as young as 12 years old.[14]

11.2 Is pediatric medical transition "rare"?

To bolster the perception that medical gatekeeping ensures patient safety, advocates of PMT frequently assert that medical interventions are "rarely prescribed" to minors. In 2022, for example, the president of the American Academy of Pediatrics (AAP) asserted in an opinion piece published in *The Wall Street Journal* that "for the vast majority of children," the "gender-affirming" approach recommends the "opposite" of medical interventions.[15] These claims are not supported by the data.

In 2025, a *JAMA Pediatrics* study utilizing insurance data reported that about 0.1% of American 17-year-olds, or one in 1,000, received CSH between 2018 and 2022. The authors concluded that hormonal interventions are therefore "rare" and decried the "politicization of gender-affirming care for transgender youth … driven by a narrative

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[7] de Vries (2020).
[8] Tetelepta (2021a). There is an English translation available: Tetelepta (2021b).
[9] Coleman et al. (2022).
[10] E.g., "A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical *and surgical treatments* (GAMSTs)" (Coleman et al., 2022, S45-S46, emphasis added).
[11] Wright et al. (2023); Ghorayshi (2022); Sapir (2024c).
[12] Milrod & Karasic (2017); Terhune et al. (2022).
[13] Ascha et al. (2022); Olson-Kennedy, Warus, et al. (2018); Tang et al. (2022).
[14] Tang et al. (2022).
[15] Szilagyi (2022a).

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that millions of children are using hormones and that this type of care is too freely given."[16]

Such claims ignore a number of critical facts. First, no serious critic or skeptic of PMT has claimed that "millions of children are using hormones." Second, whether a prevalence of 1 in 1,000 is "rare" is subjective. For context, the prevalence of Type 2 diabetes in less than one in 1,000—a rate that medical authorities have described as "high" and even as "an awakening epidemic."[17] Third, even medical interventions that are objectively "rare" can raise profound ethical concerns. For example, "only" about 600 out of millions of African American men were recruited into the highly unethical Tuskegee syphilis study.

A central question in the debate over the frequency of medical interventions, and by extension whether they are "rare" or "freely given," concerns the appropriate choice of denominator. The authors of the *JAMA* study calculated prevalence using the total population of American adolescents as the denominator. However, in a press release accompanying the study, one of the authors noted that access to hormones was "surprisingly low, given that over 3% of high school youth identify as transgender"—implicitly invoking a different denominator.

Another denominator, which yields an even higher estimated frequency, is the number of adolescents diagnosed with GD and/or referred to a gender clinic, where they ostensibly undergo an "assessment" to determine whether medical interventions are indicated. Data on the rate of medicalization among adolescents diagnosed with GD and/or referred to a gender clinic are lacking.

Reports from individual clinics suggest that medicalization is the norm, rather than the exception. For example, pediatric endocrinologist Daniel Shumer of the Comprehensive Gender Services Program (CGSP) at University of Michigan Health estimated that "65 percent" of pediatric patients referred to his clinic end up receiving CSH.[18] According to data collected by Jamie Reed, a case worker at the Washington University School of

[16] Hughes et al. (2025).
[17] Lawrence et al. (2021); Kingsbury & Greene (2025) and the research articles cited therein.
[18] Doe v. Horne, No. 4:23-cv-00185-JGZ: 265 (2025, p. 52).

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Medicine Pediatric Transgender Center at St. Louis Children's Hospital, 67 percent of the clinic's patients were prescribed endocrine interventions during her four-year tenure at the clinic.[19] Finally, WPATH has itself implied that medical interventions are appropriate for "most adolescents" who seek them. In its response to the release of the Cass Review in the U.K., WPATH issued a statement criticizing the Review as being "rooted in the false premise that non-medical alternatives to care will result in less adolescent distress for most adolescents…"[20]

11.3 Shift in objectives and the new meaning of "assessment"

The AAP and other American medical associations argue that transition-related medical decisions for minors are made in consultation with parents and only after a "robust diagnostic assessment."[21] Under the original Dutch Protocol, assessments were intended to predict lifelong transsexuality, with pubertal suppression conceptualized as part of the diagnostic process (buying "time to think"). By contrast, the "gender-affirming" model, as it has evolved in the United States, prioritizes the autonomy of children and adolescents, allowing their current "embodiment goals" to direct treatment decisions.[22]

A systematic review of recommendations for the management of GD in children and adolescents found an absence of "[d]etailed guidance" and "no consensus about the aim or clinical approach"[23] of assessment. Understanding the realities of clinical care for youth with GD in the U.S. requires appreciating the shift in the meaning of assessment, which reflects a deeper change in the goals of PMT. According to the Dutch approach, the goal was to predict lifelong "transsexualism." Mental health professionals were to ascertain whether a GD diagnosis was appropriate and if so, whether it was likely to persist through adulthood. Although advocates of this approach generally regard a

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[19] Broyles & Trakas (n.d.).
[20] Block (2024c). The original statement from WPATH/USPATH (2024, April 12) was deleted from WPATH's website (404 Not Found | WPATH, n.d.). The April 12 WPATH/USPATH statement was covered by the NPR station WBUR (Scheimer et al., 2024). WPATH subsequently changed the statement, removing the referenced passage (see World Professional Association for Transgender Health & United States Professional Association for Transgender Health, 2024a; 2024b).
[21] U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024).
[22] Block (2023d).
[23] Taylor, Hall, Heathcote et al. (2024b, s80).

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diagnosis of GD as a necessary condition for medical interventions, there is considerable disagreement about whether it is sufficient.

More recently, advocates of early intervention have argued that "trans kids know who they are"[24] and that the goal of treatment is to help them achieve their personal "embodiment goals."[25] If an adolescent's self-conception or embodiment goals later change, this is not considered a failure of treatment but part of a "gender journey."[26] In 2023, Jason Rafferty, the lead author of the AAP's 2018 policy statement, "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents," explained that PMT is about "affirming and validating the child's sense of identity from day one through to the end." If a child says, "I'm X, we operate under the assumption that what they're telling us is their truth, that the child's sense of reality and feeling of who they are is the navigational beacon to sort of orient treatment around." If patients later detransition, this does not mean that the treatments were inappropriate, even if the interventions' effects are partly or fully irreversible: "They're not treatment failures if that's what's affirming," Rafferty said.[27]

Of note, the more cautious approach, which seeks diagnostic and prognostic clarity and aims at improvements in mental health, has been found to be unsupported by evidence. No test can reliably predict the natural course of an adolescent's identity development. The U.K.'s Cass Review found that a gender dysphoria diagnosis "is not predictive that the individual will go on to have longstanding trans identity."[28] Clinicians who adopt the earlier diagnostic-oriented model might perceive their approach as more cautious relative to colleagues practicing the newer "affirming" model; however, research on outcomes from both approaches has been rated unreliable.

One indicator of the changing definition of "assessment" is that leading gender clinicians—who until recently characterized PBs as a "fully reversible" and temporary "pause button" intended to give patients "time to think"—now acknowledge that these

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[24] See Note 33 in Chapter 2.
[25] Ashley et al. (2023); Boskey et al. (2025, p. 2); Brennan et al. (2025, p. 5); Mosier-Mills et al. (2024).
[26] "Clinicians should see detransition as one of many possible steps in a person's gender journey" (Ashley et al., 2025, p. 7).
[27] Block (2023d).
[28] Cass (2024, p. 146).

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drugs function as the first step in a broader medical transition protocol and must be considered in conjunction with cross-sex hormones. For example, in an amicus brief submitted to the Supreme Court of the United States, a leading advocate for PMT, Meredithe NcNamara of the Yale School of Medicine, and colleagues, fault the University of York systematic reviews, commissioned for the Cass Review, for failing to conceptualize PBs and CSH as a single "consistent, well-organized standard of care." According to McNamara et al., if, as research suggests, "the vast majority of adolescents with gender dysphoria who receive puberty blockers progress to cross-sex hormone therapy," that is not because PBs interfere with the natural process of GD resolution but "because [the adolescents] are indeed transgender and because their diagnosis of gender dysphoria is accurate."[29] This explanation for the observed high persistence of GD lacks empirical support due to the absence of controlled prospective studies and raises concerns about motivated reasoning. Many of the brief's authors are actively engaged in the practice of PMT and therefore have intellectual and financial conflicts of interest.[30]

11.3.1 Ambiguity in SOC-8

On the surface, WPATH SOC-8 might appear to recommend a cautious approach toward assessment. Mental health providers are to conduct a "comprehensive biopsychosocial assessment" prior to initiating medical interventions in order "to understand the adolescent's strengths, vulnerabilities, diagnostic profile, and unique needs to individualize their care."[31] At the same time, however, WPATH recommends that clinicians use the *International Classification of Diseases* (ICD-11) diagnosis of "Gender Incongruence of Adolescence and Adulthood," which, unlike the DSM-5 diagnosis of "Gender Dysphoria," requires only "marked and persistent incongruence between an individual's experienced gender and the assigned sex." Because SOC-8 defines transgender in a similar way ("people whose gender identities and/or gender

[29] U.S. v. Skrmetti (No. 23-477), Expert Researchers and Physicians, Amicus curiae brief (2024, pp. 16-17).
[30] The lead author, McNamara, has positioned herself in media and court appearances as a provider of PMT to minors. However, in a deposition McNamara revealed that she does not in fact administer PMT to minors with GD. See Sapir (2024b).
[31] Coleman et al. (2022, Chapter 6).

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expressions are not what is typically expected for the sex to which they were assigned at birth") and provides no meaningful distinction between this meaning of transgender and gender non-conformity, SOC-8 effectively recognizes transgender identification as a medical condition justifying medical interventions.[32]

It is widely recognized that a fundamental tension exists between WPATH's desire to treat transgender identity (gender incongruence) as a normal and healthy variation of human development and its insistence that gender incongruence requires "medically necessary" treatment. This tension was explicitly acknowledged in medical literature supporting PMT contemporaneous with the preparation and publication of the fifth edition of the DSM. For example, in 2013, Jack Drescher, a prominent clinician-advocate of PMT, noted the significant difficulty in reconciling the "contradictory narratives" of "reducing stigma (which underlies the call for removal of the gender diagnoses [from the DSM]) and maintaining access to care (which requires the existence of a diagnosis in order to obtain needed medical treatment covered by third party payers)."[33]

In the lead-up to SOC-8's publication, *The New York Times* reported on disagreements among proponents of PMT concerning the proposed assessment recommendations for adolescents. One clinician told the *Times* it was "harmful and destructive and abusive and unethical and immoral" to require that a candidate for medical transition have longstanding GD since childhood—a key element of the Dutch Protocol. Another described the assessment recommendations as a "comprehensive inquisition of [an adolescent's] gender." The International Transgender Health Group criticized WPATH's draft chapter for its "harmful assertion of psychogatekeeping" and for "undermin[ing] patient autonomy." Asked whether it was appropriate to assess "the basis of a kid's gender identity," physician Colt St. Amand, a coauthor of SOC-8, told the *Times* that this "just reeks of some old kind of conversion-therapy-type things … People are who they say they are, and they may develop and change, and all are normal and OK." St. Amand was "less concerned with certainty around identity, and more concerned with

[32] See Chapter 13; The acronym "T/GNC" [transgender and gender-nonconforming] is commonly used in literature supportive of PMT.
[33] Drescher (2014, pp. 11-12).

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hearing the person's embodiment goals. Do you want to have a deep voice? Do you want to have breasts? You know, what do you want for your body?"[34]

11.3.2 SOC-8 guardrails abandoned

Although WPATH's guidelines do not necessarily discourage mental healthcare, they likewise do not require it as a precondition for PMT. Some guideline authors opposed even minimal requirements for mental health support, arguing that such provisions were analogous to "conversion therapy."[35] SOC-8's only formal recommendation is for a "comprehensive biopsychosocial assessment," although WPATH emphasizes that its guideline is "flexible," thereby leaving room for considerable variation in clinical practice.[36]

In 2024, leaked discussions among WPATH members illustrated the extent to which the organization's own members' practice is not always consistent with SOC-8 recommendations. Some WPATH members candidly acknowledged foregoing even minimal psychological evaluations and moving quickly toward hormonal interventions. The candid nature of these exchanges suggests that non-adherence to the guidelines is not a source of professional shame, and not an isolated phenomenon.[37] The flexibility embedded in SOC-8 has facilitated significant gaps between the guidelines' theoretical standards and the practical reality in clinical settings.

Further, this flexibility has effectively provided leaders in the field of PMT with a basis to argue that assessment should not serve the purpose of differential diagnosis or medical "gatekeeping" but rather should function primarily to inform patients and their caregivers about the nature and effects of medical interventions. In 2020, a Canadian conference presentation reported that among pediatric gender clinics surveyed, half did not require any mental health assessment prior to initiation of hormonal interventions.[38] As one group of clinicians recently stated:

[34] Bazelon (2022b).
[35] Bazelon (2022a).
[36] Coleman et al. (2022, p. S6).
[37] Hughes (2024).
[38] Lawson et al. (2020).

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> When a family comes to a mental health provider requesting a letter for a biopsychosocial assessment for pubertal suppression, work begins by explaining, in developmentally appropriate language, that this is not an assessment of whether they 'are actually transgender,' as many patients worry; rather this assessment is meant to help them understand the intricacies of pubertal suppression, so that they can make the best decision for themselves. The primary goal is to provide information, while identifying all potential avenues of support (social, educational, medical, and legal) related to gender.[39]

Jack Turban, the lead author of this statement and Director of the Gender Psychiatry Program at the University of California San Francisco, has said that differential diagnosis is pointless and may even be harmful. He disputes the notion that mental health assessment can reduce the risk of later regret, claiming that "there's not data [sic] that … any of these assessments make that [outcome] less likely."[40] According to Turban, children and adolescents "are just going to figure out the answers and then tell you what you want to hear. And you've set up this argumentative relationship with your patient or client."

Robert Garofalo of Lurie Children's Hospital in Chicago agrees that determining the causes of a child's feelings of alienation from their body through assessment is unnecessary.

> Sometimes parents will come in and be like, "I want to make sure that my young person, my child, is really trans … Can you help me with that?" And I'll turn to the child and be like, "yeah, so, you know, what gender identity do you have?" … You know, there's no form, there's no scale, there's no psychological battery of tests that needs to be done. Really, any young person can answer that question for themselves … Parents … think that they're going to come in and have this evaluation that is gonna help determine their child's gender identity, when really

[39] Turban et al. (2025, pp. 12-13).
[40] GenderGP (2021).

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> … our work sometimes is just getting them to recognize that anyone's gender identity … is a normal variation …[41]

Amy Tishelman, formerly of the Gender Multispecialty Service at Boston Children's Hospital, expressed discontent with the new model of assessment in an interview with *The Boston Globe*. "I've never been happy with that way of characterizing it. I feel like an assessment should encompass more than just, 'Should a person get medical intervention, or shouldn't they?'"[42] In contrast, physician A.J. Eckert, former medical director at Anchor Health Initiative in Connecticut, avowed: "If you are trans, I believe you." For Eckert, minors "are best equipped to make decisions about [their] own body." Eckert further clarified that while medical interventions at Anchor Health are not provided before puberty, psychological therapy is not mandatory because "being trans is not a pathology."[43]

11.3.3 Collapse of assessment times

The erosion of medical safeguarding practices within American gender clinics is evident in the significant reductions in patient assessment durations at prominent institutions.

11.3.3.1 Boston Children's Hospital

GeMS at Boston Children's Hospital is the nation's first pediatric gender clinic and is highly regarded internationally. Whereas in 2013 GeMS allocated a minimum of 20 hours for mental health assessments per patient, court records indicate that by 2021 the clinic had reduced these evaluations to approximately two hours per patient.[44] Laura Edwards-Leeper, the clinic's founding psychologist, characterized this change as "shocking." Amy Tishelman, a former GeMS psychologist and SOC-8 developer, described it as "reckless."[45] Tishelman's tenure ended following disagreements with colleagues, culminating in litigation. Current co-director Kerry McGregor defended the reduction in assessment times, stating that two-hour assessments were initiated around

[41] Figliolia (2025).
[42] Damiano (2024b).
[43] Edwards-Leeper & Anderson (2021); the quote from Eckert is in Eckert (2020).
[44] Alder (2024).
[45] Ryan (2024a).

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2017–2018 and are “appropriate” given the expanding patient load.[46] Endocrinologist and GeMS director Jeremi Carswell remarked in 2021 that puberty blockers were being prescribed “a lot like candy.”[47]

11.3.3.2 Children’s Hospital Los Angeles

Johanna Olson-Kennedy, medical director of the Center for Trans Youth Health and Development at Children’s Hospital Los Angeles, has acknowledged that she approves some of her minor patients for endocrine interventions after “a couple of hours” of assessment.[48] In December 2024, Olson-Kennedy and the hospital were named as defendants in a lawsuit filed by a former patient whom Olson-Kennedy allegedly approved for PBs at age 12 following a single consultation with no involvement of a mental health professional. The lawsuit further alleges that Olson-Kennedy told the parents of the patient that the patient faced suicide risk without medical interventions, despite no prior suicidal history. Subsequently, the patient was put on testosterone at 13, underwent a double mastectomy at 14, and was recommended for hysterectomy at 17.[49]

11.3.3.3 Lurie Children’s Hospital

In a webinar hosted by AMAZE, a producer of sex education content for students, Robert Garofalo of Lurie Children’s in Chicago explained how his clinic handles parents who have doubts about the safety of medical interventions.

> Most of the young people who come in are wanting to figure out how fast they can get on hormones and what is the safest process to do that … 80% of the young people who come are often really activist [sic] in their mindset and come dragging their parents to the medical visit … The counterweight to that is the parents who are often coming in with questions about how can this be done safely, is this really the right decision, and so it’s really a bit of a puzzle to put the pieces together to make sure that you are meeting the patient’s needs but also

[46] Damiano (2024a).
[47] Lindquist (2022).
[48] Deposition of J. Olson-Kennedy in LB v Premera Blue Cross NO. 2:23:Cv-00953-TSZ (2024, p. 63).
[49] Complaint, Breen v. Olson-Kennedy, No. 24STCV32096 (2024).

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> moving the parents along … in a way that continues to get them educated so that they feel comfortable with the decisions they're about to make, because the truth is that these young people need their parents to be well and to do this well, and so it's our job as pediatricians to make sure that the entire family unit in some ways hopefully moves forward in an ideal situation in a way that feels supportive and nurturing. So, it's usually the young person who comes in knowing exactly what they want and us trying to navigate a process to ensure that's done safely and allaying parents' fears.

Garofalo went on to elaborate on his understanding of what shared decision-making means:

> If the medical provider thinks they have the answer [to whether medical interventions are appropriate] then they're the wrong medical provider. The answer lies within the young person and the family. Your job as a healthcare provider is to help them along that path, to find the answers and the solutions that feel authentic and healthy for them.[50]

11.3.3.4 Seattle Children's Hospital

In a response to Tordoff et al. (2022), a study conducted at Seattle Children's Gender Clinic,[51] one commentator pointed out that the control group, which received only psychotherapy, might have shown comparatively worse mental health due to selection bias: "patients with coexisting mental concerns may have been potentially discouraged from accepting the treatments until their coexisting conditions were addressed."[52] Lead author Diana Tordoff responded to the comment by pointing out that "youth who reported moderate to severe depression, anxiety, or suicidal thoughts were not precluded access to PB/GAH [puberty blockers and gender-affirming hormones], especially since initiating PB/GAH is known to improve or mitigate these symptoms."[53] Eighteen-year-olds "were provided care using an informed consent model and were not

[50] Figliolia (2025).
[51] Tordoff et al. (2022); see Section 6.2.2 for further discussion.
[52] Tordoff et al. (2022) [online comment; March 7, 2022].
[53] Tordoff et al. (2022) [online comment; March 13, 2022].

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required to complete a mental health assessment." Tordoff also noted that Seattle Children's practices were consistent with the (then draft) SOC-8 guidelines.[54]

11.3.3.5 UCSF Benioff

In 2018, the organization Gender Spectrum hosted a panel with Ilana Sherer, a pediatrician and gender clinician, and Diane Ehrensaft, a clinical psychologist at UCSF Benioff and one of the principal architects of the "gender-affirming" approach in the United States. Sherer said that she sees "lots and lots of kids" who "don't have [gender] dysphoria, that really don't have mental health issues, and so to say to them 'you have to go get a letter from a mental health provider' feels challenging to me." But since a letter of support is required for medical interventions, Sherer went on to explain that "what we've started to do in our clinics is have someone like Diane [Ehrensaft] ... go in and do a brief assessment, and give their rubber—I know you [addressing Ehrensaft] said you don't rubber-stamp, but basically in my mind that's what it feels like—and so then we can move on and say 'OK, now we can talk about what you're actually here for.'"[55]

11.3.3.6 Planned Parenthood

Specialized gender clinics are not the only institutions prescribing hormonal interventions to adolescents. According to a 2024 investigative report published in *The Free Press*, Planned Parenthood is "the country's leading provider" of hormones for young people. Approximately 40% of the more than 40,000 patients for whom Planned Parenthood prescribed hormones in 2023 were between the ages of 18 and 22. Some branches, however, "offer hormones starting at age 16 with parental approval." In recent years, Planned Parenthood clinics have adopted an expedited access policy on an "informed consent" basis. Nicole Chaisson, medical director of Planned Parenthood North Central States, told *The Free Press* that "Gatekeeping is not necessary. People are the experts of their own body and of their own journey, and as long as they can

[54] Tordoff et al. (2022) [online comment; March 13, 2022].
[55] Sherer (2018).

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make decisions, they should be the agent of their own healthcare." Chaisson said it was appropriate for teenagers to "leave the clinic with their prescription" after a single visit.[56]

Jamie Reed, the former case manager at the Washington University pediatric gender clinic in St. Louis, had previously worked at Planned Parenthood. Reed testified in a deposition that the St. Louis gender clinic would refer minor patients to Planned Parenthood "when we did not have consent from legal guardians" because Planned Parenthood would get "these kid's scripts [prescriptions] when they did not meet" diagnostic criteria. Although Planned Parenthood requires consent from an adult caregiver to prescribe hormones to minors, Reed said that Planned Parenthood "would not verify who the adult is that is bringing [the minor patient] to the building."[57]

11.4 The whistleblowers

In public statements, advocates and practitioners of PMT routinely imply that assessment functions as a form of medical gatekeeping, suggesting that PBs, CSH, and surgeries are offered cautiously and only to patients who genuinely require such interventions. Meredithe McNamara has argued that it is a "misconception" that "a child's disclosure of gender dysphoria leads to impulsive, irreversible decisions." Rather, "decisions on whether, when, and how to pursue medical interventions are slow-moving, rigorous, and individualized."[58] In his testimony before the Florida Boards of Medicine and Osteopathic Medicine in 2022, Aron Janssen, of Lurie Children's, said that treatments follow a "careful and thorough assessment of a patient's mental health including co-occurring conditions, history of trauma, substance use, among many other factors."[59]

In recent years, however, whistleblowers with firsthand experience working in gender clinic environments have come forward with compelling counterexamples. Their testimonies have often been dismissed, ignored, marginalized, or disparaged by colleagues. Several have also faced retaliation because of their disclosures.

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[56] Block (2024d).
[57] Noe v. Parson, No. 23AC-CC04530 (2024, p. 172).
[58] McNamara (2024).
[59] Florida Boards of Medicine and Osteopathic Medicine Joint Rules/Legislative Committee (2022), a 43:57.

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11.4.1 Laura Edwards-Leeper and Erica Anderson

In 2021, Laura Edwards-Leeper, the founding psychologist of the first pediatric gender clinic in the United States, and Erica Anderson, a clinical psychologist and former president of the U.S. Professional Association for Transgender Health (USPATH), became the first prominent whistleblowers in the United States. In an opinion piece for *The Washington Post,* Edwards-Leeper and Anderson warned that adolescents were "being rushed into" medical interventions without sufficient psychological assessment or deliberation. "A flood of referrals to mental health providers and gender medical clinics, combined with a political climate that sees the treatment of each individual patient as a litmus test of social tolerance, is spurring many providers into sloppy, dangerous care,"[60] they wrote.

Following publication in *The Washington Post*, USPATH sought to impose a moratorium on Anderson's ability to speak to the press while WPATH was finalizing its SOC-8. Anderson resigned from the organization in protest.[61]

In an interview with journalist Abigail Shrier, Anderson cautioned that the current PMT approach involved "sloppy healthcare work," which could result in young people making decisions they would later regret. Marci Bowers, a gynecologist and surgeon who, like Anderson, identifies as transgender, echoed these concerns in the same interview. Bowers observed that although medical interventions initially seemed promising, in practice they had not yielded better—or even equivalent—outcomes compared to earlier approaches. Bowers specifically voiced concern about the long-term implications of these interventions on reproductive capacity, sexual health, and the ability of patients to experience intimacy.[62]

Despite criticizing the "gender-affirming" approach now dominant in their field, Anderson and Edwards-Leeper continue to believe that at least some children and adolescents benefit from medical transition. Bowers issued a detailed letter of apology to WPATH

[60] Edwards-Leeper & Anderson (2021).
[61] Selin Davis (2022).
[62] Shrier (2021b).

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leadership[63] and remained with the organization, serving as its president from 2022 to 2024.

11.4.2 Jamie Reed

In 2022, Christopher Lewis and Sarah Garwood, then co-directors of the Washington University School of Medicine Pediatric Transgender Center at St. Louis Children's Hospital, testified before the Missouri House Judiciary Committee that "[m]edical interventions are done with a thorough and multidisciplinary team approach, which includes mental health assessment and requires consent from all custodial parents or caregivers."[64] Opening with the unfounded assertion that PMT is "literally lifesaving" (see 4.3.4 for discussion of suicide risk), Lewis, the Center's endocrinologist, emphasized that "[f]or pubertal transgender adolescents, medical services are started only after meeting strict eligibility criteria… [This] includes mental health professionals who have adequately documented and explored various aspects of gender and mental health exploration [sic], psychosocial medical concerns and conditions, and ability to understand their decisions and provide assent."[65]

These assertions were later disputed by Jamie Reed, who worked for four years at the Center as a case manager responsible for patient intake and oversight. In deposition testimony, Reed stated that Lewis had indicated at an early stage that he "[didn't] care" if patients met criteria for gender dysphoria. It was "not a requirement for [him] to prescribe hormones."[66] An investigation by *The New York Times* provided additional details about the clinic's practices and corroborated most aspects of Reed's testimony. According to the investigation, one patient, who subsequently detransitioned, received a prescription for testosterone following a single visit, without prior assessment by any mental health professional. When WPATH SOC-8 was published in September 2022, Lewis texted Karen Hamon, the Center's nurse, saying: "Right now I have no idea how to meet what would be the most intensive interpretations of the SOC."[67]

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[63] Boe v. Marshall, No. 2:22-cv-00184: 700-5 (2024, pp. 67-71).
[64] Lewis & Garwood (2022, 9:14:55).
[65] Lewis & Garwood (2022, 9:16:40).
[66] Noe v. Parson, No. 23AC-CC04530 (2024, p. 244).
[67] Ghorayshi (2023b).

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According to Reed, the Center responded to a 5-fold increase in its patient caseload by offering mental health providers a letter-of-support template for them to sign, in the hope that this would speed up the process of approval for endocrine treatments. It "was just copy paste," Reed testified in a deposition. Reed said that when she brought her concerns to Lewis, he "didn't care and was going to pass it [the letter] anyway".[68]

Concerned that the Center was not tracking patient outcomes, Reed and Hamon created a "red flag list," a private Excel spreadsheet in which they documented cases of patients with complex mental health presentations. As reported by the *Times*, the list included "a patient on testosterone [who] stopped taking schizophrenia medication without consulting a doctor and another [who] had visual and olfactory hallucinations. Another had been in an inpatient psychiatric unit for five months."[69] Reed also described an adolescent female from an "unstable family" who was in "an uncertain living situation and had a history of drug use" and was put on hormones at age 16, followed by a double mastectomy at 18. Three months later she regretted the surgery and informed the clinic, "I want my breasts back."[70] According to the *Times*, the patient contacted the surgeon at Washington University twice about her wish for breast reconstruction, but did not receive a response.[71]

Reed recalled a 17-year-old girl who was given testosterone and reported "bleeding from the vagina." The girl was advised to use a heavy pad to absorb the blood. "In less than an hour she had soaked through an extra heavy pad, her jeans, and a towel she had wrapped around her waist. The nurse at the center told her to go to the emergency room right away." The Center "found out later this girl had had intercourse, and because testosterone thins the vaginal tissues, her vaginal canal had ripped open. She had to be sedated and given surgery to repair the damage."[72]

Reed reported that when she raised concerns regarding inadequate mental health assessment and safeguarding with the Center's physicians, her objections were

[68] Noe v. Parson, No. 23AC-CC04530 (2024, p. 165).
[69] Ghorayshi (2023b).
[70] Reed (2023a).
[71] Ghorayshi (2023b).
[72] Reed (2023a).

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repeatedly dismissed and she was advised to “Get on board, or get out.” Individuals who expressed doubts frequently faced “being called a transphobe.”[73] A similar phenomenon of intimidation was documented at the Tavistock’s Gender Identity Development Service in the U.K.[74]

Reed, who is lesbian, profoundly regrets her past involvement in PMT, and has since become a leading advocate for restrictions on practices she regards as harmful, especially for youth with emergent same-sex attraction who are overrepresented among patients.[75] The Center stopped providing PMT following the enactment of Missouri's Senate Bill 49 (SB 49).[76] Lewis, the Center’s endocrinologist, accepted a job in Colorado, where he currently practices PMT at Children's Hospital Colorado.[77]

11.4.3 Tamara Pietzke

In February 2024, Tamara Pietzke, a licensed clinical social worker and therapist at MultiCare Health System in Tacoma, Washington, disclosed harmful practices occurring in her clinical environment.[78] Pietzke described patients with significant comorbid mental health conditions and complicated life histories, who, despite these vulnerabilities, were approved for hormonal interventions.

One patient, a 13-year-old adolescent female, had diagnoses of depression, anxiety, post-traumatic stress disorder, and intermittent explosive disorder. She had experienced childhood abuse, neglect, and sexual violence, and, according to Pietzke, reported that “horror and porn movies … were the only ones available in her house.” The patient also told Pietzke that her mother practiced bestiality. She communicated in therapy sessions by displaying extremely sadistic and graphic pornographic videos to Pietzke on her phone. The patient also was reported to have autism spectrum disorder, a factor that may have contributed to her communication difficulties. Pietzke noted that the girl would “age-regress” by “watching *Teletubbies* and sucking on a pacifier.”[79] A restraining order

[73] Reed (2023a).
[74] Barnes (2023); Cass (2024).
[75] Reed (2023b).
[76] Washington University (2023).
[77] University of Colorado Anschutz Medical Campus (n.d.).
[78] Pietzke (2024a).
[79] Pietzke (2024a).

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was also in place against the patient's mother, who had previously attempted to harm the girl's sister in her presence. The girls were being raised by their mother's former boyfriend.

In addition to these obvious red flags, Pietzke noted that her 13-year-old patient never asked for testosterone and failed to demonstrate an understanding of the hormone when the subject was raised. Nevertheless, the gender clinic at Mary Bridge Children's Hospital, part of MultiCare, approved the teenager for testosterone on her first visit. The clinic requested that Pietzke sign a letter of support clearing the patient of any mental health contraindications. Pietzke refused, and the case was referred to the hospital's risk management team. Instead of siding with Pietzke, however, the risk management team reassigned the adolescent to another therapist. Pietzke wrote to Amber Rolfe, MultiCare's in-house "gender-affirming care" expert, explaining her concerns and even citing Sections 6.3 and 6.12 from the Adolescent chapter of WPATH SOC-8 in support of her decision.

Rolfe disagreed with Pietzke's clinical judgment and citations from SOC-8, insisting that nothing in the patient's history, behavior, or concurrent diagnoses was a contraindication for hormone treatment.[80] "There is not valid, evidenced based, peer reviewed research that would indicate that gender dysphoria arises from anything other than gender (including trauma, autism, other mental health conditions, etc.)," Rolfe wrote to Pietzke.[81] "At it's [sic] core the diagnosis centers on an incongruence of gender identity and assigned gender at birth." Rolfe also suggested that Pietzke examine her biases and consider transferring the client "to someone who is comfortable with providing gender affirming care."[82] Pietzke resigned from MultiCare shortly thereafter and went public with her story.

11.4.4 Eithan Haim

Eithan Haim, a surgeon formerly affiliated with Texas Children's Hospital (TCH), became a whistleblower after discovering that TCH was performing medical transition

[80] Sapir (2024a).
[81] Rolfe (2023).
[82] Rolfe (2023).

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procedures on minors despite publicly announcing a cessation of such procedures.[83] In 2022, prompted by a Texas Attorney General's opinion describing PMT as potentially abusive, TCH declared it would pause hormone interventions for transgender-identifying youth.[84] Despite this declaration, Haim became aware of ongoing practices that he asserted contradicted these claims; three days following the public statement, an 11-year-old patient received a puberty blocking implant, and similar interventions continued throughout the subsequent year involving dozens of other patients.[85] In May 2023, Haim anonymously provided de-identified hospital records and related documents to journalist Christopher Rufo, which resulted in a public exposé. The released data suggested that TCH had misled the public about halting its PMT program.[86]

Haim was charged with four felony counts under the Health Insurance Portability and Accountability Act (HIPAA). Prosecutors argued that Haim was not authorized to access patient data and that he did so with intent to maliciously harm the hospital.[87] The charges carried penalties of up to 10 years' imprisonment. Haim pleaded not guilty, denying his access to patient records was inappropriate, and asserting his disclosures were whistleblower actions aimed at safeguarding children rather than malicious acts.[88] The allegations were unusual, as HIPAA violations are typically addressed through civil rather than criminal procedure. The choice to pursue criminal charges raised suspicion that the federal government's actions were retaliatory in nature.[89]

The DOJ's indictment against Haim had to be amended multiple times after it was revealed that the government was mistaken about Haim's involvement with TCH. A second indictment had to be revised again because Haim was charged with actions as crimes that are not criminal under the law. The third indictment, which was shorn of most of the initial factual allegations, was for unauthorized access to patient records with intent to cause harm to doctors and the hospital, not patients. In January 2025,

[83] Haim (2024).
[84] Campion (2022).
[85] Haim (2024).
[86] Alder (2025).
[87] Trombly (2024).
[88] Alder (2025).
[89] Trombly (2024).

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after months of legal contention and growing public criticism of the prosecution as "lawfare," federal prosecutors dismissed all charges against Haim with prejudice, effectively exonerating him.[90]

In November 2024, Haim's lawyers informed the DOJ that the lead prosecutor in the case, Tina Ansari, and her family, had "substantial financial and political ties" to Texas Children's Hospital and Baylor College of Medicine, resulting in a potential conflict of interest.[91] Shortly thereafter, Ansari withdrew from the case.[92]

[90] House Judiciary Committee (U.S. Congress) (2025).
[91] Patrick (2024).
[92] Whelan (2024b).

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Chapter 12 Medical Association Response

This chapter examines how, despite growing recognition of its problems, the 8th version of the World Professional Association for Transgender Health (WPATH) *Standards of Care* (SOC-8) continues to have substantial influence on the medical field. This can be better understood by examining the critical role that major medical and mental health associations (MMHAs) play within the U.S. healthcare system (Section 12.1). Section 12.2 explores the reasons why MMHAs have not properly responded to updated evidence, nor to serious ethical concerns; Section 12.3 is a summary conclusion.

12.1 The role of major medical and mental health associations

Given the decentralized and fragmented nature of the U.S. healthcare system, MMHAs play a central role in shaping clinical practice guidelines, healthcare policy, and medical practices. They educate clinicians on emerging research, develop authoritative clinical practice guidelines, publish peer-reviewed journals, facilitate interdisciplinary collaboration, and engage in professional advocacy on behalf of their members. Typically, MMHAs limit full professional membership to practitioners actively engaged in clinical medicine or the mental health disciplines and enforce professional codes of conduct under which members may face sanctions or loss of privileges for noncompliance. MMHAs derive their authority in large part from their perceived adherence to rigorous professional standards and to science.

However, despite their scientific orientation, MMHAs are not immune to institutional biases, including groupthink and the disproportionate influence of vocal, specialized subcommittees. These specialized groups may receive broad deference from the larger organization, especially when their initiatives are framed in the language of civil or human rights. Consequently, MMHAs can inadvertently become echo chambers where dissent is suppressed, confirmation biases go unchecked, and professional deference is exploited. This dynamic of institutional capture is hardly unique to MMHAs: it occurs whenever support for a particular viewpoint is concentrated within a small, motivated subgroup, while opposing views are diffuse, less attentive, and less organized. As a result of this dynamic, the general public may inaccurately perceive the wider membership of individual MMHAs as uniformly aligned with the professed position of

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their professional association. It is easy to overlook the fact that fundamentally, these organizations operate as trade associations, with a primary role of protecting their members' autonomy and professional interests. Although individual clinicians generally are motivated by altruism, it should not be assumed that the collective actions of an organization always reflect the values or intentions of its individual members.[1]

Historical examples demonstrate that despite their crucial role in safeguarding patients' interests, MMHAs have at times resisted necessary medical reforms, even when confronted with strong evidence of their urgency. For instance, the American Academy of Pediatrics (AAP) delayed rescinding its 2000 guidelines discouraging early peanut exposure for two years after evidence emerged linking the policy to increased rates of peanut allergies.[2] Similarly, professional organizations resisted evidence-based recommendations to limit arthroscopic knee surgeries, lobbying against healthcare reforms despite clear evidence of limited efficacy.[3] MMHAs may impede or even oppose evidence-based medicine when the professional or financial interests of their members are threatened by medical practice reversal.

The reliance of MMHAs on WPATH is exemplified by the Endocrine Society (ES) clinical practice guideline for the treatment of gender dysphoria (GD). As discussed in Chapter 9, the close alignment of these groups' guidelines suggests a lack of robust, independently derived frameworks for care, potentially limiting critical appraisal and alternative perspectives within the field. Notably, Joshua Safer, who is leading the 2024 revision of ES guidelines, is himself closely associated with WPATH and is a prominent advocate for pediatric medical transition (PMT).[4] His leadership role raises concerns about compliance with the National Academy of Medicine's standards for trustworthy guideline development, in particular with regard to conflict of interest management (see 10.3.1).[5]

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[1] For a discussion of this phenomenon and its consequences for medical policy, see Patashnik et al. (2017).
[2] See Section 1.2.2.
[3] Patashnik et al. (2017, Chapter 2).
[4] Sapir (2024d).
[5] Graham et al. (2011, p. 87).

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MMHAs have been reluctant to transparently address the weak evidence base underlying PMT. For example, the American Psychiatric Association's (APA) textbook *Gender-Affirming Psychiatric Care*[6] has faced internal criticism for failing to acknowledge the scientific debate and the policy shifts occurring internationally.[7] A petition with over 7,000 signatures, many from medical and mental health professionals, has called for the withdrawal or correction of the textbook,[8] yet APA leadership has not issued a substantive response.[9] Similarly, the American Academy of Child and Adolescent Psychiatry (AACAP) has rejected multiple proposals addressing important evidence and dissenting perspectives that were submitted to its conferences.[10] The AAP likewise has repeatedly declined to platform critical perspectives at its events.[11] This pattern of organizational defensiveness fosters environments in which clinicians feel compelled to self-censor.

The AAP has rejected multiple internal requests to conduct systematic reviews of the evidence underpinning PMT.[12] Although AAP leadership ultimately agreed in principle to a systematic review, it simultaneously reaffirmed the existing policy[13]—a move that evidence-based medicine experts have criticized as methodologically unsound and premature, as it presupposes the outcome of a review intended to impartially evaluate the evidence.[14] To date, there is no evidence the AAP has begun the review.

After the National Health Service (NHS)-commissioned Cass Review was published in April 2024, several affiliates of the American Psychological Association (APA) prohibited its very discussion on their professional listservs. When a San Francisco-area psychologist posted information about the Cass Review on a listserv of Division 39 of the APA, the listserv moderator blocked the post, citing a 2020 "Letter of Apology to

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[6] Goetz & Keuroghlian (2023).
[7] Satel (2024).
[8] Foundation Against Intolerance & Racism (2024).
[9] Posner (2024).
[10] Sibarium (2023).
[11] Shrier (2021a).
[12] Block (2023c).
[13] Wyckoff (2023). AAP policy statements automatically expire after 5 years unless readopted, revised, or revoked.
[14] Ghorayshi (2023a).

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LGBTQ+ Communities" that forbids "speech that is injurious to LGBTQ+ members."[15] The Pennsylvania Psychological Association (PPA), a state affiliate of the APA, sent an email to all its members informing them that the Cass Review was "no longer welcomed for discussion" on its professional listserv. The PPA explained that the Review "fail[s] to meet" the PPA's "professional standards," and that "LGBTQIA+" members and their "allies" might feel "targeted, harmed, and hurt by this literature being repeatedly shared."[16] A clinical psychologist who describes herself as "a liberal feminist" and who has "marched in Pride marches" told the *BMJ* that she was "reprimanded" by the Illinois Psychological Association after posting about the Cass Review on a therapist listserv.[17]

12.2 Factors contributing to neglect of evidence and open debate

Hilary Cass, past president of the Royal College of Paediatrics and Child Health and leader of the U.K.'s comprehensive review of pediatric gender medicine services, has stated that American physicians are "out of date" in their approach to pediatric gender medicine.[18] Several factors may help explain the reluctance of American MMHAs to engage fully with the shifting perspectives on evidence and ethics in this area of practice.

First, in managing unusual or complex conditions, primary care providers and generalist clinicians often rely on the expertise of specialists to inform their clinical decisions.[19] When the former also hold leadership positions in medical organizations and are tasked with shaping policies for the treatment of youth with GD, they often defer to specialized committees—such as committees devoted to LGBT issues—whose members they regard as the organization's content experts. These committees typically are composed of professionals whose careers are closely tied to supporting or delivering medical transition, limiting their ability to impartially evaluate the evidence due to significant intellectual and financial conflicts of interest. While reliance on specialist committees

[15] Selin Davis (2024a).
[16] Ryan (2024c).
[17] Block (2024b).
[18] Ghorayshi (2024a).
[19] Tzartzas et al. (2019).

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poses fewer risks in well-established subspecialties with decades of robust research,[20] pediatric gender medicine remains a new, highly controversial field characterized by a limited and low-certainty evidence base.

Second, the framing of PMT as a civil rights matter[21] may have contributed to premature and uncritical support at both the individual and institutional levels. Most medical professionals are broadly supportive of civil rights.[22] U.S. specialty committees often frame PMT as a morally righteous or progressive cause, leading many professionals reflexively to adopt supportive positions. Given that transgender identification is relatively common among youth—estimated at 2–5%, though precise figures remain uncertain—many clinicians and policymakers also may have personal connections, such as friends or loved ones who identify as transgender. These personal ties, combined with a genuine desire to be compassionate and supportive, may understandably make it more difficult for professionals to critically and objectively evaluate the evidence base or ethical considerations underlying PMT.

Third, by the time the weak evidence and growing international retreat from the practice became difficult to ignore, several major U.S. MMHAs had been actively promoting PMT and denouncing its critics.[23] As a result, some organizations responded to international developments defensively rather than reflectively, viewing the shifts as a potential challenge to their institutional credibility.[24] The only notable exception to this pattern appears to be the American Society of Plastic Surgeons which, following the publication

[20] It should be noted, however, that with respect to developing reliable clinical practice guidelines the role of clinicians with intellectual conflicts of interest should be minimal: see Graham et al. (2011); McCartney et al. (2022).
[21] In 2016 psychologist Diane Ehrensaft, leading proponent of the "gender-affirming" approach, explicitly conceptualized her work as having “finally created a civil rights movement” (Ehrensaft, 2016, p. 355). Some medical guidelines in this field also call for specific political activism on the part of clinicians; e.g., the AAP policy statement (Rafferty et al., 2018). The editorial board of *The Washington Post*, recognizing the failure of pediatric gender specialists to self-regulate in the U.S., recently called for “new research of maximum possible rigor, overseen by scientists *who are not gender medicine practitioners*” (Washington Post Editorial Board, 2024, emphasis added).
[22] Levine & Abbruzzese (2023).
[23] Szilagyi (2022b).
[24] E.g. Endocrine Society (2024); Hoffman (2024).

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of the Cass Review, publicly adopted a more cautious stance regarding the use of surgical interventions for treating pediatric GD.[25]

Experts within pediatric gender medicine hold sharply divergent views about best practices.[26] However, the absence of professional consensus is often obscured, as dissenting voices are seldom included on specialty committees responsible for policy development. Researchers who study detransition, investigate social influences underlying epidemiologic changes in GD presentations, express concerns about PMT, or advocate for a more cautious approach to pediatric GD frequently encounter hostility and a lack of support from major publishers, medical societies, and academic institutions.[27] Organizations advocating for higher evidentiary standards, journalists reporting on the controversies, and academics writing about issues related to sex and gender have also faced hostility and attempts at public shaming.[28] Activist organizations have contributed significantly to this dynamic, often targeting individuals and groups that question or critically examine prevailing practices in gender medicine.[29]

When MMHAs update their treatment guidelines and position statements, experts who question the evidence supporting PMT are excluded from guideline development

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[25] American Society of Plastic Surgeons (2024).

[26] As the Cass Review found, "clinicians who have spent many years working in gender clinics have drawn very different conclusions from their clinical experience about the best way to support young people with gender-related distress. Some feel [they should] access a medical pathway at an early stage. Others feel that we are medicalising children and young people whose multiple other difficulties are manifesting through gender confusion and gender-related distress" (Cass, 2024a, p. 13). Examples of divergent clinical opinions can be found by comparing two papers on the role of mental health assessments: Levine (2024); Turban et al. (2025). Differing treatment approaches are also described in Levine et al. (2022a) and two follow-up articles: Drescher (2023); Levine et al. (2022b).

[27] For some examples, see Barnes (2023); Bazelon (2022a); Brown University (2019); Byrne & Gorin (2025); Edwards-Leeper & Anderson (2021); Gecsoyler (2024); Jenkins & Panozzo (2024); Keenan & Lovett (2025); LGBTQIA+ Coalition (2022); Pietzke (2024a, 2024b); Reed (2023a); Schenck (2022); Society for Evidence-Based Gender Medicine (2023d); Turley (2024).

[28] 100 signatories (2023); GLAAD (2023a, 2023b); Hansford (2024); Hooven (2023); Singal (2023a, 2023b); Weale (2025).

[29] In addition to the examples above, a recent article recounted therapists' experiences of attending a training workshop where the representative of the political activist group Southern Poverty Law Center (SPLC) spoke about efforts to "hunt" therapists who practice exploratory therapy, with the goal of leveling complaints leading to licensure revocations. Another therapist reported having been formally investigated by her graduate school for sharing information about new pediatric gender medicine evidence from Europe, an investigation which remains on her permanent record (Jenkins & Panozzo, 2024). SPLC also chose to wield the emotional power of the "hate group" label on several groups that have engaged in evidence-based evaluation of PMT or the development of alternative approaches.

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committees.[30] Efforts to exclude dissenting perspectives from conferences and publications have been documented.[31] In addition, there is growing evidence of self-censorship among clinicians and researchers, driven by concerns about professional repercussions and reputational risks.[32] Some proponents of PMT explicitly endorse the use of silencing tactics and reputational attacks:

> The point of activism is sometimes 'silencing,' if by that one means destroying the credibility of professionals that activists deem dangerous.[33]

Medical professionals' years of training and social status leave them acutely aware of and sensitive to reputational risks. Fear of online attacks and social disapproval within professional medical societies may have contributed to widespread self-censorship among clinicians, mirroring similar trends observed across academia.[34] This dynamic is further reinforced when PMT is framed as a civil rights issue or a struggle against discrimination and oppression. Under this framing, critics—even those raising evidence-based concerns—are labeled "anti-trans" or intolerant by reputable, influential sources.[35] As Hilary Cass observed in the introduction to the Cass Review,

> There are few other areas of healthcare where professionals are so afraid to openly discuss their views, where people are vilified on social media, and where name-calling echoes the worst bullying behaviour. This must stop. Polarisation and stifling of debate do nothing to help the young people caught in the middle of a stormy social discourse, and in the long run will also hamper the research that is essential to finding the best way of supporting them to thrive.[36]

The American healthcare system relies heavily on MMHAs to create, organize, and disseminate knowledge and to referee scholarly dialogue through journals and

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[30] Marci Bowers, president of WPATH when its 2022 guidelines were published, acknowledged that it was "absolutely" important for someone to be an "advocate" of the "gender-affirming" approach to be considered for the committee. See Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024). Furthermore, most members of the guideline development committee had conflicts of interest, which were poorly managed.
[31] Curlin (2024); Kaliebe & Johnson (2024); Kaltiala (2023); Mason (2021); Sapir (2025).
[32] Clark et al. (2024); Pfaus (2023).
[33] Nichols (2008).
[34] Clark et al. (2024); Curlin (2024); Pfaus (2023).
[35] E.g., Endocrine Society (2024); Szilagyi (2022b).
[36] Cass (2024, p. 13).

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conferences. Regardless of the underlying causes, major MMHAs have issued advocacy-driven recommendations prematurely, without adequate scientific support.[37] This contributed to a degradation of the norms of open inquiry and constructive disagreement—norms that are essential for the credibility of MMHAs and their capacity to issue trustworthy, evidence-based guidance.

12.3 Conclusion

The significant influence MMHAs exert over professional opinion, clinical practice, and healthcare policy extends broadly across the healthcare landscape. In the area of pediatric gender medicine, prominent MMHAs have aligned their clinical guidelines and policy statements with WPATH SOC-8. This reliance on WPATH guidelines effectively imported into MMHAs many of the methodological and ethical deficiencies documented in WPATH's guideline development process. Consequently, problems originating within WPATH have not remained isolated but have instead propagated through influential MMHAs, contributing to a broader erosion of clinical standards, scientific rigor, and open academic discourse.

Today, MMHAs wield considerable influence over both public and professional perceptions of medical practices through statements frequently cited in the media. These shape broader societal attitudes toward both the medical field generally and the practices within that field specifically. The implicit social contract underlying MMHAs' self-regulatory privileges rests on the expectation that these organizations will prioritize the best interests of patients and society. However, MMHAs' handling of issues related to PMT illustrates how institutional biases, reliance on external guidance from advocacy-oriented groups, and internal political dynamics can undermine their regulatory effectiveness and scientific credibility.

[37] See also Chapters 6-8.

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PART 4

ETHICS REVIEW

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Chapter 13 Ethical Considerations

This chapter discusses central ethical issues in pediatric medical transition (PMT), which involves the use of puberty blockers (PBs), cross-sex hormones (CSH), and surgery to suppress or alter the development of sex- and age-typical sex characteristics in physically healthy children or adolescents.[1] These interventions are used as treatment for the conditions of "Gender dysphoria" (GD) in the *Diagnostic and Statistical Manual* (DSM-5-TR) or "Gender incongruence of adolescence or adulthood" in the *International Classification of Diseases* (ICD-11).[2] In assessing the effects of PBs, CSH, and surgery, researchers typically focus on conventional psychiatric outcomes such as depression, anxiety, and suicidality; recently, some have added novel outcome measures such as "chest dysphoria," "appearance congruence," and "gender euphoria."[3]

However, some clinician-researchers have called into question what they call the "logic of improvement," according to which PMT is justified only if it enables "a progression from 'doing worse' to 'doing better,' ultimately leading to an overall improvement in the individual's functioning and well-being."[4] Acknowledging that the evidence that PMT has this effect is weak, these clinicians argue that conventional outcome measures should be supplemented with—if not replaced by—patient-determined outcomes.[5] In the same vein, other advocates of PMT claim that focusing on clinical improvement is "pathologizing" and question the need for any clinical indication beyond the adolescent's "embodiment goals"[6] or mere desire for the intervention.[7] The guiding question of this chapter is whether the provision of hormonal or surgical interventions for these shifting and sometimes contradictory purposes is consistent with well-established principles of

[1] Patients may reach Tanner Stage 2 of puberty by age 8 or 9. An 8- or 9-year-old person is uncontroversially a child. However, for the sake of brevity the remainder of this chapter will use "adolescents" rather than "children and adolescents" in most cases to refer to this patient population.
[2] American Psychiatric Association (2022); World Health Organization (2022b).
[3] See, respectively, Olson-Kennedy, Warus et al. (2018); Chen et al. (2023); Blacklock et al. (2025).
[4] Oosthoek et al. (2024, p. 10).
[5] Oosthoek et al. (2024, p. 17).
[6] Ashley (2019, pp. 480-482).
[7] Chu (2024).

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medical ethics. Despite the high stakes—medical, social, political, and legal—this urgent question has received relatively little critical attention from bioethicists.

After a brief note on consent (Section 13.1), Section 13.2 summarizes how the medical profession's shift away from medical paternalism toward shared decision-making has strengthened patient protections against unwanted medical interventions via the mechanism of informed consent. This move toward greater respect for patient autonomy, however, does not negate clinicians' professional and ethical obligation to protect and promote their patients' health.

Section 13.2.3 turns to the pediatric context, where the latter obligation is especially strict due to the distinctive vulnerability of children and adolescents as well as their underdeveloped decision-making capacity. The best available evidence indicates an unfavorable risk/benefit profile for the prescription of hormonal and surgical interventions for adolescents with GD. The prescription of these interventions also raises justice-related concerns for members of this medically and socially vulnerable population.

Section 13.3 examines an alternative justification for PMT, one grounded in a purported right to access the medical resources needed to satisfy the patient's preferences for body modification. The shift to this alternative justification, which follows researchers' decades-long inability to demonstrate clear medical benefit, suggests that advocates of PMT have significantly altered the criteria for success.[8] The chapter then turns to a brief discussion of patient regret in Section 13.4 before concluding with some remarks on research ethics in Section 13.5.

13.1 Consent

Some disagreements in this field center on the question of whether adolescents have medical decision-making competence (MDC)—that is, whether they can provide

[8] "Clinicians remarked that there is no agreed fixed point of reference on which to judge the success of an intervention, let alone a societal consensus on the appropriate response" (Cass, 2024a, Appendix 3, p. 9).

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informed consent or assent to transition-related medical interventions.[9] Some proponents of these interventions believe they can.[10] In support of this position, some point to research showing that many adolescent patients have MDC as assessed using a quantitative semi-structured interview tool.[11] They also note that there are other invasive, life-shaping interventions to which adolescents and their guardians commonly and unproblematically assent or consent. For example, an adolescent may assent to treatment of leukemia, even when the treatment may cause future infertility. An adolescent also may assent to amputation of a limb that is diseased or damaged beyond repair. There are many similar situations in which assent by the adolescent, and legal consent by the parents, is given to an intervention necessary to preserve the adolescent's overall health but which also causes foreseen serious adverse side effects.

Some critics of PMT, on the other hand, maintain that patients—some of whom are only 8 or 9 years old when they reach Tanner Stage 2 of puberty and thereby become candidates for PBs[12]—are too immature[13] to adequately understand the full range of consequences of medical transition. These young people cannot deliberate about the relevant considerations in a manner that is appropriately attentive to the seriousness and complexity of the decision. Critics point out that even proponents of PMT recognize that children and adolescents lack the cognitive and social maturity to deliberate well about their future fertility.[14]

Moreover, critics assert—reasonably[15]—that providers of PMT often fail properly to inform patients and their guardians about the uncertainty of the clinical evidence for medical benefit and that they overstate the probability and magnitude of the harms of

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[9] "Consent" and "assent" here are technical terms. In the U.S. minors cannot provide *legal consent* for medical treatment (there are limited exceptions, e.g. for emancipated minors or for a narrow range of interventions such as treatment for sexually transmitted infections). Guardians provide legal consent while minors provide *assent*, or agreement to the intervention.
[10] Giordano et al. (2021); Mosier-Mills et al. (2024).
[11] Vrouenraets et al. (2021); See also Marino et al. (2024).
[12] See Chapter 7.
[13] Diekema (2020).
[14] Vrouenraets et al. (2022).
[15] See Chapter 11.

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non-medicalization.[16] Finally, as noted in Chapter 2, clinicians providing PMT routinely employ euphemistic and morally loaded language, which can mislead or unduly influence patients and their guardians. The concern, then, is that this combination of high pressure, low information, and reflexive "affirmation" undermines the possibility of genuinely informed consent or assent.

Informed consent is critically important, but before it is even a consideration, the intervention must be otherwise ethically permissible. For example, before asking whether patients can consent to any proposed intervention, from antibiotics to lobotomy, a clinician must determine whether the intervention has a favorable risk/benefit profile as a treatment for the patient's condition. Thus, while informed consent plays a central role in medical ethics and clinical practice and informs discussions about the distinctive challenges that attend decision-making in pediatrics, this Review's ethical analysis of PMT focuses primarily on the necessarily prior step. Namely: do these interventions have favorable risk/benefit profiles?

13.2 From paternalism to shared decision-making and patient-centered care

Over the course of the 20th century, advances in the biomedical sciences, expansion of healthcare delivery systems, increasing professionalization in medicine, and a series of medical scandals and seminal legal cases led to greater sensitivity among clinicians and researchers to the rights of patients and participants in medical research. Judges, regulators, lawmakers, and ethicists introduced constraints on the power of clinicians to impose their values, preferences, and perspectives on patients.[17] The "paternalistic model" in medicine, according to which "doctor knows best," gave way to a more egalitarian model of "shared decision-making" that emphasizes respect for the autonomy and authority of competent patients and research participants. There is now universal consensus that respect for patient autonomy requires clinicians to provide patients with information relevant to their medical options and to act on competent

[16] Reluctant parents have reported being asked by their child's clinicians whether they (the parents) preferred having "a dead son or a living daughter." In an interview, Dr. Johanna Olson-Kennedy stated, "We often ask parents, Would you rather have a dead son than a live daughter?" (ABC News, 2011).
[17] Faden et al. (1986).

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patients only with patients' consent. As the American Medical Association's *Code of Medical Ethics* puts it, patients have the right "[t]o make decisions about the care the physician recommends and to have those decisions respected. A patient who has decision-making capacity may accept or refuse any recommended medical intervention."[18] Patients are protected from unwanted medical interventions not only by professional and ethical norms but by the law. As Justice Cardozo famously wrote, "a surgeon who performs an operation without his patient's consent, commits an assault, for which he is liable in damages."[19]

13.2.1 Respect for autonomy vs *caveat emptor*

Crucially, the shift from medical paternalism to shared decision-making does not absolve clinicians of their ethical and professional obligation to protect and promote the health and well-being of their patients. Beneficence "undergirds all medical and health care professions and their institutional settings."[20] As mentioned in Chapter 1, clinicians have ancient but enduring ethical duties to avoid harming their patients and to promote their health and welfare: "The health and well-being of my patient will be my first consideration."[21]

The principle of respect for patient autonomy does not justify subjecting patients to interventions that pose medically unnecessary risks of harm, or which are otherwise nonbeneficial, even when patients prefer, request, or demand those interventions. An ethical analysis of PMT published by Finnish health authorities provides a succinct explanation:

> In healthcare, self-determination primarily manifests as the right to refuse treatments within the available service spectrum. This principle must be balanced against the freedom of individuals to express their own gender identity. Nevertheless, autonomy in healthcare does not imply unrestricted freedom to select treatments based purely on personal preference; rather, patient autonomy

[18] American Medical Association (2016).
[19] Schloendorff v. Society of New York Hospital (1914).
[20] Beauchamp & Childress (2019, p. 217)
[21] Parsa-Parsi (2017, p. 1971).

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> involves the choice among treatments *that are medically justified* and included within the recognized service options.[22]

The well-established moral and legal right of competent patients to refuse any medical intervention does not entail a corollary right to receive nonbeneficial interventions. The Institute of Medicine's Committee on Quality of Health Care in America warns clinicians against providing interventions based on this illicit inference, stating, "When a patient seeks inappropriate health care services, the challenge for clinicians is to find ways of reducing this conflict … If a conflict cannot be resolved through counseling, the clinician should refuse to provide nonbeneficial services."[23]

In refusing requests for nonbeneficial interventions, clinicians do not force anything upon their patients. They do not threaten, deceive, or mislead them. Nor do they withhold relevant information about risks, benefits, and available alternatives. In other words, withholding nonbeneficial interventions does not entail acting on patients without their informed consent. Conflating the right of patients to refuse medical intervention or to choose among the beneficial options offered by their clinicians with the wholly separate "right" to determine which interventions must be offered transforms the ethos of beneficent respect in medicine to the crude, responsibility-abdicating ethos of medical consumerism: *caveat emptor.*

> Using patient autonomy to justify acquiescence to patients' requests for nonbeneficial services violates professional integrity. Professional integrity requires physicians to adhere to standards of intellectual and moral excellence. Physicians achieve intellectual excellence by submitting clinical judgment to disciplined, evidence-based reasoning. Physicians achieve moral excellence by protecting patients' health-related interests as a primary concern, keeping self-

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[22] Saarni & Uusitalo (2020, p. 41, emphasis added). Original text: "Itsemääräämisoikeus terveydenhuollossa toteutuu ensisijaisesti oikeutena kieltäytyä palveluvalikoimaan kuuluvista hoitotoimista. Tämä on tasapainotettava sen näkökulman kanssa, että ihmiset saavat itse vapaasti ilmaista omaa sukupuolista identiteettiään. Autonomialla ei terveydenhuollossa kuitenkaan tarkoiteta vapaata oikeutta valita hoitoja omien preferenssien perusteella, vaan potilas voi valita palveluvalikoiman ja lääketieteellisesti perusteltujen hoitomuotojen sisällä."

[23] Committee on Quality of Health Care in America, Institute of Medicine (2001, p. 77). See also the "Physicians Charter" mentioned in Section 1.3.

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> interests systematically secondary. Commitment to professional integrity requires that physicians challenge requests for nonbeneficial interventions.[24]

13.2.2 Nonmaleficence, beneficence, and autonomy in pediatrics

Uncontroversially, then, the norms of medicine require clinicians to protect and promote the health and well-being of their patients. This means they must abstain from providing nonbeneficial interventions even when such interventions are requested by competent patients. In the domain of pediatrics, these norms limit the authority not only of patients (who in any case lack full decision-making capacity) but of parents as well. The American Academy of Pediatrics' (AAP) Committee on Bioethics puts it as follows:

> Pediatric health care providers have legal and ethical duties to provide a standard of care that meets the pediatric patient's needs and not necessarily what the parents desire or request. Parental decision-making should primarily be understood as parents' responsibility to support the interests of their child and to preserve family relationships, rather than being focused on their rights to express their own autonomous choices. It is important to note that parental authority regarding medical decision-making for their minor child or young adult who lacks the capacity for medical decision-making is constrained compared with the more robust autonomy in medical decision-making enjoyed by competent adults making decisions regarding their own care.[25]

The "constraint" on patient and parental authority is grounded in the medical best interests of the child:

> In pediatrics, the duties to protect and promote health-related interests of the child and adolescent by the physician are also grounded in the fiduciary relationship (to act in the best interest of the patient and subordinating one's own interests) between the physician and patient, but these duties may conflict with the parent's or patient's wishes …[26]

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[24] Brett & McCullough (2012, p. 149).
[25] Committee on Bioethics et al. (2016, p. e5). First published in 2016, this report was reaffirmed by the AAP in 2023.
[26] Committee on Bioethics et al. (2016, p. e2).

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In its influential policy statement, "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents," the AAP states that in navigating disagreements between parents and children clinicians should "maintain their primary responsibility to the welfare of the child."[27] Thus, while the statement recommends that "transgender and gender-diverse" youth have access to PMT, this recommendation is contingent not on the autonomy rights of patients or their guardians,[28] but rather on these interventions' purported contribution to patient health and well-being. [29] This affirms the longstanding, consensus view of medicine's fundamental aim as protecting and promoting the health and well-being of patients.

13.2.3 Risk/benefit in pediatric medical transition

To discharge their duties of nonmaleficence and beneficence, clinicians must ensure, insofar as reasonably possible, that any interventions they offer to patients have clinically favorable risk/benefit profiles relative to the set of available alternatives, which includes doing nothing.[30] As described in Chapter 5, systematic reviews (SRs) of the

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[27] Rafferty et al. (2018, p. 8).
[28] Bester (2024).
[29] It is worth noting, however, that while the AAP and WPATH support PMT, they do not promote intervening over a patient's objections. Neither group holds that a patient with gender dysphoria/incongruence who refuses puberty blockers, cross-sex hormones, or surgery should be strongly encouraged or, if necessary, forced to receive them. This distinguishes medical transition from other interventions claimed to offer great, potentially lifesaving benefit. In gender medicine and perhaps nowhere else, whether transition-related medical interventions are deemed medically necessary seems to hinge largely on whether the patient desires them. See Chapter 11 for more on this issue.
[30] An intervention has a clinically favorable risk/benefit profile when the expected medical benefits outweigh the expected medical harms. Expected benefits and harms are determined by their probabilities and magnitudes. This is a standard method for guiding action and policy, including in medicine, though the precise manner in which it is carried out can vary and depends on many variables, including risk tolerance, the way "benefit" and "harm" are defined and measured, the way probabilities are assigned, and the way uncertainty/ignorance is accounted for. Of course, it would not be difficult to adopt expected utility theory, defining "benefit" and "harm" and assigning values to the relevant variables, in a way that would render a verdict markedly different from the negative one reached in this Review. That said, the claims made here about the probability and magnitude of harms and benefits are grounded in the best available evidence. Sometimes, the probabilities are known with a high degree of certainty. For example, the probability that mastectomy will lead to an inability to breastfeed is 1.0 or close to it. Puberty blockers and cross-sex hormones threaten sexual function, though the precise magnitude of the problem and its distribution in the treated patient population is unknown. Where precise or even rough values are not available due to the absence of quality research, the analysis in this Review assumes plausible, if rough, estimates. As for the nature of medical benefits and harms and their relative weights, the Review's working assumptions cohere with common moral intuition, standard medical judgment as revealed in medical diagnostic criteria, and the outcomes of interest to clinicians and researchers, as well as the law. For example, the analysis would conclude that a minor improvement in depressive symptoms does count

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evidence for benefit of hormonal or surgical intervention in the treatment of GD in adolescents have concluded that this evidence is of low or very low certainty. This means that the true effects of the interventions may or are likely to be substantially different from the effects reported in the studies.[31] In other words, the best available evidence indicates that PBs, CSH, and surgery have not been shown to improve mental health outcomes.

At the same time, there is increasing recognition of the risks and harms associated with PMT, which are supported by clinical research or grounded in established biological theory.[32] While the value or disvalue of some outcomes, such as hirsutism in females, may be determined primarily by the preferences or tastes of patients, other possible outcomes, such as impaired cognitive function, greater susceptibility to hormone-sensitive cancers, cardiac disease, reduced bone density, sexual dysfunction, infection, and infertility[33] are objectively detrimental to health. Such medical harms, or plausible

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as a benefit but that such a benefit, even if assured, does not outweigh moderate or even low but non-negligible risks of infertility or serious sexual dysfunction, loss of breastfeeding function, or lifelong medical dependency, which the Review considers harms.

[31] Balshem et al. (2011).

[32] See Chapter 5 and Chapter 7.

[33] It may be objected that infertility is not necessarily a harm. One version of this objection is that for some young patients, perhaps those who have very clearly expressed that they do not want and will never want genetically-related children, infertility is not a harm since it is consistent with their chosen life plan. The response to this objection is that the medical profession does not ordinarily permit voluntary permanent contraception (sterilization) in children or adolescents and always takes the risk of infertility seriously in assessing the risk/benefit profile of any intervention that plausibly may impact reproductive health. That is to say that as a matter of well-established sociological fact, infertility is recognized by the medical profession as a harm (Geis et al., 2024). The second version of the objection relies on the claim that some patients are willing to accept infertility as a consequence of medical transition, even if they do not intend infertility. These patients prefer to remain fertile, all else being equal, but because all else is not equal they accept interventions that will undermine their fertility. The response to this objection is that such preferences reveal that these patients view infertility as a harm. The real question in the latter case is whether there is good reason to believe that the benefits of medical intervention outweigh this harm, and the answer to this question will depend on the evidence regarding benefits. Finally, research suggests that many transgender-identified people do want children and that some who medically transition experience decisional regret over their infertility. This suggests they also view infertility as a harm even if they do not regret their transition. See Asseler et al. (2024); Stolk et al. (2023).

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risks thereof,[34] should not be imposed on children or adolescents in the absence of a reasonable expectation of proportionate medical benefit.[35]

Although a favorable risk/benefit profile is necessary to justify an intervention, it is not sufficient.[36] The intervention must be favorable relative not only to doing nothing but also to other known alternatives. With respect to PMT, a relevant alternative is some combination of psychotherapeutic interventions.[37] Like the evidence for hormonal and surgical interventions, evidence regarding alternative approaches to GD is sparse and inconclusive,[38] though as Chapter 14 reveals there is good reason to believe that psychotherapy can be an effective intervention. Regarding the potential harms of psychotherapy for adolescents with GD, a systematic review of the evidence found no evidence of negative or adverse effects in any of the studies examined.[39]

One possible objection is that although the evidence supporting hormonal and surgical interventions is of low or very low certainty, this does not prove that the interventions are ineffective. For all we know, the interventions may be *more* effective than researchers have reported. The methodological weaknesses of the studies do not prove inefficacy—they tell us only that we cannot infer much of anything about beneficial effects. The same limitations apply to evidence on harms—after all, because there are no well-designed randomized controlled trials (RCTs) of PMT, it follows that there are no well-designed RCTs demonstrating sexual dysfunction, infertility, bone density loss, impaired cognitive function, susceptibility to hormone-sensitive cancers, and other potential harms. Some argue that in the face of uncertain evidence both for benefit and for harm, patients themselves (and their families), with expert clinicians providing relevant clinical

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[34] Sweden's National Board of Health and Welfare concluded that "the risks of puberty blockers and gender-affirming treatment are likely to outweigh the expected benefits of these treatments" (Socialstyrelsen, 2022a, p. 3).
[35] The "should not" here is a moral "should not." It does not entail any conclusions about what the law should permit or require. The relationship between ethics and the law is complex and is not taken up in this Review.
[36] If considerations not directly related to health are included in the risk/benefit analysis, there may be cases where an intervention that is marginally less effective in promoting health may be recommended (e.g. when the marginally more effective treatment is much more expensive). And of course, to say that the clinicians should offer the more favorable intervention is not to say that patients do not have the right (in most cases) to refuse it.
[37] See Chapter 14.
[38] Cass (2024a, pp. 153-154).
[39] Heathcote et al. (2024, pp. s19-s32, Suppl. 2).

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information, should decide how to proceed.[40] Medical decisions under uncertainty, the reasoning goes, should be made by those with the greatest personal stake in the outcome. In pediatrics, this means children and adolescents, supported (usually) by their families.

This objection properly expresses concern for patient health and well-being as well as respect for the developing decision-making capacity of children and adolescents (and the greater capacity of their guardians). But it fails, for two reasons.

First, the objection understates the cumulative case for evidence of harm. We can be certain in the ordinary sense of "certain" that these interventions cause harm, even if we do not have "high certainty" evidence in the technical sense employed in evidence-based medicine (EBM).[41] We do not need results from RCTs to be certain that removing an adolescent's breasts will eliminate or substantially impair capacity for breastfeeding. Nor do we need RCTs to establish that PBs and CSH stunt growth of the penis, increasing the risks associated with future surgery.[42] And apart from any systematic reviews of published studies, basic human physiology indicates that blocking puberty at Tanner Stage 2 and following with CSH will negatively impact fertility. That advocates of PMT recommend fertility counselling before undergoing these interventions is evidence that they, too, anticipate the risk of infertility and regard it as a harm. Other forms of evidence, such as indirect evidence from research on adults, also contribute to the case that these interventions cause harm.[43] Finally, research on PMT has focused largely on potential benefits to mental health, with less attention given to potential physical harms, compounding the problem of publication bias.[44]

Second, even granting that the uncertainty of the evidence makes it impossible to assign precise values to the probabilities or magnitudes of various potential outcomes, it does not follow that clinicians are dependent on their patients to guide clinical decision-

[40] Antommaria (2024).
[41] Smith & Pell (2003)
[42] Terhune et al. (2022).
[43] See Chapter 7.
[44] See Chapter 6 for discussion of publication bias.

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making.[45] Rather, the obligation to avoid serious harm justifies a precautionary approach, particularly in the absence of evidence for a proportionately serious threat to the patient's health without the intervention. In their seminal textbook on medical ethics, Beauchamp and Childress write:

> Depending on what is valued and what is at risk, it may be ethically justifiable and even obligatory to take steps, in the absence of conclusive scientific evidence, to avoid a hazard where the harm would be both serious and irreversible—that is, a catastrophe. Triggering conditions for these measures include plausible evidence of potential major harm where it is not possible to adequately characterize and quantify risk because of scientific uncertainty and ignorance. The process of developing precautionary norms should not be viewed as an alternative to risk analysis and scientific research. It should instead be viewed as a way to supplement risk appraisals when the available scientific evidence does not permit firm characterizations of the probability or magnitude of plausible risks.[46]

It seems clear that the triggering conditions for adopting a precautionary approach to the use of hormonal and surgical interventions for the treatment of pediatric GD have been met. When precautionary considerations are added to the cumulative case for harm, the ethical argument against PMT becomes compelling.

> The importance of avoiding harm is emphasized by the fact that many treatments (e.g., surgery, hormone therapy) can lead to relatively common and potentially serious long-term adverse effects. This necessitates particularly strong justification (i.e., clear evidence of benefits and the decision-maker's competence) before administering such treatments or accepting these risks. In practice, physically modifying healthy bodies is generally associated with potential harms or risks. Empirical evidence concerning the long-term benefit-to-harm ratio of these interventions is often limited. In other words, avoiding harm

[45] One would hope this would come as a relief to clinicians and especially to pediatricians, though some seem happy to let children lead the way. See Chapter 11.
[46] Beauchamp & Childress (2019, p. 250)

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> prompts considerations similar to those raised by competence: when evidence of benefit is uncertain, but risks are probable, the ethical imperative to minimize harm is further underscored.[47]

The unfavorable risk/benefit profile distinguishes PMT from many other off-label uses of drugs and medical devices. Advocates for PMT point to the prevalence of off-label prescribing in pediatrics,[48] but the legitimacy of some off-label uses does not license the prescription of any pharmaceutical to any patient for any reason. The favorable risk/benefit threshold, or, more minimally, the precautionary threshold, must be met irrespective of whether the intervention is approved by FDA. Off-label use of an intervention is sometimes justifiable based on studies of the intervention in a different patient population or for a different indication. Such use may be warranted when there is a reasonable expectation of benefit, when there are no superior alternatives, and when the prognosis, absent medical intervention, is predicted to be worse for the patient than the negative effects of the off-label drug.

This is decidedly not the situation with PMT. The natural history of pediatric GD is poorly understood[49] and decades of research has shown that early-onset GD usually resolves without medical intervention.[50] There is no compelling evidence that the same will not prove true in the case of adolescent-onset symptoms, and limited evidence suggesting it will.[51] And in any case, it is widely acknowledged that clinicians are unable to distinguish patients whose GD will persist from those whose GD will resolve.[52] Further,

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[47] Saarni & Uusitalo (2020, p. 41); our translation. Original text: “Haittojen välttämisen tärkeyttä korostaa se, että monista hoidoista voi seurata varsin yleisiä ja vakaviakin pitkän tähtäimen haittoja (esim. kirurgia, hormonihoidot), jolloin hoitojen antamiselle (eli näiden riskien ottamiselle) pitää olla erityisen hyvät perusteet (eli näyttö hyödyistä sekä päätöksentekijän kompetenssista). Käytännössä terveiden kehojen fyysiseen muokkaukseen voidaan katsoa useimmissa tapauksissa liittyvän haittoja tai riskejä. Empiirinen näyttö hoitojen pitkän tähtäimen hyöty/haitta-suhteesta on useissa tapauksissa vähäistä. Toisin sanoen haitan välttäminen johtaa siis samankaltaiseen pohdintaan kuin kompetenssikysymys: jos näyttö hyödyistä on epävarmaa mutta haitat todennäköisiä, haittojen minimoinnin tärkeys eettisenä periaatteena korostuu.”

[48] Meng et al. (2022).

[49] See Chapter 4.

[50] Ristori & Steensma (2016); Singh et al. (2021).

[51] Bachmann et al. (2024); Byrne (2024a); Rawee et al. (2024); Sun et al. (2023)

[52] “Although a diagnosis of gender dysphoria has been seen as necessary for initiating medical treatment, it is not reliably predictive of whether that young person will have longstanding gender incongruence in the future, or whether medical intervention will be the best option for them.” (Cass, 2024a, p. 29). The

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there are concerns about the role medicalization itself may play in contributing to the persistence of the conditions being treated,[53] and less invasive and less risky interventions are available.[54] Lastly, medical intervention has known and plausible harms,[55] and decades of research conducted by leading academic institutions have failed to produce reliable evidence of medical benefit.[56]

13.2.4 Justice

According to the Belmont Report, published in 1978 in the wake of the U.S. Public Health Service's Untreated Syphilis Study at Tuskegee, "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly."[57] While the Belmont report set out ethical principles to guide human subjects research, the principle of justice applies also to clinical medicine. Advocates for PMT sometimes claim it is unjust to withhold PBs, CSH, or surgeries from youth with GD.[58] They cite research finding that this patient population has significant healthcare needs and also suffers from social marginalization and stigma.[59] These patients indeed are vulnerable along multiple axes, and it would be an injustice to deny them safe and effective medical care. It would also be unjust, however, to subject them to serious hormonal and surgical interventions that lack a favorable risk/benefit profile. In fact, it seems particularly unjust to subject youth struggling with complex psychiatric, neurodevelopmental, and psychosocial challenges to the harms associated with these interventions. The justice principle has been rightly invoked but wrongly applied.

In both her Interim and Final Reports, Cass notes concerns brought to her by patients and families about "diagnostic overshadowing."[60] Diagnostic overshadowing is a form of

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recent German clinical guidelines note that its own review found no studies that could supply empirical criteria to determine whether GD or gender incongruence would persist into or beyond adolescence (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP), 2025, p. 188).

[53] Jorgensen (2023a).
[54] See Chapter 14.
[55] See Chapter 7.
[56] See Chapter 5.
[57] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (2010).
[58] Kimberly et al. (2018); Maung (2024).
[59] Hatzenbuehler & Pachankis (2016); Rider et al. (2018).
[60] Cass (2022a, p. 46; 2024b, p. 200).

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bias that leads clinicians to misattribute symptoms of one condition to a different previously diagnosed condition. This can happen, for example, when clinicians mistakenly attribute patients' complaints of physical discomfort to the patient's previously diagnosed psychiatric condition, a mistake that may lead to misdiagnosis and inadequate treatment.[61] Diagnostic overshadowing is especially salient in mental health care contexts, where a patient with psychiatric problems, neurodevelopmental challenges, or cognitive disabilities may be treated one-dimensionally as a "case" of some psychiatric diagnosis rather than holistically as a person susceptible to a range of health problems unrelated to that diagnosis.

In the context of PMT, the concern is that the diagnosis of GD tends to obscure causes of distress and crowd out other mental health care needs, particularly when patients are referred to specialty gender clinics. The gender clinic model of care becomes Maslow's hammer to which every problem appears as a nail. The risk of diagnostic overshadowing increases insofar as (1) clinicians fail to provide comprehensive psychiatric evaluations;[62] (2) clinicians face pressure from colleagues, patients, and parents to "affirm" patients prematurely, that is, prior to providing them sufficient time to develop and mature;[63] and (3) co-occurring mental health challenges or problem behaviors are reflexively assumed to be minority stress-mediated sequelae of the patient's GD diagnosis.[64] To neglect the mental health care needs of members of an already vulnerable population of youth with complex psychiatric, neurodevelopmental, and psychosocial challenges is to deny them a benefit to which they are entitled, and to expose them to medically unnecessary risk of harm is to impose a burden unduly.

There are additional problems related to justice. Compared to their age-matched peers, same-sex attracted youth are significantly overrepresented among patients presenting to gender clinics.[65] As noted in Chapter 3, this phenomenon has been observed from the beginning. Of the 70 patients recruited by de Vries and colleagues in the

[61] Hallyburton (2022); Jones et al. (2008); Reiss et al. (1982).
[62] Damiano (2024a).
[63] Edwards-Leeper & Anderson (2021).
[64] Papers claiming minority stress explains various health problems of transgender-identified adolescents include Delozier et al. (2020); Dolotina & Turban (2022); Hunter et al. (2021).
[65] Drescher & Yarbrough (2024); Singh et al. (2021); Wood et al. (2013).

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Netherlands from 2000 to 2008, 62 reported being exclusively same-sex attracted, six reported being bisexual, and one reported being exclusively opposite-sex attracted.[66] That is, the original Dutch Protocol patient cohort was comprised almost entirely of gay, lesbian, and bisexual patients[67]—one of whom died as a result of surgical complications from vaginoplasty following pubertal blockade and cross-sex hormones.[68] Reports of negative attitudes towards homosexuality, which may be internalized, are not uncommon in this field.[69] One of the earliest clinical reports on adolescent transition describes a family concerned that their son's gender nonconformity was a sign of homosexuality.

> It is of interest to note that [the patient's family] were all reassured to discover that George was not a *homosexual*. The diagnosis of 'transexual' provided an explanation for his feminine behavior and was, especially for the parents, psychologically relieving.[70]

Given the medical profession's history of pathologizing and medicalizing same-sex attraction,[71] serious justice-related concerns are raised by the overrepresentation of gay, lesbian, and bisexual adolescents among patients receiving unproven interventions that adversely impact fertility and sexual function.

13.3 Alternative clinical rationales

Clinical research on pediatric medical transition has focused primarily on its effects on psychiatric morbidity and to a lesser extent on psychosocial function. The original Dutch

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[66] de Vries et al. (2011, Table 1). The remaining one patient reported "don't know yet."
[67] Biggs (2023b).
[68] Biggs (2023b); de Vries et al. (2014); Negenborn et al. (2017) Bachmann et al. (2024); Sun et al. (2023).
[69] Barnes (2023); Sansfaçon et al. (2023); Littman (2021).
[70] Newman (1970). Given clinician reports of his self-reported sexual behavior and desires, it is almost certain that George was gay.
[71] Hodge (1950); Murphy (1992); Shidlo et al. (2001). From Hodge: "Male aged 37 years, who came voluntarily, being concerned by his definite homosexual bias which, though it had not since puberty found overt expression, was nevertheless a source of great worry and unhappiness … He appeared after close investigation to be a homosexual deviant of very long standing—an 'innate' pattern rather than one of traumatic 'level fixation'—and he failed to respond to psychotherapy. Treatment by oestrone has been followed by loss of sexual libido and he reports considerable 'mental relief.'" (p. 135) See also Chapter 3 for the influential case of George/Christine Jorgensen and the subsequent wave of lesbian and gay people who sought medical transition.

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Protocol required patients to have "Gender Identity Disorder" (GID), as GD was then called. The diagnostic criteria for GID and its DSM-5 successor GD include clinically significant distress and/or functional impairment.[72] While the diagnostic criteria for GD closely mirror the previous criteria for GID, the DSM-5 more explicitly emphasizes that cross-sex identity, by itself, does not constitute a pathology. The attendant distress, if present, is what is pathological. As such, medical interventions target the patient's distress or impairment, not the underlying identification.

That patients must have a mental health disorder to access medical resources has long troubled some patients and advocacy groups.[73,74] Some clinical protocols require patients to undergo assessment to determine if they meet (*inter alia*) the distress or impairment criterion—it is not enough that a patient attests to cross-sex identification or incongruence. These criteria thereby create an impediment[75] for people who do not suffer distress or impairment but who nevertheless wish to medically alter their bodies. To access the interventions they want, these patients may need to exaggerate or feign symptoms or else shop for clinicians willing to rubber stamp a diagnosis.[76]

One possible solution to this challenge is simply to eliminate any requirement for a medical diagnosis. Doing this would remove the obstacle of assessment from the path of patients seeking medical interventions. The problem with this solution for the DSM and the ICD working groups was that removing the diagnoses altogether would make reimbursement for medical intervention difficult or impossible. The tension between

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[72] Because GID and GD are DSM diagnoses and the DSM is a manual of mental disorders, this is not surprising. However, it does constrain the options available to clinician-researchers insofar as reimbursement requires a DSM diagnosis, i.e. the categorization of the patient as suffering from a mental disorder.

[73] Drescher (2017).

[74] Objections to medical "gatekeeping" and tensions between patients and clinicians regarding the pathologization of cross-sex identification predate the Dutch Protocol and the medicalization of pediatric gender distress by decades. Adults, wishing for hormones and surgeries to satisfy their longing to modify their bodies and to be perceived as members of the other sex, have butted heads with psychiatrists, psychologists, endocrinologists, and surgeons since the early 20th century when the first "sex change" procedures took place. Disciplinary turf wars between experts, with each field vying for authority over diagnosis and treatment, contributed to the ongoing professional uncertainty over the fundamental aims of medical intervention and the appropriate balance of power between patients and clinicians. See Meyerowitz (2009); Shuster (2021).

[75] Jacobsen (2024).

[76] For accounts of patients feigning symptoms and manufacturing histories in order to convince clinicians of their medical need, see Ashley (2019); Pimenoff & Pfäfflin (2011); Shuster (2021).

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ensuring reimbursement and thereby access, on the one hand, and satisfying the demands of patients and activist groups for depathologization, on the other, required compromises on the part of DSM and ICD developers.[77] The DSM developers depathologized incongruence and pathologized distress. The ICD-11 developers had more options because unlike the DSM, which is devoted exclusively to mental disorders, the ICD catalogues all diseases and health conditions. Having considered the various possibilities,[78] the ICD-11 working group decided to move the diagnosis out of the mental health chapter, where it was believed to contribute to stigma, and into a new chapter, "Conditions Related to Sexual Health," where it would be less stigmatizing but still useful for purposes of reimbursement.

Consequently, present DSM and ICD diagnoses comprise different frameworks shaped by historical contingencies—including, crucially, payment considerations.[79] According to the DSM-5, experiencing gender incongruence itself is not pathological, while associated distress or impairment are, rendering GD a mental disorder. Meanwhile, according to the ICD-11, gender incongruence (that is, being transgender according to contemporary understandings of what it is to be transgender) itself is pathological, but not a mental health disorder. ICD-11's diagnosis, Gender Incongruence of Adolescence or Adulthood, includes no requirement of distress or impairment for medicalization. Thus, DSM-5 and ICD-11 differ on whether hormonal and surgical interventions are treatments for a mental health problem or rather some other kind of pathology, on whether transgender identity itself is pathological, and on whether a patient must be distressed or impaired to receive reimbursable medical intervention. Despite these differences and inconsistencies, both diagnoses are employed to justify and reimburse the provision of hormonal and surgical interventions to adolescents.

The more permissive approach to medicalization is defended by some clinicians,[80] bioethicists, and activists.[81] For example, bioethicist Florence Ashley argues that the

[77] Drescher (2015).
[78] Drescher et al. (2012).
[79] See Drescher (2015); Drescher & Yarbrough (2024).
[80] See Chapter 11.
[81] Chu (2024).

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provision of hormonal and surgical interventions to adolescents is justified by the interventions' capacity to satisfy patients' "gender embodiment goals":

> Adolescent medical transition aims at preventing or altering the development of sexual characteristics to achieve the individual's gender embodiment goals. Given its purpose, the effectiveness of adolescent medical transition is defined by its ability to achieve the sought physiological outcomes—a standard undisputedly met.[82]

While the Dutch Protocol was designed to alleviate adolescents' psychiatric distress and improve psychosocial functioning, Ashley's approach drops the requirement of clinical improvement—achieving the patient's embodiment goals is enough.[83] Elsewhere, Ashley explains that some people seek hormonal or surgical interventions not because they are suffering from a pathology but rather because these treatments can deliver certain desired experiences such as "gender euphoria" and "creative transfiguration." Gender euphoria is a "distinct enjoyment or satisfaction caused by the correspondence between the person's gender identity and gendered features associated with a gender other than the one assigned at birth."[84,85] Creative transfiguration, Ashley writes, "is more difficult to capture in words. Foregrounding creativity and aspirational aesthetics, creative transfiguration sees the body as a gendered art piece that can be made ours through transition-related interventions."[86]

Because contemporary gender medicine countenances a multiplicity of "genders," this newer emphasis on embodiment goals moves beyond the "sex change" framework of previous decades, in which male patients acquired female-typical characteristics to "live as women" and female patients acquired male-typical characteristics to "live as men"

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[82] Ashley (2022a, p. 127).
[83] See Gorin (2024). It is notable that de Vries, the lead author of the two seminal papers (de Vries et al 2011 and 2014) that established the Dutch Protocol, has more recently questioned the "logic of improvement" that undergirds that original clinical rationale and has favorably cited the approach advocated by Ashley (Oosthoek et al., 2024).
[84] Ashley & Ells (2018, p. 24). The definition of gender euphoria offered by Ashley and Ellis entails that no one who does not experience incongruence can experience gender euphoria. According to other writers, however, gender euphoria is "quite common… among trans and cis folks alike." (Kukla, 2024, p. 288).
[85] Researchers recently have developed a scale intended to measure gender euphoria (Blacklock et al., 2025).
[86] Ashley (2019, p. 481).

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(see Chapter 3). Nothing in the newer "gender affirming" approach limits the number of bodily variations clinicians may be asked to create. Some girls or women want just a bit of stubble while others want full beards and flat chests; some boys or men want softer skin and breasts but wish to keep their penises intact. Expanding clinical offerings reflect these expanding embodiment goals. Surgeons provide penis-preserving vaginoplasty for patients who want both male and female genitals and offer "nullification" procedures for patients who identify as nonbinary and want no external genitals at all. There are at least as many physical combinations for patients to acquire as there are "gender identities"—indeed more, since presumably each gender identity can be embodied in different ways.[87]

While the ICD-11 does not mention "gender euphoria" or "gendered art pieces," the diagnostic criteria for Gender Incongruence of Adolescence or Adulthood implicitly formalize the "embodiment goals" approach to medical transition. The diagnosis is explained as follows:

> Gender Incongruence of Adolescence and Adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.[88]

According to Jack Drescher, a member of the World Health Organization's (WHO) Working Group on the Classification of Sexual Disorders and Sexual Health, which was tasked with making recommendations for the ICD's eleventh edition, to qualify for the diagnosis of Gender Incongruence of Adolescence or Adulthood, a patient need satisfy only two of the following four criteria:

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[87] James et al. (2015).
[88] World Health Organization (2022b).

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1. Strong dislike or disagreement with primary or secondary sexual characteristics due to incongruence with the experienced gender.

2. Strong desire to get rid of some of those sexual characteristics due to the incongruence with the experienced gender.

3. Strong desire to have the primary or secondary sexual characteristics of the experienced gender.

4. Strong desire to be treated and accepted as a person of the felt gender.[89]

It is hard to see how either of the first two criteria could be used to diagnose gender incongruence. ICD-11 says that gender incongruence is "characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex …"[90] Criteria (1) and (2) themselves include incongruence and so the diagnosis, when met by the first two criteria, suggests that a person has gender incongruence because they have attitudes or desires due to incongruence.[91]

Setting problems of circularity aside, an adolescent can be diagnosed with gender incongruence by satisfying (3) and (4),[92] which amount to having certain strong embodiment goals. A male who strongly desires to have (some? all?) the sex characteristics of a female and to be treated or accepted as such, or a female who strongly desires to have (some? all?) the sex characteristics of a male and to be treated or accepted as such, qualifies for the diagnosis. According to the ICD-11, a patient with such desires has a "condition related to sexual health" and, therefore, clinicians have a rationale for providing, and being reimbursed for, hormonal or surgical interventions.

It is noteworthy that the ICD-11 employs identical diagnostic criteria for adolescents and adults, despite the clear physiological and psychological developmental differences

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[89] Drescher & Yarbrough (2024, p. 2508).
[90] World Health Organization (2022a).
[91] The problem of circularity is also discussed in Chapter 2. It is also unclear what it could mean to be in a state of "disagreement" with one's sex characteristics. Perhaps the authors mean that one finds one's sex characteristics disagreeable, that is, unpleasant. This makes sense, as long as the unpleasantness does not rise to the level of distress, which would transform gender incongruence into something like gender dysphoria and thereby undermine the rationale for moving the gender incongruence diagnosis out of the mental disorder chapter of ICD-11.
[92] Whether the criteria must be met for a specific period of time is unclear. ICD-11 does not specify a time requirement; Drescher and Yarbrough say "several months" (Drescher & Yarbrough, 2024, p. 2508).

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between these populations and their respective capacities for decision-making and self-understanding. Neither DSM-5-TR nor ICD-11 provide any explanation for why children or adolescents might desire to modify their sex traits or to be treated or accepted as someone other than a member of their sex, and counseling approaches that might explore possible explanations with patients often are labeled "conversion therapy" by advocates of the "gender-affirming" approach.[93] As far as the DSM-5-TR and ICD-11 diagnoses are concerned, it makes no difference that a patient of 10 or 13 or 17 might wish to modify their body and be perceived and treated as someone other than a member of their sex for any number of reasons. These may include discomfort with one's homosexuality, a history of sexual trauma, pubertal distress, the rejection of perceived sex-based roles, and/or psychiatric comorbidities. For the ICD-11, desire alone is sufficient to justify a medical diagnosis and, within the "gender-affirming care" framework, set the adolescent on a course of PMT.

If using hormonal and surgical interventions to reduce psychiatric morbidity associated with gender dysphoria lacks a favorable risk/benefit profile, using these interventions merely to satisfy adolescents' embodiment goals veers from clinical error into clinical recklessness.

13.4 Regret

Patient regret has begun to receive significant attention in discussions of PMT. Proponents of PMT claim that regret is extremely rare.[94] Some also claim that since mental health assessments have not been shown to reduce regret rates, they should not be required prior to prescribing.[95] The tacit assumption is that absence of regret is an indication of medical benefit or at least of absence of harm. Other researchers point out that research on regret, like most research in PMT, is severely lacking and that we do not know the true prevalence of regret.[96] Whether implicitly or explicitly, proponents and critics alike consider the question of regret as central to the ethics of PMT.

[93] Ashley (2023). See Chapter 14.
[94] Crabtree et al. (2024); Kidd & Sequeira (2024); McNamara et al. (2024); Turban et al. (2021).
[95] Ashley et al. (2023); Wu & Keuroghlian (2023). See also Chapter 11.
[96] Cohn (2023); Jorgensen (2023b); MacKinnon, Expósito-Campos et al. (2023).

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That some patients report profound regret after undergoing invasive, life-changing medical interventions is clearly of importance. However, regret alone (just like satisfaction alone) is not a valid indicator of whether an intervention is medically justified. Not only is regret a complex phenomenon itself,[97] but its relation to ethical considerations in medicine, and to benefit and harm in particular, is tenuous. Patients sometimes come to regret consenting to interventions that were in fact well-justified, that is, interventions that did offer a favorable risk/benefit profile at the time the intervention was proposed. Patients may come to regret such interventions because they suffer harmful complications that were unlikely to occur but did occur in their case. Or they may come to regret the interventions for other reasons. For example, a woman may undergo a spine surgery for which there is compelling evidence of net benefit to her health and yet come to regret the surgery because the modest relief of pain seems to her retrospectively to have not been worth the cost or hassle involved in recovering from the surgery. Or perhaps the improvement in her health allowed her to take some course of action that turned out to make her life worse, all things considered. That she comes to regret the surgery does not mean that it was clinically or ethically unjustified, nor that her clinician violated medical ethics.

Conversely, humans have a remarkable capacity to incorporate suffering and loss into their life stories. A man may be paralyzed as the result of a spine surgery that did not prospectively offer a favorable risk/benefit profile, and which should never have been attempted by the surgeon. Yet months or years later the man may report that he does not regret undergoing the surgery, because the injury and debility it caused led him to focus more attention on the love and care of his family and friends. Or perhaps, as able-bodied, he was isolated and lonely but now, due to his greater physical dependency, he finds a supportive community within which he develops a new identity that imbues his life with structure and purpose. Or maybe as a result of his injury he simply comes to appreciate more deeply the gift of life in its fragility. That this man does not regret the surgery does not imply that his decision to consent to it was prudent, nor that the surgeon was justified in offering the surgery.

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[97] Landman (1987).

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The implications for PMT are complex. The provision of hormonal or surgical interventions to physically healthy adolescents cannot be vindicated by purportedly low rates of regret. Some patients who have suffered objective medical harm and then detransitioned nevertheless do not regret having been medicalized.[98] Nor can the interventions be condemned based on the fact that some adolescents who have undergone them do report regret. The central question for PMT is not: "Do these medically transitioned patients have regret?" A more fundamental question is, "Does medical transition provide health benefits proportionate to its harms?" The best available evidence, along with a risk/benefit analysis and precautionary approach ethically appropriate to pediatrics, shows that the answer to the latter question is almost certainly "no."

13.5 Research Ethics

Multiple SRs, commissioned by leading international health authorities and conducted by independent academic researchers, have concluded that the evidence underpinning the expected benefits of PMT is of low or very low certainty.[99] A natural response among researchers to the absence of higher quality evidence is to conduct more and better research. Whether and how such research should be conducted, however, is a matter of significant ethical controversy.

One controversy concerns RCTs, the "gold standard" for clinical research.[100] Some proponents of PMT claim that RCTs on the effects of PBs or CSH would be infeasible and unethical.[101] With respect to feasibility, because the effects of PMT interventions are so apparent, it is not possible to blind researchers and participants in an RCT for which the control group receives only psychotherapeutic support. Some worry that many adolescents would refuse to participate in a study that does not guarantee they receive hormonal interventions, or that they would drop out if randomized to the control group. These challenges may be harder to overcome in the current climate in which adolescents have been led to believe that hormonal and surgical interventions are well-

[98] For some real examples, see Sansfaçon et al. (2023).
[99] See Chapter 5.
[100] Hariton et al. (2018).
[101] Ashley et al. (2024, 407-418).

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supported by the evidence and even life-saving.[102] However, randomization does not require blinding, and until an RCT is attempted, speculation about how potential participants will respond is just that—speculation.

With respect to research ethics, one objection to conducting RCTs is that such research would violate the principle of equipoise. In their textbook, *Principles of Biomedical Ethics*, Beauchamp and Childress explain that "[t]he community of reasonable physicians is … in a state of 'clinical equipoise'" when "[n]o one knows, prior to conducting the research, whether it is more advantageous to be in the control group or in the experimental group … In this model, no patient, then, will receive something known to be less effective or to have a higher risk than an available alternative."[103]

Advocates for PMT allege that it would violate the principle of equipoise to conduct an RCT of PMT in which the control group receives only psychological counseling, "given the numerous studies associating adolescent gender-affirming interventions with improved mental health."[104] This allegation is unfounded, however, because it mischaracterizes the state of the science. Indeed, if equipoise were violated, it plausibly would be in the other direction, given the more certain evidence of harm. In the end, while their reasons differ, there may be a point of agreement between proponents of PMT and some of its critics concerning the impermissibility of conducting RCTs for hormonal or surgical interventions for pediatric GD.

It is not clear that hormonal or surgical interventions for GD can ethically be offered in a trial, irrespective of trial design. Currently, researchers in the U.K. are planning a PB trial. At the time of this Review's writing, the trial has not yet received official ethics approval, and details regarding the trial's design, which outcomes will be studied, what the inclusion and exclusion criteria will be, and so on, have not been published. Some critics of PMT already are raising concerns about the proposed study. They worry about prescribing PBs even in research settings given the recognized inability of clinicians to distinguish between patients whose GD will persist into adulthood from those whose GD

[102] Clayton, A. (2023).
[103] Beauchamp & Childress (2019), p. 365; See also Freedman (1987).
[104] Ashley et al. (2024, p. 408).

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will resolve on its own,[105] and the high likelihood that any patient who begins PBs will go on to CSH and possibly surgery.[106] Since most adolescents who take PBs go on to CSH, and since it is CSH and surgery that provide the sought-after physical characteristics in PMT, it is unclear whether PBs are a stand-alone treatment and should be studied as such.

Other critics point out that safer types of research—for example, research into various psychotherapeutic approaches—have yet to be explored with this population of patients. They also point out that U.S. gender clinics have yet to collect longitudinal data on existing patients.

There are other important ethical problems to consider. The Nuremberg Code is a foundational and internationally accepted statement of norms guiding human subjects research and it includes the following:

> The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results justify the performance of the experiment.[107]

This suggests that, insofar as PMT poses risks that can be explored through animal studies, such studies should be conducted before these treatments are further tested on humans. Animal studies could help clarify how hormonal interventions affect fertility, brain development,[108] bone development (including future risk of fracture), and cardiovascular outcomes. Such studies also could help clarify to what extent and under what conditions fertility can be recovered after suppression by hormonal interventions.

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[105] Feinmann (2025).
[106] E.g. Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[107] BMJ (1996).
[108] Chen and colleagues, for example, write, “studies in rodents show ovarian hormones, acting during puberty, program cognitive flexibility by exerting long-lasting effects on excitatory-inhibitory balance in the pre-frontal cortex . . . [and] testosterone, acting during puberty, programs the ability to adapt behavior as a function of social experience” (Chen et al., 2020, Table 2).

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The World Medical Association's Declaration of Helsinki is another foundational and internationally accepted statement of guidance for human subjects research. It includes the following:

> All medical research involving human participants must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimize the risks and burdens must be implemented. The risks and burdens must be continuously monitored, assessed, and documented by the researcher.
>
> Physicians and other researchers may not engage in research involving human participants unless they are confident that the risks and burdens have been adequately assessed and can be satisfactorily managed.[109]

It is not ethical to subject adolescents to hormonal and surgical interventions used in PMT, even in a research trial, until and unless the state of the evidence suggests a favorable risk/benefit profile for the studied intervention, *and* the researchers have well-grounded confidence that the foreseeable "risks and burdens have been adequately assessed and can be satisfactorily managed." As explained in this Review, the state of the science does not support a favorable risk/benefit profile, nor does it give researchers a basis for confidence that the risks of PMT can be satisfactorily managed.

Finally, the Belmont Report, authorized by the National Research Act of 1974 and published in 1979 by the United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, is a landmark statement of ethical principles to guide human subjects research in the United States. The Belmont Report affirms that research on humans should not be conducted until and unless that research is "justified on the basis of a favorable risk/benefit assessment" arrived at through "systematic, nonarbitrary analysis of risks and benefits." It continues:

[109] World Medical Association (2025).

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> Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible … It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies … [and] When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject …).[110]

As demonstrated throughout this Review, the presuppositions that guide PMT have not been shown to be valid; the nature, probability and magnitude of risks associated with PMT have not been distinguished with sufficient clarity; PMT proponents' estimates of the probability of harm and benefit have not been shown to be reasonable, as judged by known facts and available studies; and the risks of serious impairment that PMT involves have not been shown to be justified. For these reasons, administering PMT to adolescents, even in a research context, is in tension with well-established ethical norms for human subjects research.

[110] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (2010).

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PART 5

PSYCHOTHERAPY

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Chapter 14 Psychotherapy

This chapter reviews psychotherapy (talk therapy) for gender dysphoria (GD).[1] First, the chapter describes relevant trends in society at large and in the medical profession; specifically, trends in youth mental health (Section 14.1) and in diagnostic and social labels (Section 14.2). Section 14.3 discusses the role of mental health assessment in the care of youth with GD. Section 14.4 briefly recounts the re-emergence of psychotherapy as the primary treatment for this patient population in Europe, and Section 14.5 discusses psychotherapy and its specific application to GD.

14.1 Youth mental health

Puberty is the biological, developmental process during which a child becomes a sexually mature adult.[2] Puberty overlaps significantly with adolescence, the period between childhood and adulthood.[3] During puberty, hormonal fluctuations can affect mood and behavior.[4] The onset of puberty often coincides with heightened sensitivity to social dynamics and self-image along with increasing vulnerability to stress and anxiety. Emotional regulation can become challenging as adolescents navigate the complexities of identity formation and peer relationships. Cognitive development accelerates, allowing deeper abstract thinking and self-reflection, which can contribute to existential questioning and emotional instability.[5] Adolescence also involves learning to function independently, as part of identity formation and individuation from the family of origin. Rebellion and resistance to parents and other caregivers or authority figures frequently occur during this process. Adolescents often struggle with long-term planning and are more susceptible to risk taking, as drives for stimulation and affiliation increase but the prefrontal cortex, responsible for executive functions, is still maturing.[6]

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[1] Gender Dysphoria is a formal diagnosis in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5): see Appendix 2. In this chapter and throughout the Review the term “gender dysphoria” is used to refer to sex-related distress or discomfort, not the formal diagnosis (see Chapter 1, Note 1).
[2] See Chapter 7.
[3] According to the American Academy of Pediatrics (AAP), adolescence spans ages 12-21 (Hardin et al., 2017). See also National Academies of Sciences, Engineering, and Medicine (2019, pp. 22-23).
[4] Viner (2015).
[5] E.g., Reena (2015); Steinberg (2005).
[6] Steinberg (2009).

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14.1.1 Trends in youth mental health

In 2021, the American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry (AACAP), and the Children's Hospital Association declared a "National State of Emergency in Children's Mental Health."[7] In December of that year, U.S. Surgeon General Admiral Vivek Murthy issued an Advisory on Protecting Youth Mental Health, highlighting rising rates of depression, anxiety, hopelessness, and self-harm among youth—trends that worsened during the COVID-19 pandemic. The Lancet Psychiatry Commission on youth mental health noted a similar worldwide trend.[8]

In the U.S., there has been a significant increase in mental illness among teens and young adults since 2010.[9] Data reveal sharply increased rates of diagnosed depression and anxiety; some studies indicate that these rates have more than doubled.[10] Increases also have been documented in rates of suicidal ideation and behavior and self-harm,[11] emergency room visits and hospitalizations for self-harm,[12] and death by suicide.[13] Young people today experience weaker social connections and greater feelings of loneliness. Since 2010, adolescents have had fewer in-person social

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[7] American Academy of Child and Adolescent Psychiatry et al. (2021).
[8] McGorry et al. (2024).
[9] Twenge (2020).
[10] Data from a large national database showed that rates of major depressive episodes among adolescents aged 12 to 17 increased by 52% from 2005 to 2017 (from 8.7% to 13.2%) and by 63% among young adults aged 18 to 25 from 2009 to 2017 (from 8.1% to 13.2%) (Twenge et al., 2019). The "Anxious Generation" website, using Centers for Disease Control and Prevention (CDC) data, shows that rates of major depressive disorder from 2010 to 2022 more than doubled for both boys and girls, with major depression in boys increasing by 161% and in girls by 145%. Mental illness for college students increased, with a 134% increase in anxiety and 106% increase in depression over that same period (Rausch & Haidt, 2023). A cohort study of approximately 1.7 million individuals aged 5 to 22 years in Southern California revealed that from 2017 to 2021 the overall incidence of depression increased by approximately 60%, and anxiety by 31% (Xiang et al., 2024). A survey of a Midwestern school district found from 2012 to 2018 there was a 29% increase in youth screening positive for past-month anxiety (Parodi et al., 2022). See also Goodwin et al. (2020); Keyes & Platt (2024).
[11] See CDC trends report, 2013-2023 (Centers for Disease Control and Prevention, 2023).
[12] See Gutiérrez-Sacristán et al. (2022) for information about increase in psychiatric hospitalizations during the COVID-19 pandemic, for example. See also McGorry et al. (2024).
[13] Suicide death rates for children and young adults aged 10 to 24 years increased 62% from 2007 (6.8 per 100,000 individuals) to 2021 (11.0 per 100,000 individuals) (Curtin et al., 2023). Youth suicides began to rise in the 2000s, with a sharper upward trend starting around 2012; see Farah et al. (2023); Miron et al. (2019); Twenge (2020).

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interactions with peers compared to previous generations.[14] The deterioration in youth mental health has no one simple explanation. Researchers and theorists have identified several potential factors, including overprotective parenting,[15] the decline in free play,[16] and the ubiquity of smartphones and social media.[17] In 2023, the Surgeon General released an Advisory of Social Media and Youth Mental Health, which called attention to the potential risks associated with social media use for children and adolescents.[18]

14.2 Diagnostic and social labels

The rise in reported mental health problems may be partly attributable to overdiagnosis. Some argue that the rise in mental health awareness campaigns aimed at reducing stigma and increasing understanding may have led some young people to interpret normal behaviors and typical developmental challenges as a mental health disorder.[19] Being labeled with a mental health diagnosis can influence how young people see themselves, affect their belief in the possibility of change, and shape how others perceive them. The very act of classifying psychiatric conditions changes the behavior of patients and clinicians. Although diagnostic labels are important for research—where categorizing people or experiences is often necessary—they can oversimplify the

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[14] Twenge et al. (2021); Twenge (2023). Based on CDC data, adolescents have, over time, reported increased feelings of meaninglessness, as well as less willingness to engage in risk-taking behaviors. This includes behavior such as drug and alcohol consumption, but also encompasses developmental experiences such as working or learning to drive a vehicle (Haidt, 2024).
[15] Wang et al. (2024); Winnicott (1965); Zhang & Ji (2024).
[16] According to the AAP: "Children need to develop a variety of skill sets to optimize their development and manage toxic stress. Research demonstrates that developmentally appropriate play with parents and peers is a singular opportunity to promote the social-emotional, cognitive, language, and self-regulation skills that build executive function and a prosocial brain" (Yogman et al., 2018).
[17]Increased use of technologies, including social media, caused a displacement of other activities, such in-person socializing, schoolwork, sleep, sports, reading, and other hobbies. Heavy use of smart phones and social media is ubiquitous among teenagers today (Rothwell, 2023; Twenge et al., 2022; Twenge & Campbell, 2019; Vogels et al., 2022), and common among pre-teens (Rideout et al., 2022). Social media in particular may result in worsening mood and negative self-image in adolescent girls (Choukas-Bradley, 2024; Rodgers & Rousseau, 2022; Scott et al., 2023), and in some cases may play an etiologic role in increasing presentations of specific psychiatric and neurologic issues (Giedinghagen, 2023; Haltigan et al., 2023; Hull & Parnes, 2021; Padín et al., 2021; Pringsheim et al., 2021; Weigle & Shafi, 2024). Social media has introduced a new sociomedical phenomenon in which individuals may find a sense of belonging online through identification with an illness or condition, which may place them at risk of inappropriate or unnecessary medical care (Corzine & Roy, 2024). For a meta-analysis that found reasons for skepticism about the evidence for the effects of social media on mental health, see Ferguson (2025).
[18] Office of the Surgeon General (2023).
[19] Foulkes & Andrews (2023).

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richness and complexity of human experiences for the benefit of a standardized clinical language. To some extent, skillful clinicians can compensate for this reductionism,[20] but they cannot prevent diagnostic labels from escaping the clinic and being used in unintended ways in the wider culture.[21]

Overdiagnosis can lead to overtreatment; unnecessary tests, procedures or medical interventions may cause harm rather than helping. Loosening the diagnostic criteria for a condition will likely increase overdiagnosis and the risk of iatrogenic harm, so definitions should be formulated responsibly:

> … any changes [to diagnoses] should use a systematic, transparent approach where benefits and harms are explicit, especially when they lead to an increase in the prevalence of disease, and broadening of definitions should require evidence of clinical benefit.[22]

Although the term "gender identity" was used in the 1960s,[23] it did not appear in the *Diagnostic and Statistical Manual of Mental Disorders* until 1980 (third edition, DSM-III). "Gender Identity Disorders" was a subcategory of "Psychosexual Disorders," further divided into "Transsexualism" (for late adolescents and adults) and "Gender Identity Disorder of Childhood."[24] In the DSM-IV, published in 1994,[25] "Transsexualism" vanished, and "Gender Identity Disorder" (GID), covering both adults and children, appeared under "Sexual and Gender Identity Disorders." The DSM-5, published in 2013,[26] replaced "Gender Identity Disorder" with "Gender Dysphoria" and designated it as a separate category. This last change "focused the diagnosis on the gender identity-related distress that some transgender people experience (and for which they may seek

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[20] Johnstone (2018).
[21] Hacking (1998); Shorter (1993). See also Brossard (2019); Elliott (2000); Haslam (2016); Lindholm & Wickström (2020); Smids & Vasterman (2025).
[22] Kale & Korenstein (2018, p. 8). The field of psychiatry is no stranger to the phenomenon of misdiagnosis, overdiagnosis and overtreatment; see, for example, Harris & Carey (2008), Havens et al. (2022), and Moreno et al. (2007) for discussion of controversies related to overdiagnosis of pediatric bipolar disorder.
[23] See Chapter 2.
[24] American Psychiatric Association (1980).
[25] American Psychiatric Association (1994).
[26] American Psychiatric Association (2013).

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psychiatric, medical, and surgical treatments) rather than on transgender individuals or identities themselves."[27]

The intention of the DSM's linguistic evolution—from "Transsexualism," to "GID," to "GD"—was to reduce stigma. A parallel linguistic evolution in society at large has resulted in the increasing adoption of labels such as "nonbinary," "genderqueer," "queer," "gender-fluid," "two-spirit," and "transgender."[28] The individuals who identify with these labels—unlike historical or contemporary "transsexuals"[29]—are not a patient group of any kind. "Transgender," "nonbinary," and similar words are not medical terms: they apply to a diverse group of individuals, many of whom are neither dysphoric nor desire any medical or surgical interventions. If there is a common experience, it is "incongruence" between "experienced gender" or "gender identity" and "assigned sex." As the 2022 Text Revision of the DSM-5 explains, "not all individuals will experience distress from incongruence."[30]

As discussed in Chapter 4, social influences have plausibly contributed to the dramatic increase in adolescents presenting to pediatric gender medicine (PGM) clinics over the past decade.[31] Adolescents' need for belonging and acceptance[32] can be met by online communities and spaces centered around identity. The growing use of identity labels such as "transgender" and "nonbinary" among adolescents is an important topic for social science research. In the current U.S. healthcare environment, self-labeling of this kind increases the likelihood that a young person will seek input from a gender clinic,

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[27] Drescher (2017). According to a systematic review of cross-sex hormones and mental health outcomes commissioned by the World Professional Association for Transgender Health (WPATH), "[the diagnostic changes] clarify that the target of gender-affirming medical interventions is not the person's gender identity itself but rather the clinically significant distress that can accompany a misalignment between gender identity and sex assigned at birth" (Baker et al., 2021, p. 2). For the diagnostic criteria, see Appendix 2.

[28] See James et al. (2015), and also Section 13.4 of the previous chapter, on "gendered art pieces."

[29] Some individuals who have medically and surgically transitioned still claim this label: e.g., "I do consider myself more as a Transsexual person, which to me is somebody who wanted to switch genders. I always wanted to be a man, I identify as a man, that's what I am, I don't identify as a Transperson at all" (LOTL staff, 2014). See also American Psychological Association (2023), and Chapter 3.

[30] American Psychiatric Association (2022). See also Chapters 2 and 11.

[31] See also the discussion of rapid-onset gender dysphoria (ROGD) in the same chapter.

[32] Especially in girls, e.g., Archer (2019); Prinstein et al. (2005); Rose & Rudolph (2006).

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where medical transition may be recommended as early as the first appointment (see Chapter 12).[33]

14.3 Controversies regarding assessment and the role of the psychotherapist

In the Dutch research that underpins the contemporary pediatric medical transition (PMT) approach, the psychotherapist occupied an essential role. The original Dutch approach involved an intensive assessment process.[34] Adolescents who began medical transition were required by the protocol to continue to receive regular mental health care.[35]

When discussing contemporary applications of PMT in the U.S., providers often describe a similar approach: multidisciplinary, slow, careful, and methodical.[36] For healthcare providers, the term "multidisciplinary" may connote the lengthy, intensive deliberations that occur at "tumor boards"[37] or during organ transplantation assessments. In inpatient psychiatric units, it is considered preferable to have a multidisciplinary approach, for example involving nursing staff, psychologists, occupational therapists and social workers.[38]

However, in PGM, multidisciplinary teams (MDTs) often do not function like the collaborative model just described. They are more similar to the common healthcare scenario in which a patient sees a cardiologist for cardiac clearance before undergoing

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[33] Discussion of labels is also salient to the treatment of the prepubertal patient cohort with GD. As discussed in Chapter 2, the relatively recent practice of calling gender dysphoric youth "transgender children" may increase the likelihood these patients will be placed on a medicalized pathway.
[34] As described in Delemarre-van de Waal & Cohen-Kettenis (2006), "[In] the first diagnostic phase, information must be obtained from both the adolescent and the parents on various aspects of general and psychosexual development of the adolescent, the adolescent's current functioning and functioning of the family. Standardized psychological assessment is a part of the procedure. The patient is always seen by two members of the gender team. If a child and adolescent psychologist makes the diagnosis, the child is also seen by a child and adolescent psychiatrist and vice versa" (p. S132).
[35] Delemarre-van de Waal & Cohen-Kettenis (2006). Mental health visits were required every 3 months.
[36] E.g., from ABC News: "[Kellan] Baker [the executive director of the Whitman-Walker Institute, an LGBTQ research organization and care provider] said the decision to pursue gender-affirming care is often a lengthy process that includes teams of medical care providers and mental health professionals who work with families to talk about their child's experience, their needs, their choices, and more…'We're talking months of appointments with a mental health specialist. We're talking lots of conversations between providers, parents, and kids,' Baker said" (Alfonseca & Geho, 2024).
[37] Okasako & Bernstein (2022).
[38] Russ (2021).

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an orthopedic procedure. Under some models, the mental health professional (MHP) seeing the minor with GD writes a note or may just fill in a pre-written template; this is taken to an endocrinologist, who prescribes, or a surgeon, who operates.[39] Further, individuals who comprise the MDTs may all subscribe to the PMT model of care, which prioritizes administration of endocrine and surgical interventions to patients who desire them.[40] This is different from traditional MDTs where various specialties approach problem-solving from different perspectives, enhancing the accuracy of the diagnosis and identification of effective treatments.[41]

The MDT model in the context of PMT has created considerable uncertainty about whether the MHP or the physician providing the medical (and/or surgical) interventions bears the ultimate responsibility for the decision. This may have resulted in "diffusion of responsibility," a phenomenon in which "individuals can underperform in circumstances of shared accountability."[42] With respect to the U.K.'s National Health Service (NHS), the Cass Review's interim report provided some clarity by stipulating that the pediatric endocrinologist, as the physician providing the intervention, should be responsible for assessing the patient and formulating a full differential diagnosis. In other words, according to the interim report, receipt of a therapist's letter should not be sufficient for the prescription of hormonal intervention.[43]

In the U.S., no such clarity exists regarding which MDT professionals are ultimately responsible for medical interventions. Endocrinologists and surgeons may believe that the medical necessity of any intervention has been determined by the MHPs who made the diagnosis.[44] Whether the MHP "letter of approval" for hormones or surgery

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[39] See description of the university-based multidisciplinary clinic in Reed (2023a). See description of two-hour long assessments at Boston Children's Hospital in Damiano (2024a).
[40] To further mitigate the potential biases of established MDT teams who subscribe to the PMT model, the National Health Service (NHS) in England issued a new clinical policy for cross-sex hormones in 2024. It calls for independent oversight, specifying that new national MDTs must include "clinicians *not directly involved* in the formation of the individual's care plan," who must agree "on the suitability of the individual receiving [CSH]" (National Health Service England, 2024c).
[41] Morabito et al. (2024).
[42] Marcotte et al. (2020, p. 802).
[43] Cass (2022a).
[44] See, for example, the role of endocrinologists as described in Karakılıç Özturan et al. (2023b). The field of pediatric gender medicine is unusual in this respect: "It [is] not the norm for doctors to prescribe powerful medication to people—especially children—they themselves [did] not diagnos[e]" (Barnes, 2023, p. 337).

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constitutes a formal treatment indication will likely be determined by ongoing lawsuits brought by young people against the clinicians who treated them. In practice, these MHP approval letters may primarily serve to ease the ethical concerns of the physicians.[45]

Some prominent PMT advocates assert that children and adolescents should not receive *any* mental health assessment prior to initiation of hormonal interventions or surgeries.[46] As a principal investigator of NIH-funded research on PMT, Johanna Olson-Kennedy, a U.S. pediatrician and president-elect of the U.S. Professional Association for Transgender Healthcare (USPATH), likened the initiation of PMT to treating diabetes, asserting: "I don't send someone to a therapist when I'm going to start them on insulin."[47]

14.4 Psychotherapy for GD: Re-emergence in Europe

Three European countries—Sweden, Finland, and England—have conducted independent systematic reviews of evidence commissioned by their public health authorities.[48] All three concluded that the risks of medicalization may outweigh the benefits for children and adolescents with GD at the population level, and subsequently sharply restricted access to medical gender transition interventions for minors.[49] All three countries now suggest traditional mental health approaches and have begun efforts to de-exceptionalize GD. Psychotherapy is now the recommended first-line treatment, as it is for all psychological distress based on the conventions of "conservative management."[50]

Per England's National Health Service (NHS):

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[45] Levine (2024, p. 4).
[46] As described in McDeavitt (2025, p. 1298), "The argument for doing away with mental health assessments is often articulated alongside the opinion that the presence of a DSM-5 diagnosis of gender dysphoria (or indeed any type of psychological distress) should not have to be required in order for an adolescent to be initiated on PBs/GAH." See Mosier-Mills et al. (2024), for example, and similar arguments in Ashley (2022a, 2022b, 2023).
[47] Singal (2018).
[48] Ludvigsson et al. (2023); National Institute for Health and Care Excellence (2020b, 2020a); Pasternack et al. (2019); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024).
[49] See Chapter 4.
[50] Adhiyaman & Ambalavanan (2021).

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> The primary intervention for children and young people … is psychosocial (including psychoeducation) and psychological support and intervention; the main objective is to alleviate distress associated with gender dysphoria and promote the individual's global functioning and wellbeing.[51]

Per Finland's Council for Choices in Health Care in Finland (COHERE):

> The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.[52]

Per Sweden's National Guidelines:

> The psychosocial care of young people with gender dysphoria needs to be adapted to the needs of the individual adolescent. Psychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures. For those suffering from mental health problems, measures such as supportive counseling, psychotherapy, child psychiatric treatment, and suicide prevention need to be offered and adapted to the nature and severity of the mental health problem and the young person's overall situation.[53]

14.5 Psychotherapy and its application to gender dysphoria

Psychotherapy is the least invasive intervention for addressing psychological distress, regardless of its etiology, and it has been recognized as the international standard of care for a wide range of mental health diagnoses. However, the evidence for psychotherapy for GD is of very low certainty. As noted in Chapter 5, there are multiple reasons for the paucity of data, and "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[54]

[51] National Health Service England (2022, p. 2).
[52] Council for Choices in Healthcare Finland (2020b, p. 5).
[53] Socialstyrelsen (2022b, p. 45).
[54] Cass (2024a, p. 155).

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14.5.1 Psychotherapy for conditions frequently co-occurring with gender dysphoria

The etiology of GD in youth remains understudied. However, patients presenting to PGM clinics today have a range of neurodevelopmental disorders and mental health conditions, including comorbid depression, anxiety, eating disorders, self-harm, and suicidality.[55] Some studies suggest that in more than 70% of cases, other DSM diagnoses appeared before the GD.[56] Etiologically, the relationship between the GD and the high rate of co-occurring mental health conditions in this population is unclear. [57] As explained by psychologist Kenneth Zucker,

> it may be that the gender dysphoria has emerged as secondary to another, more "primary" mental health diagnosis, such as autism spectrum disorder or borderline personality disorder, or as a result of a severe trauma (e.g., sexual abuse). Another explanation is that gender dysphoria is inherently distressing, i.e., the marked incongruence between one's felt gender and somatic sex—even within psychosocial milieus that are largely "affirming/supportive"—which leads to clinically significant symptoms such as anxiety or depression.[58]

Regardless of its etiology, psychotherapy as an effective intervention for depression, the most common mood disorder, has been studied extensively and is supported by high-quality evidence. For example, cognitive behavioral therapy (CBT), an (often) manualized therapy that helps patients recognize the reciprocal relationships between

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[55] See Section 4.3.
[56] Becerra-Culqui et al. (2018); Kaltiala-Heino et al. (2015); Kozlowska et al. (2021).
[57] Littman (2021), a study that analyzed online survey data from a convenience sample of detransitioners, found that 40.6% of females and 25.8% of males reported that their "feelings of being transgender actually were the result of a mental health condition." 44.9% of females and 16.1% of males reported that "feelings of being transgender actually were the result of trauma" (p. 3364). The Cass Review reported that "Clinicians have described … how in patients with [body dysmorphic disorder, or BDD], the intense focus on appearance is most commonly on facial features, but that some experience distress about genitalia or breasts. In this situation it can be difficult to determine whether the distress is due to BDD or gender dysphoria. However, at the end of a treatment package for BDD some young people say they no longer feel ill at ease with their birth-registered gender, while some may have less distress about their genitalia or breasts but still have marked gender incongruence and proceed to a social or medical gender transition" (Cass, 2024a, p. 92).
[58] Zucker (2019). In addition to these two possibilities, a third theory is that "co-occurring mental health issues are simply secondary to factors such as family rejection or social ostracism within the peer group vis-à-vis the gender dysphoria" (p. 3). This "minority stress model" is discussed later in the present chapter.

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thoughts, feelings, physiology, and behaviors, has evidence for benefit across age groups.[59] Psychodynamic psychotherapy (PDT) focuses on relational interactions, the role of formative life events, and unconscious processes, with the aim of facilitating emotional expression and interpersonal effectiveness.[60] Research indicates that PDT is effective in adults with depression, and there is also evidence of benefit for younger populations.[61] Another approach for adolescent depression with evidence for benefit is family-based treatment (FBT).[62]

Anxiety disorders also are highly prevalent in children and adolescents. The AACAP clinical practice guidelines strongly recommend that children and adolescents (ages 6-18) be offered CBT to address social anxiety, generalized anxiety, separation anxiety, specific phobias, or panic disorder.[63] PDT is less-well studied for anxiety, but may also be effective.[64]

For suicidality and self-harm in adolescents, evidence suggests that dialectical behavioral therapy (DBT), an approach that combines CBT with mindfulness and

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[59] "Manualized" therapeutic approaches follow specific, standardized guidelines. CBT is the most well-studied. A recent meta-analysis of CBT for depression, including more than 50,000 patients across all age groups and 409 randomized controlled trials (RCTs), found that "CBT is effective in the treatment of depression with a moderate to large effect size, and that its effect is still significant up to 12 months (Cuijpers et al., 2023, p. 114). Other forms of psychotherapy were also found to be significantly beneficial. With respect to studies specifically focused on children and adolescents, evidence suggests CBT had modest positive effects on depressive symptoms (Espada et al., 2023).

[60] Opland & Torrico (2025).

[61] A systematic review of PDT for adults, which used the GRADE framework for evidence assessment, found "high quality evidence for depressive disorders and somatic symptom disorders, and moderate quality evidence for anxiety and personality disorders, that PDT achieves clinically meaningful effects in target symptoms and functioning compared to controls and is associated with low risk of harms and reasonable costs" (Leichsenring et al., 2023, p. 286). Midgley et al. (2021) is a narrative review of studies on PDT for children and adolescents (including some RCTs), finding "evidence of effectiveness for psychodynamic therapy in treating a wide range of mental health difficulties in children and adolescents" (p. 1).

[62] For example, attachment-based family therapy is an evidence-based approach to treating adolescent mood disorders, including depression, using a combination of separate (adolescent-only and parents-only) and joint family sessions (Diamond et al., 2021).

[63] This recommendation was based on a commissioned Agency for Healthcare Research and Quality (AHRQ)/Mayo Clinic systematic review and meta-analysis that included 60 RCTs and almost 7,000 pediatric patients. It found moderate-strength evidence that CBT improves primary anxiety symptoms and global functioning (Walter et al., 2020).

[64] Leichsenring et al. (2015); Midgley et al. (2021).

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interpersonal skills training,[65] is an effective treatment.[66] Guidance published by the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2020 found strong evidence that DBT was associated with reductions in suicidality (ideation, non-suicidal self-injury, and suicide attempts).[67] Another evidence-supported intervention, attachment-based family therapy, supports adolescents and parents as they rebuild trust and safety within their relational patterns, gradually reducing the risk of self-harm and suicidality.[68]

Eating disorders also frequently co-occur with GD.[69] CBT has shown some effectiveness as treatment for eating disorders in adults,[70] and CBT, DBT, and family-based treatment or family therapy for eating disorders (FT-ED) have shown effectiveness in adolescents.[71] Such approaches initially target the presenting issue by helping parents and caregivers support their children more effectively, while issues related to identity development are addressed as the condition improves. These family-based treatments are considered first-line interventions for treating adolescent eating disorders, particularly anorexia nervosa and bulimia nervosa.

Body dissatisfaction, which is common in adolescence, is treated with specific evidence-informed protocols. A combination of CBT and selective serotonin reuptake inhibitors (SSRIs) is recommended by the National Institute of Health and Care Excellence (NICE) in the U.K. for body dysmorphic disorder. It also recommends that parents and caregivers actively participate in the treatment process.[72]

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[65] DBT originated as a treatment for adults with borderline personality disorder with chronic suicidality. Its focus is on helping patients achieve mindfulness, interpersonal effectiveness, emotional regulation, and distress tolerance (Substance Abuse and Mental Health Services Administration, 2020).
[66] This is in direct contrast to hormonal interventions, which have *not* been shown to reduce suicidality or suicide in minors with GD. See Section 4.3.4 and Chapter 5.
[67] This SAMHSA guidance considered evidence to be "strong" if positive impact was demonstrated by two or more RCTs (or other controlled trials). Nine studies (of varying methodologies) of DBT for suicidality in adolescents were included in this evidence review; two were RCTs (Substance Abuse and Mental Health Services Administration, 2020).
[68] Diamond et al. (2010).
[69] From a theoretical standpoint, eating disorders and GD both have been conceptualized as arising, in some cases, out of a subconscious desire to avoid the development of adult sex characteristics, perhaps in part due to maladaptive coping strategies or to avoid sexual objectification (Nadrowski, 2023).
[70] Öst et al. (2024).
[71] Datta et al. (2023); Lock et al. (2010); Vogel et al. (2021).
[72] National Institute for Health and Care Excellence (2005).

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When discussing the broader issue of the high prevalence of GD in patients presenting with conditions like eating disorders, body dysmorphic disorder, and functional tic-like behaviors, the Cass Review noted that "[t]he distressing symptoms that occur in these 'body and mind' conditions are real, and like pain or discomfort that arises from other causes can be addressed and helped with psychological interventions. It is very important that gender-questioning young people are able to access these evidence-based treatments."[73] The Cass Review also observed,

> Some therapies, which are well proven for associated mental health problems, already have a strong evidence base. Where it is clear that children/young people have such problems, they should receive the appropriate therapies in the same way as any other young person.[74]

14.5.2 Psychotherapy for gender dysphoria

The overview of systematic reviews (Chapter 5 and Appendix 4) found a dearth of evidence for psychotherapeutic interventions for youth with GD. As summarized in the Cass Review,

> there is a lack of evidence about alternative approaches for managing gender-related distress, and it is difficult to obtain information about routine clinical practice or pathways of care for children and young people who do not receive medical interventions. An explicit clinical pathway must be developed for non-medical interventions, as well as a research strategy for evaluating their effectiveness.[75]

Although several studies suggest that psychotherapy for GD may effectively resolve the condition noninvasively,[76] the quality of the evidence is very low certainty.[77] At the same time, the overview identified two SRs deemed as trustworthy (i.e., at low risk of bias),

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[73] Cass (2024a, p. 93)
[74] Cass (2024a, p. 155).
[75] Cass (2024a, p. 157).
[76] Churcher Clarke & Spiliadis (2019); Cohen-Kettenis & Kuiper (1984); Costa et al. (2015); Smith et al. (2001); Spiliadis (2019).
[77] See Chapter 5.

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and noted that "neither systematic review suggested that there is indication of harm from psychotherapy." One of the SRs concluded:

> Most analyses of mental health, psychological and/or psychosocial outcomes showed either benefit or no change, with none indicating any negative/ adverse effects of the interventions offered.[78]

Although there is no reliable evidence to suggest that psychotherapy for GD is harmful, some proponents of PMT have alleged that it is a form of "conversion therapy." This allegation is addressed in the following section; the final section surveys psychotherapeutic approaches to GD.

14.5.2.1 The charge of "conversion therapy"

Although psychotherapy for GD is described by its practitioners as "neutral" and "unbiased,"[79] some advocates for PMT maintain that such "exploratory" approaches are equivalent to conversion practices.[80]

"Conversion therapy"—sometimes called "reparative therapy"—originally referred to efforts to change the sexual orientation of gay and lesbian people. In 1973, homosexuality was officially de-pathologized by the American Psychiatric Association (APA) when it was declassified as a mental disorder (via its removal from the DSM).[81] While proponents of PMT have characterized exploratory psychotherapeutic approaches for GD as a form of "conversion therapy," others have claimed that PMT

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[78] Heathcote et al. (2024, p. s19).
[79] D'Angelo et al. (2021, p. 12).
[80] E.g. Ashley (2022b, 2023); see also the quotation by Colt St. Amand conflating psychological assessments for minors seeking medical or surgical transition with conversion therapy in Bazelon (2022a). Turban, Beckwith et al. (2020), a widely-cited peer-reviewed analysis of data from the 2015 U.S. Transgender Survey (USTS) concluded that individuals who recalled having been exposed to "gender identity conversion efforts" in the past were more likely to have experienced recent psychological distress and lifetime history of suicidal thoughts, but D'Angelo et al. (2021, p. 12) pointed out that this analysis was based on a "simplistic 'affirmation' versus 'conversion' binary … The notion that all therapy interventions for GD can be categorically classified into this simplistic binary betrays a misunderstanding of the complexity of psychotherapy. At best, this blunt classification overlooks a wide range of ethical and essential forms of agenda-free psychotherapy that do not fit into such a binary; at worst, it effectively mis-categorizes ethical psychotherapies that do not fit the "affirmation" descriptor as conversion therapies" (p. 7). For methodological concerns about the USTS itself, see Chapter 4, Note 117.
[81] Drescher (2010, p. 434); McNally (2011, pp. 21-24). The first edition (1952) of the DSM classified same-sex attraction as a type of "sociopathic personality disturbance" (American Psychiatric Association, 1952, pp. 38-39).

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itself deserves that label. This latter group contends that altering a person's body in response to distress rooted in internalized social disapproval is no more appropriate than attempting to change someone's sexual orientation for similar reasons.[82] Public and academic debates over what constitutes "conversion" in the context of youth with GD have been hindered by the politicization of the issue.[83]

Critics of exploratory psychotherapy for GD claim that therapists are trying to "promote gender identities that are aligned with the person's sex assigned at birth."[84,85] A less theoretically-laden description would be that some therapists are trying to help children and adolescents come to terms with their bodies.[86] Discomfort with the sexed body or with societal sex-based expectations is common during puberty and adolescence. For this and other reasons, characterizing as "conversion therapy" any approach focused on reducing a minor's distress about their body or social role is a problematic and potentially harmful rhetorical device.[87] There is evidence that the specter of being

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[82] See Bannerman (2019) and Hamedani (2014). A recent bioethics article argues that "a society that marginalizes youth who do not conform to gender norms must, as a matter of justice, change its ways. The burden of enacting this change is all of ours to bear. It should not be borne by the bodies of our youth" (Gorin, 2024, p. 43).

[83] Defenses of psychotherapy for GD have roundly rejected the label of "conversion therapy": e.g., "Psychotherapy resides outside the affirmation-conversion binary and aims to address the distress of gender-dysphoric youth rather than to correct a sense of misalignment. Psychotherapy does not attempt to force change or impose any predetermined notion … A core ethical principle of psychotherapy is that therapists must respect patient autonomy and self-determination and refrain from any attempt to influence the patient … A genuine psychotherapeutic process starts from a position of not knowing and seeks to open things up. Anything else is a misuse of psychotherapy" (D'Angelo, 2023, p. 3).

[84] The full quotation is: "Trans conversion practices refer to sustained efforts to promote gender identities that are aligned with the person's sex assigned at birth and/or to discourage behaviours associated with a gender other than the person's sex assigned at birth" (Ashley, 2022b, p. 26). This seems to more broadly characterize conversion therapy as an attempt to encourage conformity with sex stereotypes. However, as explained by D'Angelo, "Psychotherapy does not impose restrictive gender stereotypes, as is sometimes claimed, but critically examines them" (D'Angelo, 2023, p. 1). Such examination is necessary, because restrictive stereotypes could plausibly have contributed to the patient's GD.

[85] The 2020 United Nations (UN) Report on Conversion Therapy begins by explaining that "conversion therapy" refers to "interventions of a wide-ranging nature, all of which have in common the belief that a person's sexual orientation or gender identity (SOGI) can and should be changed. Such practices aim (or claim to aim) at changing people from gay, lesbian or bisexual to heterosexual and from trans or gender diverse to cisgender" (United Nations, 2020). See Lawford-Smith (2024) for discussion of recent legislation banning "conversion therapy" as the UN understands it.

[86] Once it is recognized that the operative notion of "gender identity" has not been properly explained (Chapter 2), the charge of "conversion therapy" makes little sense. If gender identity is obscure, the goal of changing the patient's gender identity is equally obscure.

[87] E.g., D'Angelo (2023); D'Angelo et al. (2021); Edwards-Leeper & Anderson (2021); Jenkins & Panozzo (2024); McDeavitt (2025); Sinai & Sim (2024). Also, as noted in the Cass Review, "The role of

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labeled a “conversion therapist”— a damaging accusation given the profession’s history with the mistreatment of gay people—has created a climate of anxiety among mental health professionals. Therapists worry that failing to affirm or recommend medical interventions for youth who meet the World Professional Association for Transgender Health’s (WPATH) eligibility criteria could jeopardize their careers and reputations.[88]

Equating “exploratory therapy” with “conversion therapy” is misguided for two additional key reasons. First, exploratory therapy was a fundamental and mandatory element of the original Dutch Protocol, which serves as the foundation for the current PMT model.[89] Second, quality psychotherapy is exploratory *by definition*: it is “a process of shared decision making in which the therapist … guides the patient in exploration of their material but does not input their own beliefs or ideas.”[90]

The conflation of psychotherapy with conversion therapy has been condemned not only by expert therapists who question the current emphasis on medical transition and surgical transition for youth, but also by practitioners and researchers in the PMT field itself.[91]

14.5.2.2 Psychotherapeutic approaches

The effectiveness of psychotherapy for a wide range of mental health problems, including those that often present with GD, suggests it may also be beneficial for GD specifically. The Cass Review’s emphasis on the de-exceptionalization of youth with GD underscored the observation that clinicians

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psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an unhelpfully polarised debate around conversion practices. Terms such as ‘affirmative’ and ‘exploratory’ approaches have been weaponised to the extent that it is difficult to find any neutral terminology” (Cass, 2024a, p. 150).

[88] Jenkins & Panozzo (2024). As summarized in McDeavitt (2025): “Some therapists who engage in exploratory talk therapy with [transgender and gender diverse] youth have faced licensure complaints related to accusations of “conversion therapy”—complaints made not by patients, but by activists and colleagues. One therapist reported having attended a workshop … in which activists described “hunting” for such therapists with the goal of bringing lawsuits and prompting licensure revocation.”

[89] Weaknesses of the original Dutch research are discussed in Chapter 4.

[90] Sinai & Sim (2024, p. 148); see also Churcher Clarke & Spiliadis (2019).

[91] For example, psychologist Laura Edwards Leeper has stated that “Conflating conversion therapy and identity exploration is perhaps the largest threat to both gender-distressed cisgender youth and transgender youth, alike. The rhetoric being used to conflate the two must stop immediately” (McDeavitt, 2025, p. 1298). See also Edwards-Leeper & Anderson (2021).

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> just need the appropriate training, support and most importantly the confidence to do what [they] have been trained to do and treat this population as [they] would any other young person in distress.[92]

Unfortunately, efforts to research the influence of cultural and social factors, trauma, or co-occurring mental health conditions on GD have been denigrated as "harmful."[93] When combined with the highly charged accusation of "conversion therapy," therapists may be under significant pressure to assume—often without critical evaluation—that mental health issues co-occurring with GD are primarily the result of minority stress.[94] This pressure may cause clinicians to overlook the significant possibility that in some patients, GD has *arisen from* trauma, "primary" mental health concerns, or neurodevelopmental conditions (see Section 14.1 above). Publications by psychotherapists working with this population have noted that patients with GD may seek hormonal or surgical interventions in response to experiences of sexual violence, negative attitudes towards homosexuality, or bullying related to self-expression, interests, or behaviors that deviate from sex stereotypes.[95]

If these possibilities are ignored, medical and surgical interventions may be recommended as the obvious treatment.[96] The mischaracterization of psychotherapy for GD as "conversion therapy" or "doing nothing" may also contribute to a nocebo effect, disincentivizing therapists from providing care and patients from engaging in it.[97] In this way, the denigration of psychotherapy has "a chilling effect on the ethical

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[92] Cass (2024a, p. 15).
[93] E.g. Coalition for the Advancement and Application of Psychological Science (2021).
[94] Application of minority stress theory to mental health disparities in sexual minority adults was originally done in Meyer (2003). As defined in Chelliah et al. (2024), the "minority stress framework…has been used to conceptualize relationships between…mental health disparities and stressors associated with a minority identity or status." This framework, which (like all other conceptual frameworks) has its limitations (Bailey, 2020; Zucker et al., 2016), has over the past 5-10 years been widely-relied upon in the pediatric gender medicine literature (see examples in Chapter 13). Although it is important for therapists to elucidate patient experiences of bullying or hostility, it is not psychotherapeutically sound practice to make reflexive assumptions, especially when these assumptions could lead to inappropriate treatment recommendations.
[95] Churcher Clarke & Spiliadis (2019); D'Angelo et al. (2021); Lemma (2018); Sinai & Sim (2024); Spiliadis (2019).
[96] E.g. Tordoff (2022).
[97] Clayton (2023).

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psychotherapists' willingness to take on complex GD patients, which will make it much harder for GD individuals to access quality mental health care."[98]

The practice of reflexive assumption contravenes fundamental principles of the psychotherapeutic approach, which emphasizes curiosity and consideration of *all* factors that may have contributed to the patient's problems.[99] It is also challenged by research on desistance and detransition.[100]

Stephen Levine, professor of psychiatry at Case Western Reserve University, has explained how the psychotherapeutic approach includes biological, psychological and social factors to formulate GD holistically:

> [If] the evaluator understands the focus of the [mental health assessment] to be on identifying the predisposing, precipitating, and maintaining forces on the patient's identity, a long list of influences will be explored. Problems such as autism, ADHD, difficulty making friends, crises of loneliness, depression, restrictive or excess eating, sexual abuse, and feedback from virtual friends will be investigated. The [therapist] will explore suicidality, self-harm, pre- and post-trans-identity psychiatric problems, and relationships with each parent. The parents will provide a developmental history beginning with pregnancy.[101]

Psychiatrist and psychoanalyst Roberto D'Angelo, a proponent of psychotherapy for GD, describes the role of psychotherapy for minors with GD as follows:

> Psychotherapy does not impose restrictive gender stereotypes, as is sometimes claimed, but critically examines them. It empowers young people to develop creative solutions to their difficulties and promotes agency and autonomy. Importantly, an exploratory psychotherapeutic process can help to clarify whether

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[98] D'Angelo et al. (2021, p. 13).
[99] As the Cass Review noted, "a single focus on gender raises the issue of 'diagnostic overshadowing' … children [may have] more than one presenting issue, but different services … dealing with each issue in isolation, without considering how they might impact on each other" (Cass, 2024a, p. 200). See also discussion of diagnostic overshadowing in Section 13.2.4.
[100] E.g. Littman (2021).
[101] Levine (2024, p. 775).

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gender dysphoria is a carrier for other psychological or social problems that may not be immediately apparent.[102]

Given that this population often presents with complex psychosocial histories and multiple mental health concerns, psychotherapy takes a holistic approach—addressing the full range of issues rather than focusing exclusively on GD. "Transdiagnostic psychotherapy"—that is, therapy that works across or with multiple diagnoses or problems—is already a convention.[103] While there is a clear need to develop and study therapeutic approaches tailored specifically for GD, effective therapy need not always center on a single issue. Psychotherapy for adolescents with GD is a well-suited intervention, as it is intended to help patients develop self-understanding, engage with emotional vulnerability, and build practical strategies for managing distress.

Human psychology is complex and the presence of one psychiatric diagnosis often increases the likelihood of others. A transdiagnostic psychotherapeutic approach—designed to address underlying patterns across multiple conditions—may be particularly effective in reducing distress among youth with GD, as it has been in other complex cases. The goals of psychotherapy remain the same regardless of a young person's self-identification: to alleviate distress and improve interpersonal and social functioning.

Table 14.1 below presents a brief overview of psychotherapeutic modalities that are relevant for children and adolescents with GD.

[102] D'Angelo (2023, p. 1).
[103] Jeppesen et al. (2021).

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Table 14.1

Type of psychotherapeutic modality	Definition of modality	Application to GD
Manualized approaches[104]	These approaches are performed according to manualized instructions that provide structure and standardization. The most-studied approach is cognitive behavioral therapy (CBT), which helps patients identify thoughts, feelings, and behaviors and the way they impact one another. Manualized therapies focus on development of coping skills and behavioral activation. Dialectical behavioral therapy, commonly used to address self-harm and suicidality, fosters distress-management techniques and interpersonal effectiveness. Manualized approaches typically involve several months of weekly individual or group sessions, and patients complete therapy-related assignments between sessions.	Manualized approaches are an evidence-based treatment for mental health problems that co-occur with GD, such as depression, anxiety, and eating disorders. For GD, manualized approaches can help patients identify thoughts and feelings related to sex-based distress, including cognitive distortions. Therapists can help patients develop healthy coping skills for managing this specific type of distress and can encourage behavioral activation. For example, engaging in physical activity, in-person social socialization, and/or mindfulness practices, can over time, decrease ruminations, including ruminations on sex-related discomfort.

[104] In Austin et al. (2018), mental health outcomes (including depression) improved with CBT in 8 adolescents who identified as transgender (subgroup of study population; unclear if hormonal interventions were used). Hollinsaid et al. (2020) re-analyzed data from four RCTs of standard manualized psychotherapeutic approaches, focusing on the cohort of 64 patients who had expressed desire to be the other sex (it is unclear how many would have met criteria for GD, however; additionally, there was no information about hormonal interventions). These patients' internalizing and externalizing symptoms improved, albeit more slowly than other patients. In Lucassen et al. (2021) the depression outcome measure did not change after online CBT in 14 patients who identified as transgender. In Silveri et al. (2021) mental health outcomes improved in 62 adolescents who self-identified as transgender/gender-expansive after CBT, DBT, and family therapy, integrated into a two-week long residential treatment program for psychiatric problems. In a study reporting longitudinal data on 26 adolescents (Bluth et al., 2023), mental health outcomes (including depression and suicidality) improved after eight sessions of mindfulness-based group therapy in transgender-identified patients who were not taking hormonal interventions.

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Type of psychotherapeutic modality	Definition of modality	Application to GD
Psychodynamic approach[105]	This is a psychoanalytic approach that involves exploration of ego defenses and unconscious motivations. Through exploration of transference, patients come to better understand their interpersonal dynamics. Psychodynamic psychotherapy classically involves biweekly or weekly sessions and is not time-limited.	This approach is evidence-based for mental health conditions that co-occur with GD. Additionally, psychodynamic work around the theme of cross-sex identification or sex-related distress can facilitate exploration of patients' early childhood experiences, family of origin, beliefs/values system, and interpersonal patterns in familial and romantic relationships as well as in school/work environments. This approach can help patients gain deeper understanding of their personal identity, including any external factors that may contribute to their cross-sex identification and desire for medical/surgical interventions. Patients can gain clarity about their own wishes or desires for medical or surgical transition interventions.
Family therapy[106]	This approach identifies problems affecting the patient and the family unit and aims to strengthen familial bonds and improve communication skills, by supporting work around attachment ruptures, communication and understanding different family members' perspectives. It may involve parental education and development of strategies for improved interpersonal effectiveness within the family unit.	A child or adolescent exhibiting GD may occasionally lead to intense conflict and distress within the family unit. In family-based approaches a knowledgeable therapist can provide education about GD to parents and promote well-being of the family by bolstering effective communication and interpersonal skills. Family therapy is an evidence-based approach to treating adolescent eating disorders, where familial distress and embodied distress are heightened, as in GD. Family therapy is either the first-line intervention or the treatment of choice for many diagnoses in adolescence.

14.5.2.3 Evidence for benefit

As discussed earlier, the overview of systematic reviews conducted for this Review found that evidence for the effectiveness of psychotherapy for GD (or for co-occurring mental health problems in patients with GD) is of very low certainty. When direct evidence for the role of psychotherapy in children and adolescents with GD is lacking, the best available evidence can be obtained from the robust evidence supporting

[105] For case reports, vignettes, and case series describing the incorporation of dynamic aspects into exploratory work, see Churcher Clarke & Spiliadis (2019); D'Angelo (2020); Spiliadis (2019). For descriptions of dynamic approaches, see D'Angelo (2023); Sinai & Sim (2024).
[106] For a case report of family therapy for an adolescent with suicidality, see Russon et al. (2022). See also Silveri et al. (2021) and Churcher Clarke & Spiliadis (2019). For example of parent psychoeducation, see Levine (2024).

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treatment effectiveness for children and adolescents with similar types of psychological distress. Psychotherapy is a noninvasive intervention that can be used transdiagnostically. It generally promotes improved mental health and psychosocial functioning and carries little risk.[107] As the Cass Review noted,

> the focus on the use of puberty blockers for managing gender-related distress has overshadowed the possibility that other evidence-based treatments may be more effective.[108]

[107] See also Baron & Dierckxsens (2022); Clayton (2023); Levine et al. (2022b).
[108] Cass, 2024a (p. 31).

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Limitations, Strengths, and Conclusion

Limitations

The present Review has some limitations.[1]

1. This document is not intended to serve as a clinical practice guideline and does not aim to issue treatment recommendations.[2] The Review was shaped by a distinct set of goals: namely, to clarify the evidentiary landscape; identify areas of uncertainty; and support the development of accountable care models. As such, it does not follow formal guideline development procedures, such as the use of GRADE to inform clinical recommendations. The purview of this Review is limited to evidence and best practices for the care of minors.
2. This Review does not make any specific policy recommendations regarding the regulation of medicine. For instance, it does not make policy recommendations about the treatment of children and adolescents who have already begun puberty blockers or cross-sex hormones.

Strengths

This Review also has some strengths.

1. Although not a CPG, this document provides clinicians and other decision makers with essential pieces of knowledge regarding PGM.
    a. *Quality of evidence*: This Review describes the very low-quality evidence underpinning treatment approaches in pediatric gender medicine (Chapter 5).
    b. *Risk profile of hormones and surgeries*: This Review contains an extensive description of potential or plausible harms associated with certain treatment options (namely, hormonal interventions and surgeries), some of which are significant (Chapter 7).

[1] For strengths and limitations specific to the overview of systematic reviews (SRs), see Chapter 5.
[2] This is not technically a limitation (as this Review does not purport to be a CPG), but a clarification.

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c. *Ethics review*: This Review contains an ethical assessment of the use of hormonal interventions and surgeries for treatment of GD in children and adolescents. It concludes that these interventions are inconsistent with widely endorsed principles of medical ethics (Chapter 13).

d. *Consideration of alternative treatments*: The role of psychotherapy, which has been sidelined in discussions of PGM, is one focus of this Review. This Review examines psychotherapy for GD in detail and concludes that its risk/benefit profile is favorable (Chapter 14).

2. The review of guidelines (Chapter 9) demonstrates that CPGs recommending psychotherapy for pediatric GD are higher-quality and are commensurate with evidence from PGM SRs. In contrast, CPGs recommending an approach involving standard-of-care use of PBs, CSH, or surgery are lower-quality, with recommendations that are not commensurate with evidence from SRs. CPGs followed in the U.S., in particular that of WPATH, are of the latter type and are inadequate to inform clinical practice for a vulnerable and distressed population of children and adolescents. High quality CPGs are urgently needed in this field.
3. This Review describes the enforced professional insularity of the field of pediatric gender medicine and the intense and hostile nature of the debates around PGM. Stakeholders should keep these in mind when presented with claims of medical consensus among U.S. medical organizations (Chapter 12).

Conclusion

> The delegation of authority to the medical profession rests on an implicit social contract: Doctors as a profession receive the 'privilege of self-regulation' and financial awards on the expectation that they will serve the health needs of individual patients and society.[3]

A central theme of this Review is that many U.S. medical professionals and associations have fallen short of their duty to prioritize the health interests of young patients. First,

[3] Patashnik et al. (2017, p. 10).

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there was a rapid expansion and implementation of a clinical protocol that lacked sufficient scientific and ethical justification. Second, when confronted with compelling evidence that this protocol did not deliver the health benefits it promised, and that other countries were changing their policies appropriately, U.S. medical professionals and associations failed to reconsider the “gender-affirming” approach. Third, conflicting evidence—evidence that challenged the foundational assumptions of the protocol and the professional standing of its advocates—was mischaracterized or insufficiently acknowledged. Finally, dissenting perspectives were marginalized, and those who voiced them were disparaged.

While no clinician or medical association intends to fail their patients—particularly those who are most vulnerable—the preceding chapters demonstrate that this is precisely what has occurred.

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APPENDICES

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Appendix 1. Abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
APA	American Psychological Association/American Psychiatric Association
ASD	Autism Spectrum Disorder; also ASC (Autism Spectrum Condition)
BDD	Body Dysmorphic Disorder
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and prevention
CMS	Centers for Medicare and Medicaid
COHERE	Council for Choices in Health Care (Finland)
COI	Conflict of Interest
CPG	Clinical Practice Guideline
CPP	Central Precocious Puberty
CSH	Cross-Sex Hormones
DBT	Dialectical Behavioral Therapy
DSD	Disorder (Difference) of Sex Development
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DSM-5-TR	DSM, 5th edition, Text Revision (latest version, 2024)
DSM-5	DSM, 5th edition (2013)
DSM-IV	DSM, 4th edition (1994)
DSM-III	DSM, 3rd edition (1980)
EBM	Evidence-Based Medicine
EPC	Evidence-based Practice Center (at Johns Hopkins)
ES	Endocrine Society
FAERS	FDA's Event Reporting System

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FBT	Family-Based Treatment
FDA	Food and Drug Administration
FM	Female-to-Male
FP	Fertility Preservation
FSH	Follicle-Stimulating Hormone
FT-ED	Family Therapy for Eating Disorders
GD	Gender Dysphoria (DSM-5; formerly Gender Identity Disorder (GID) in the DSM-IV)
GDG	Guideline Development Group
GeMS	Gender Multispeciality Service (at Boston Children's; formerly Gender Management Service)
GICE	Gender Identity Conversion Efforts
GIDS	Gender Identity Development Service (U.K.)
GnRHa	Gonadotropin Releasing Hormone Agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBIGDA	Harry Benjamin International Gender Dysphoria Association
HH	Hypogonadotropic Hypogonadism
HPG	Hypothalamic-Pituitary Gonadal axis
HRC	Human Rights Campaign
ICD-11	WHO's International Classification of Diseases, 11th edition (latest version, 2022)
IQ	Intelligence Quotient
ITJH	*International Journal of Transgender Health*
JAMA	*Journal of the American Medical Association*
JHU	Johns Hopkins University
LH	Luteinizing Hormone
MDC	Medical Decision-making Competence
MDT	MultiDisciplinary Teams
MF	Male-to-Female
MHP	Mental Health Professional
MMHA	Major Medical and mental Health Association

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NAM	National Academy of Medicine
NEJM	*New England Journal of Medicine*
NGCF	Netherlands Gender Care Foundation
NHS	National Health Service (U.K.)
NICE	National Institute for Health and Care Excellence (U.K.)
NIH	National Institutes of Health
NLM	National Library of Medicine
NOS	Newcastle-Ottawa Scale
OCD	Obsessive Compulsive Disorder
PBs	Puberty Blockers
PCOS	Polycystic Ovary Syndrome
PDT	PsychoDynamic Therapy
PGM	Pediatric Gender Medicine
PICO	Population, Intervention, Comparator, Outcome
PMT	Pediatric Medical Transition
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RoB 2	Cochrane Risk-of-Bias tool
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
ROBIS	Risk of Bias In Systematic reviews
ROGD	Rapid-Onset Gender Dysphoria
RSG	Review of Data, Statistics and Research on Sex and Gender (U.K., 2025)
SAMHSA	Substance Abuse and Mental Health Services Administration
SOC-8	*Standards of Care for the Health of Transgender and Gender Diverse People*, Version 8 (latest version, 2022)
SOC-7	*Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, Version 7 (2012)
SOC-6	*Standards of Care for Gender Identity Disorders*, Version 6 (2001)
SR	Systematic Review
SRS	Sex Reassignment Surgery
SSRI	Selective Serotonin Reuptake Inhibitor

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TGD	Transgender and Gender Diverse
UCSF	University of California, San Francisco
USPATH	United States Professional Association for Transgender Health
USTS	US Transgender Survey
WHO	World Health Organization
WPATH	World Professional Association for Transgender Health

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Appendix 2. Diagnostic Criteria

DSM-III (1980)[1]

Diagnostic criteria for Transsexualism

A. Sense of discomfort and inappropriateness about one's anatomic sex.

B. Wish to be rid of one's own genitals and to live as a member of the other sex.

C. The disturbance has been continuous (not limited to periods of stress) for at least two years.

D. Absence of physical intersex or genetic abnormality.

E. Not due to another mental disorder, such as Schizophrenia.

Diagnostic criteria for Gender Identity Disorder of Childhood

For females:

A. Strongly and persistently stated desire to be a boy, or insistence that she is a boy (not merely a desire for any perceived cultural advantages from being a boy).

B. Persistent repudiation of female anatomic structures, as manifested by at least one of the following repeated assertions:

(1) that she will grow up to become a man (not merely in role)

(2) that she is biologically unable to become pregnant

(3) that she will not develop breasts

(4) that she has no vagina

(5) that she has, or will grow, a penis

C. Onset of the disturbance before puberty.

For males:

[1] American Psychiatric Association (1980, pp. 261-266).

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A. Strongly and persistently stated desire to be a girl, or insistence that he is a girl.

B. Either (1) or (2):

(1) persistent repudiation of male anatomic structures, as manifested by at least one of the following repeated assertions:

(a) that he will grow up to become a woman, (not merely in role)

(b) that his penis or testes are disgusting or will disappear

(c) that it would be better not to have a penis or testes

(2) preoccupation with female stereotypical activities as manifested by a preference for either cross-dressing or simulating female attire, or by a compelling desire to participate in the games and pastimes of girls

C. Onset of the disturbance before puberty.

DSM-IV (1994)[2]

Diagnostic criteria for Gender Identity Disorder

A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex). In children, the disturbance is manifested by four (or more) of the following:

(1) repeatedly stated desire to be, or insistence that he or she is, the other sex

(2) in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing

(3) strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex

[2] American Psychiatric Association (1994, pp. 537-538).

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(4) intense desire to participate in the stereotypical games and pastimes of the other sex

(5) strong preference for playmates of the other sex

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.

B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.

In children, the disturbance is manifested by any of the following: in boys, assertion that his penis or testes are disgusting or will disappear or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, or assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.

In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.

C. The disturbance is not concurrent with a physical intersex condition.

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

DSM-5 (2013)[3]

Gender Dysphoria

[3] American Psychiatric Association (2013, pp. 452-453).

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Diagnostic Criteria

Gender Dysphoria in Children

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).

2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire: or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.

3. A strong preference for cross-gender roles in make-believe play or fantasy play.

4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.

5. A strong preference for playmates of the other gender.

6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.

7. A strong dislike of one's sexual anatomy.

8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

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Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).

2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).

3. A strong desire for the primary and/or secondary sex characteristics of the other gender.

4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).

5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).

6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning.

ICD-11 (2022)[4]

Gender incongruence of adolescence or adulthood

[4] World Health Organization (2022b).

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Gender Incongruence of Adolescence and Adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.

Gender incongruence of childhood

Gender incongruence of childhood is characterized by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.

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Appendix 3. Systematic Reviews and Evidence-Based Medicine

Imagine a courtroom where guilt or innocence is decided solely by the police, drawing on their extensive experience of investigating crime. Someone can be convicted of murder, say, on the verdict of these criminal experts, who have seen many murders before, and who have firm opinions about the sort of people most likely to commit them.

Such a courtroom would be better than nothing. The police have relevant knowledge and experience and are not simply guessing. But it would be far inferior to a real courtroom, where police testimony is just part of the evidence brought before judge and jury: the blood-stained knife, fingerprints, cellphone records, eyewitness testimony, and so on, are all included. Moreover, every piece of evidence is critically examined, weighed, and compared. The attitude is more scientific. Not all evidence is equal: eyewitness testimony can be unreliable, whereas properly collected DNA evidence is of high quality. Independent pieces of evidence (DNA, cellphone records) can point to the same conclusion, making the verdict more secure. Of course, the process is imperfect, but it's a vast improvement over simply relying on the opinions of police officers.

Medicine used to be more like the first (hypothetical) courtroom than the second:

> Clinical practice was historically viewed as the "art of medicine." Expert opinion, experience, and authoritarian judgment were the foundation for decision making. The use of scientific methodology, as in biomedical research, and statistical analysis, as in epidemiology, were rare in the world of medicine.[1]

Starting in the 1970s, evidence-based medicine (EBM) has attempted to move medicine from the first courtroom to the second, towards more empirical rigor.

EBM "is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[2] The fundamental EBM principle is that clinical practice and practice guidelines should be based on the totality of evidence,

[1] Sur & Dahm (2011, p. 487).
[2] Sackett et al. (1996, p. 71).

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assessed and synthesized in clear and reproducible ways from the medical literature. EBM contrasts with "eminence-based medicine," in which physicians make clinical decisions based on personal experience and expertise, and treatment guidelines themselves are created using a process humorously described as "GOBSAT" ("good old boys sitting around a table").[3]

It is important to emphasize that EBM does not say that evidence about treatments should be the *only* factor in medical decisions. Quite the opposite. According to the American Medical Association's (AMA) *User's Guides to Medical Literature: Essentials of Evidence-Based Clinical Practice*:

> [E]vidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits and risks, burden, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and values and preferences.[4]

Evidence is never sufficient to make health policy either, although policy makers have different priorities than clinicians. A clinician's primary concern is for the individual patient and their "unique predicament"; policy makers need to set general rules and standards with public health in mind. They may consider the cost-effectiveness of treatment, public values and preferences, the feasibility of widely offering the treatment, how its benefits can be distributed fairly, and so forth.

EBM uses a "hierarchy of evidence," often depicted as pyramid with colored layers, as in Figure A.1. Since the layers represent different types of study, the hierarchy is more strictly a hierarchy of *research methods* than a hierarchy of evidence. The pyramid in Figure A.1 should not be taken too seriously: many pyramids have been proposed, with varying numbers of layers and kinds of labels, not to mention colors.[5] In fact, the AMA's

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[3] Lima, Tangamornsuksan et al. (2023, p. 1).
[4] Guyatt et al. (2015, p. 10, emphasis omitted). "Burden [of treatment]" means "the inconvenience of attending to the treatment's optimal use, of its monitoring, the limitations in lifestyle that it entails, and the possibility of interactions with other treatments" (p. 426). "Values and preferences" refer to "the collection of goals, expectations, predispositions, and beliefs that individuals have for certain decisions and their potential outcomes. The incorporation of patient values and preferences in decision making is central to evidence-based medicine" (p. 490).
[5] Blunt (2022). For another pyramid, see Cass (2024a, p. 55).

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User's Guides to Medical Literature contains no such illustration.[6] But the basic point these pyramids make is sound: some ways of gathering evidence about the effects of a treatment are better than others. Systematic reviews (SRs, to be explained below) and meta-analyses are better than randomized controlled trials (RCTs), which are better than cohort studies and case reports,[7] with expert opinion coming in last. The medical consensus based on expert opinion or experience has been shown to be wrong many times before, after rigorous experimental studies were conducted. (See Section 1.2.2.)

EBM prioritizes findings from population-level research, such as RCTs and observational epidemiological studies. This can have drawbacks, sometimes resulting in insufficient consideration of biochemical or physiological evidence from laboratory, animal, or in vitro studies.[8]

In the last few decades EBM has been refined and improved. This appendix includes a brief introduction to SRs, the methodology to systematically identify, synthesize, and assess the best available evidence, and to Grading of Recommendations Assessment, Development, and Evaluations (GRADE), the methodology to assess the quality of evidence and determine the strength of recommendations.

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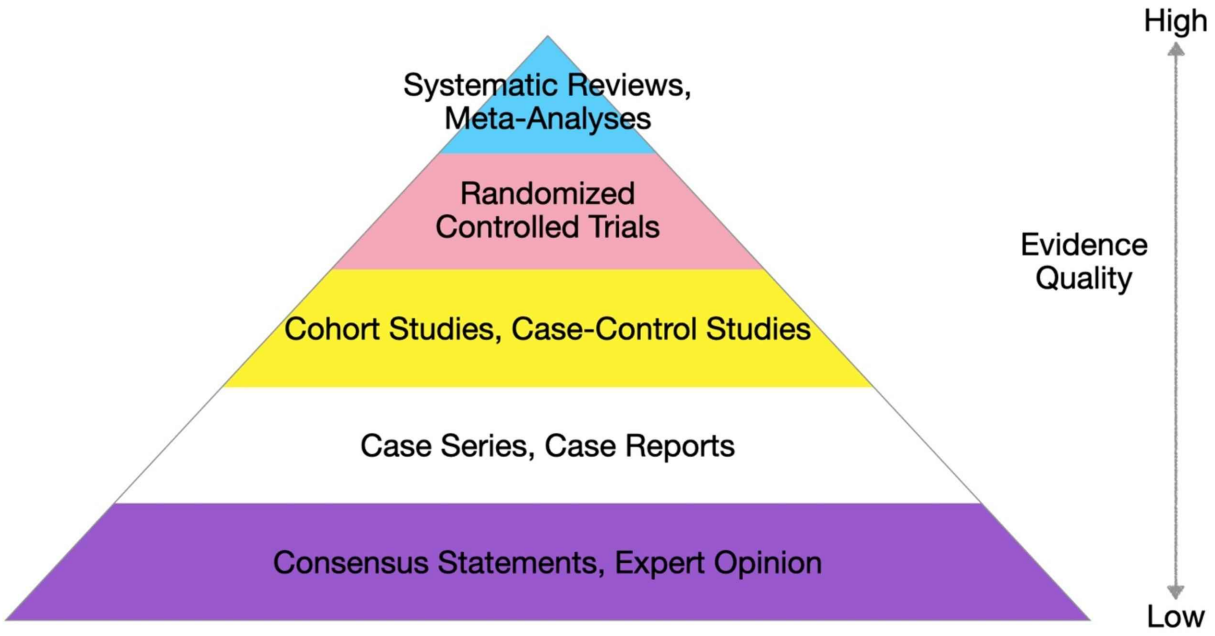
[6] See Guyatt et al. (2015, p. 48, Figure 4-1), which displays a simple three-level hierarchy of evidence in a blue box.

[7] A *meta-analysis* combines data from separate similar studies and statistically analyses the result. Two studies may investigate the same treatment in sufficiently different ways so that a meta-analysis of both is not possible. SRs may involve meta-analyses but need not. A *randomized controlled trial* (RCT) allocates treatment/non-treatment randomly to a group (*cohort*) of patients and follows them over time; the no-treatment group is the *control* group. Control groups may receive another kind of treatment, a *placebo* (an inert pill or procedure that superficially mimics the treatment), or no treatment at all. In a *double-blind* RCT neither the patients nor the attending medical staff know who is in the treatment group and who is in the control group. *Cohort studies* (or *longitudinal* studies) examine groups of patients over time, either *prospectively* (data collected as the study proceeds) or *retrospectively* (the data has already been collected, say in past medical records); there is no randomization to treatment/non-treatment as in an RCT. A *case-control* study starts with two groups, those who have the disease or condition of interest (the *cases*), and those who don't (the *controls*), and examines them retrospectively. The latter two kinds of study are called *observational*, to contrast them with RCTs. A *case report* describes a single patient's treatment and outcome; a *case series* is a collection of similar case reports.

[8] Clarke et al. (2014).

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Figure A1.1 Example EBM Pyramid



1. Systematic reviews

Systematic reviews (SRs) synthesize evidence from multiple studies in the medical literature and assess its quality, using a standard and reproducible methodology. The general steps are outlined below:[9]

Research questions and study eligibility criteria

SRs begin by asking four questions. What is the population being studied? What is the intervention or treatment? What groups are being compared to the group that received the treatment? What results or outcomes are of interest? This is the "PICO" framework: Population, Intervention, Comparator, Outcome. Study eligibility criteria are defined accordingly and documented.

Comprehensive search

Having defined the eligibility criteria for studies, the next step is to locate them. A properly conducted search requires expertise, and includes searching a variety of

[9] What follows is simplified; for more detail see Higgins et al. (2019).

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medical databases, for instance Embase (produced by the publisher Elsevier) and Medline (produced by the U.S. National Library of Medicine (NLM)). The search could also cover registries of clinical trials and so-called grey literature (material outside academic publishing, such as reports and government documents).

Study selection

Reviewers then screen the search results, looking at a study's title and abstract, and then its full text to determine if the study is eligible to be included in the SR. This study selection process follows the pre-defined eligibility criteria. To minimize the risk of bias in the review process, independent duplicate screening may be applied in both the stage of title and abstract screening, and the stage of full text screening.

Data extraction and effect estimate computation

The reviewers extract all relevant data from the studies. The procedure is standardized, and the same kind of data is extracted from all studies. Most of this is in the methods and results sections of the study (and the supplementary material). Depending on the data, there are various ways of measuring the effect of an intervention; the extracted data may need to be converted to a consistent format so the treatment effect estimates reported across eligible studies can be combined as a pooled effect estimate.

Risk of bias assessment

Bias is "systematic error, or deviation from the truth, in results. Biases can lead to under-estimation or over-estimation of the true intervention effect and can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be due entirely to bias)."[10] Two or more independent reviewers assess the risk of bias of each study, using appropriate tools. One major consideration for choosing a risk of bias tool is the type of study design. For example, Version 2 of the Cochrane Risk-of-Bias tool for randomized trials (RoB 2) is the recommended tool to assess the risk of bias in randomized trials included in

[10] Higgins et al. (2019, pp. 177-178). Note that "biased" here does not mean *prejudiced*. Fair and impartial researchers may produce a "biased" study in the sense relevant to this Appendix.

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Cochrane Reviews, while Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) is the recommended tool to assess the risk of bias in non-randomized studies.

Data synthesis and analysis

One key step for SRs is evidence synthesis, which means the results from the different studies are synthesized or combined. Meta-analyses of effect estimates, the quantitative synthesis strategy, may be performed, as well as sensitivity analyses (which examine whether the results would change if different statistical assumptions were made, if outcomes were defined slightly differently, and so on). If a meta-analysis is not feasible, other ways of synthesizing the results are available. A narrative that describes results study by study is not acceptable.[11]

Quality of evidence assessment

The quality of the evidence is now evaluated using, e.g., the methodological framework Grading of Recommendations Assessment, Development, and Evaluations (GRADE) (explained in the following section).

Discussion and conclusion

The discussion section of the SR includes: "Summary of main results (benefits and harms); potential biases in the review process; overall completeness and applicability of evidence; certainty of the evidence; agreements and disagreements with other studies or reviews."[12] The conclusions section considers the implications for clinical practice and for research.

High-quality SRs organize their PICO information, search strategy, methodologies, and findings according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, which facilitates completeness, accuracy, transparency,

[11] McKenzie & Brennan (2024).
[12] Higgins et al. (2019, p. 404, quotation marks and capitalization omitted).

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and replicability.[13] Registering the protocol for a SR in a system such as PROSPERO increases transparency and trustworthiness of an SR.

2. GRADE

Grading of Recommendations Assessment, Development, and Evaluations (GRADE) is a widely adopted framework for assessing the quality (or "certainty") of the evidence and strength of recommendations.[14] GRADE uses four tiers to classify quality:

> *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
>
> *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
>
> *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
>
> *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.[15]

There is frequent confusion about the relationship between GRADE and tools that assess individual studies for risk of bias such as RoB 2 and ROBINS-I. When assessing risk of bias, the reviewers are assessing individual studies. When SR authors assess the quality or certainty of evidence with GRADE, they are assessing the total body of evidence. They ask: How confident should we be in the effect estimate (e.g., the estimate of average mortality, level of depression, degree of disease progression), given the evidence derived from all the included studies? GRADE does consider risk of bias in the individual studies that yielded the estimate, but that is just one of five factors that can downgrade the quality of the evidence. The other four are *inconsistency* (how consistent the results are across all the studies reporting on the same outcome);

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[13] Page et al. (2021). See also Santesso et al. (2020).
[14] However, because GRADE "has become increasingly complex, such that new as well as existing users may find it unwieldy," a simplified and slightly revised version has recently been proposed, "Core GRADE" (Guyatt et al., 2025).
[15] Balshem et al. (2011, Table 2). See also M. Prasad (2024, p. 2).

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indirectness (how applicable the evidence is to the PICO in question); *imprecision* (whether the sample is too small or confidence intervals[16] surrounding the estimates too wide), and *publication bias* (e.g. whether studies with negative results have not been published).[17] Evidence quality can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors would likely reduce the observed effect but did not.

GRADE not only provides guidance on assessing the quality of evidence, but guidance on recommending treatments. Key determinants for the strength of recommendations include the balance between benefits and harms of the alternative treatments, the certainty of evidence, values and preferences, and cost and resource allocation. Values and preferences of patients are a major consideration, especially when the certainty of evidence is low or very low.

In GRADE, there is an "explicit separation of the process for assessing the quality of a body of evidence from the process for making recommendations based in part on those assessments. Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not imply a particular strength of recommendation. Sometimes, low or very low-quality evidence can lead to a strong recommendation."[18] For example, a low-cost safe treatment supported by low-quality evidence could lead to a strong recommendation if the potential benefits are large and there is no alternative. Conversely, a treatment might be supported by high quality evidence and yet not be strongly recommended, because it has side effects that some patients would not be willing to accept.

A treatment might be potentially promising but have harmful side effects with only weak evidence of benefit. In such cases a recommendation for "treatment-only-in-research" may be given under the following conditions:

[16] A confidence interval is a range of effect values and is used to quantify uncertainty about effect estimates.
[17] Higgins et al. (2019, Table 2-1).
[18] Balshem et al. (2011, p. 402).

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> [T]here is insufficient evidence supporting an intervention for a panel to recommend its use; further research has a large potential for reducing uncertainty about the effects of the intervention; and further research is deemed good value for the anticipated costs.[19]

3. Overviews of reviews

Overviews of reviews, or "umbrella reviews," such as the one performed to systematically assess the clinical evidence for this Review, use a similar methodology to SRs to evaluate SRs themselves. Overviews employ explicit and systematic methods to identify and analyze multiple systematic reviews that address related research questions within a common topic area, with the goal of synthesizing results across key outcomes.[20] This approach is particularly useful when multiple systematic reviews exist on overlapping or related research questions within the same topic area, or when stakeholders need a high-level synthesis to inform clinical, policy, or public health decision-making. Like SRs, overviews use GRADE or related tools and standardized reporting practices.

The process of an overview follows these steps:

1. Systematically search for all SRs addressing the relevant PICOs.

2. Identify and include the eligible SRs

3. Extract information about the estimated treatment effects, and assess each SR for risk of bias using the tool such as "Risk of Bias In Systematic reviews" (ROBIS)

4. Collect, analyze, and present the data from included systematic reviews, including characteristics of the SRs and their included primary studies; risk of bias of included primary studies; outcome data; and certainty of evidence for pre-defined, clinically important outcomes. Specifically, for each outcome of interest, reviewers summarize the information about treatment estimates from the SRs.

[19] J. Andrews et al. (2013, p. 724).
[20] Pollock et al. (2024).

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To assess the certainty of evidence, reviewers may opt to summarize and report the original GRADE ratings reported by the SRs in the included systematic reviews. However, reviewers may need to re-analyze outcome data from systematic reviews or conduct GRADE assessments themselves using the information reported in the SRs, for example, when the SRs do not include GRADE assessment, or when there is disagreement across included SRs.

Performing a new SR is preferred when there is a lack of recent SRs or when existing SRs are limited in quality; but if the literature contains several recent high-quality SRs the overview is an approved option.[21]

4. Other types of reviews

Not every medical publication with "review" in its title is an SR or an overview of SRs. Such publications can be useful but are not systematic and reproducible syntheses of evidence. Other types of reviews include:

Narrative reviews

Also called *literature reviews*, a narrative review is "a review article (such as a typical book chapter) that is not conducted using methods to minimize bias (in contrast to a systematic review)."[22] For this reason, narrative reviews must be treated with caution, although they can be helpful as an introduction to a research topic.

Scoping reviews

The purpose of a scoping review is to survey the available research on a specific topic. Scoping reviews are systematic and reproducible like SRs but are usually not as rigorous. The aim of a scoping review is to survey existing research and suggest areas for future study, not to assess the evidence for a particular intervention.[23]

[21] Pollock et al. (2024).
[22] Guyatt et al. (2015, p. 461).
[23] Tricco et al. (2016).

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Appendix 4. Overview of Systematic Reviews: Methodology, Evidence Synthesis, Tables

This Appendix is published separately.

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Overview of Systematic Reviews

Methodology, Evidence Synthesis, Tables

Appendix 4:

Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices

Department of Health and Human Services

May 1, 2025



KS-AG-26-1037-A-000418

Minor corrections made May 15, 2025: see Errata

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1 Methodology

The methodology of this overview followed the recommendations for an overview of systematic reviews (SRs) in the *Cochrane Handbook for Systematic Reviews of Interventions*.[1]

Literature search: Medline, Embase, and the psychological database PsycINFO were searched for potentially eligible records. The search strategy included terms related to SRs ("systematic review," "meta-analysis," etc.) and others related to gender dysphoria ("gender incongruence," "gender-affirming hormones," "puberty blockers," etc.), using Boolean operators AND and OR as appropriate. The search was limited to items from 2015 to Feb 20, 2025. A complementary literature search was conducted in other databases including ACCESSSS (a service providing current evidence for clinical decisions) and Epistemonikos (a database of SRs), and grey literature search was conducted through the systematic review registry PROSPERO and Google Scholar, as well as a manual search of reference lists of eligible SRs. Box 1.1. provides an example of search strategies used in Medline.

Literature screening: After the removal of duplicate records, two reviewers reviewed titles and abstracts and independently determined study eligibility. Once potentially eligible records were identified, a thorough review of full-text articles with a standardized and piloted screening form was performed. Reviewers resolved disagreement by discussion.

A record was included if it met the following criteria:

1. It is an SR.
2. The study population is youth with GD whose age is below 26 years old.[2]

[1] Higgins et al. (2019).
[2] Empirically, SRs in this area are usually provided for patients under 18 or those under 26. This decision of age below 26 years balances the comprehensiveness and the directness (applicability) of the evidence review. Though there is a concern regarding the directness of evidence, the evidence for <18 and for <26 years did not identify any significant differences in outcomes.

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3. The study assesses at least one of the following: social transition, psychotherapy, puberty blockers (PBs), cross-sex hormones (CSH), or surgery.

The exclusion criteria were the following:

1. Comingling of mature adult (≥ 26 years old) and youth, which means systematic reviews with more than 25% of included studies on mature adults were excluded because these reviews were not applicable (too indirect) to inform the outcomes on youths.[3]

2. Overlapping efforts.

Data extraction and appraisal of included reviews: Data extracted included review authors, research team, and research question answered; number and characteristics of included studies; study population; treatment; outcomes of interest; analysis and synthesis strategy; risk of bias assessment used for included studies.

The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) tool[4] was used to assess the risk of bias for included SRs. The data extraction and risk of bias assessment was completed by one reviewer and checked by a second reviewer. ROBIS assesses the quality of the systematic review according to four domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis of findings. Additionally, ROBIS assesses the overall risk of bias in a systematic review process and SRs with concerns identified in the four domains can still be assessed at low risk of bias if the SRs have properly addressed these concerns in the evidence interpretation.

Evidence synthesis and certainty of evidence: The evidence synthesis summarizes the outcome data across SRs that were published in English and classified at low risk of bias.[5] The evidence synthesis was organized by types of treatment, and the outcomes

[3] The SRs including both >26 years old and <26 years old skew toward the >26 population, and so are less directly applicable to this overview than SRs on youth with GD.
[4] Whiting et al. (2016).
[5] One non-English systematic review was considered eligible and included and classified at low risk of bias. This overview did not summarize the results by outcomes from this review. Nevertheless, its conclusions were similar.

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of interest included GD, mental health and well-being, treatment goal (for example, puberty suppression for puberty blockers), need for or progression to further treatment, safety outcomes including side effects and adverse outcomes, and regret. For each outcome, this overview summarized the effect estimates and the certainty of evidence (confidence in the effect estimates, the quality of evidence).

The certainty of evidence was summarized following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[6] In GRADE, certainty of evidence can be downgraded for: risk of bias (study limitations), inconsistency (unexplained variation in results), indirectness (evidence not directly applicable), imprecision (wide confidence intervals or small samples), and publication bias (selective reporting).[7] Evidence can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors expected to reduce the observed effect did not do so.[8] Evidence could be classified into four levels of certainty: high, moderate, low, or very low.[9] This overview summarized the GRADE rating from the original review for the respective outcome wherever it is available. Nevertheless, there were two modifications made:

1. Where a formal GRADE appraisal had not been performed by the systematic review, but expressions such as “we are very uncertain” and “no conclusions could be drawn” were used in SRs’ conclusions, these statements were considered equivalent to a “very low quality” GRADE assessment.[10]

[6] In GRADE, quality of evidence is equivalent to certainty of evidence. “The quality of evidence is very low” is equivalent to “the certainty of evidence is very low.” See Guyatt et al. (2008), Balshem et al. (2011).
[7] Balshem et al. (2011); Guyatt et al. (2008); Guyatt, Oxman, Kunz, Brozek, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al. (2011); Guyatt, Oxman, Montori, et al. (2011); Guyatt, Oxman, Vist, et al. (2011).
[8] Guyatt, Oxman, Sultan, et al. (2011).
[9] According to GRADE, high certainty evidence means that “we are very confident that the true effect lies close to that of the estimate of the effect” and very low certainty evidence indicates that “we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect” (Balshem et al., 2011).
[10] Balshem et al. (2011); Santesso et al. (2020).

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2. If SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale for the assessment.

Box 1.1 Search strategy in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations 1996 to Feb 20, 2025

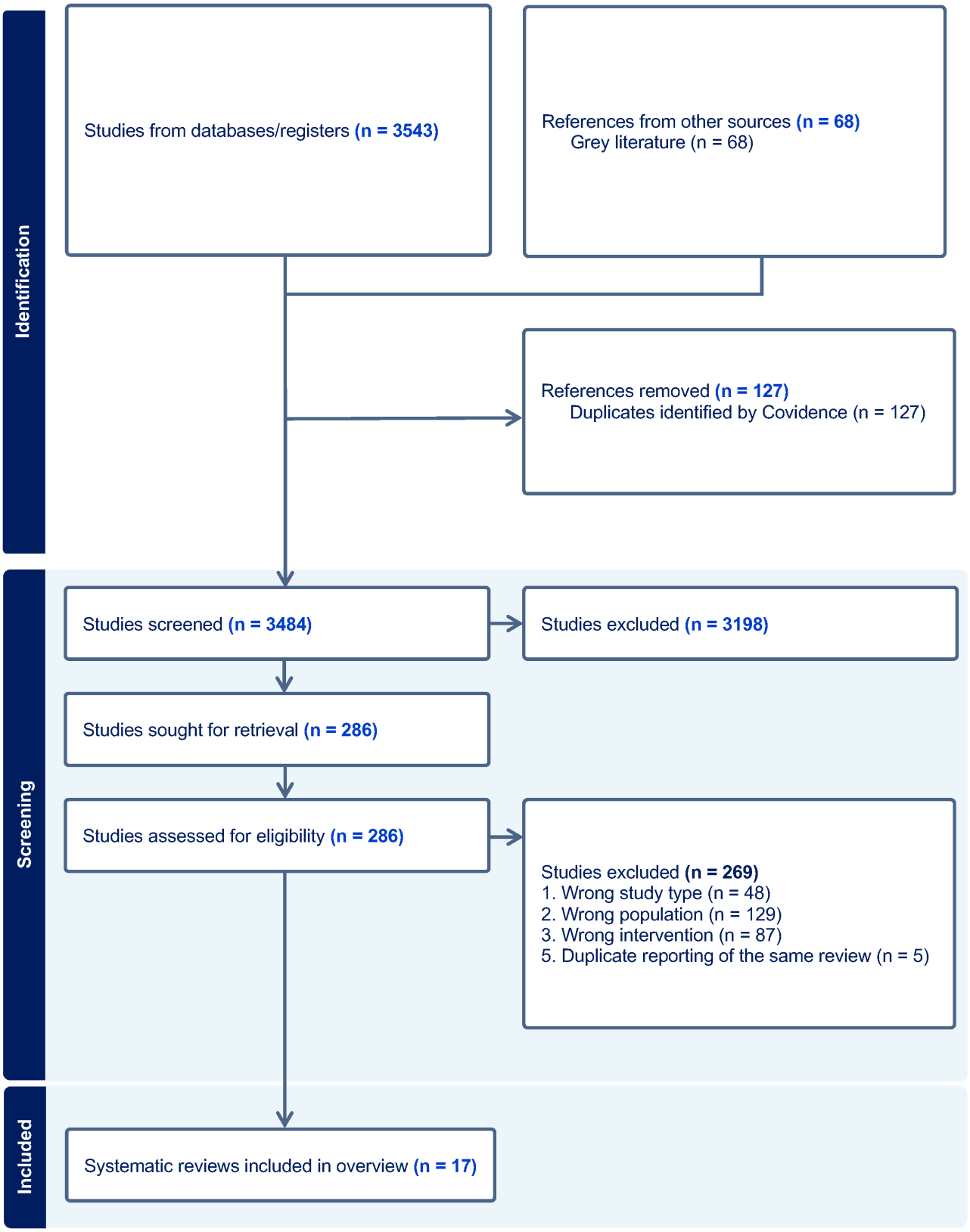
1	exp "Sexual and Gender Minorities"/
2	Gender Dysphoria/
3	Gender Identity/
4	Gender Role/
5	"Sexual and Gender Disorders"/
6	Transsexualism/
7	Transgender Persons/
8	Health Services for Transgender Persons/
9	exp Sex Reassignment Procedures/
10	gender identity disorder.mp.
11	non-binary.mp.
12	transgender.mp.
13	(gender* adj3 (dysphori* or disorder* or distress or nonconform* or non-conform* or atypical or incongru* or identi* or disorder* or confus* or minorit* or queer* or variant or diverse or creative or explor* or question* or expan* or fluid)).tw.
14	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
15	(transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw.
16	(genderfluid or genderqueer or agender).mp.
17	((correct or chosen) adj3 name).mp.
18	(trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
19	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
20	(male-to-female or m2f or female-to-male or f2m).tw.
21	or/1-20
22	exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/
23	Minors/
24	(child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn.
25	(young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn.
26	pediatrics/
27	(pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn.
28	Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/
29	Puberty/
30	(adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn.
31	Schools/ or Schools, Nursery/
32	exp Child Day Care Centers/ or Child Care/

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33	(school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	systematic review/
36	meta-analysis/
37	(meta anal* or meta-anal* or metaanal*).ti,ab.
38	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
39	((pool* or combined) adj2 (data or trials or studies or results)).ab.
40	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41	(search* adj4 literature).ab.
42	or/35-41
43	21 and 34 and 42

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Figure 1.1 Searching, screening, and inclusion process



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2 Literature screening results

Following the removal of duplicates, 3,484 records were screened by title and abstract. Of these, 286 full-text articles were assessed for eligibility. A total of 269 full-text articles were excluded for the following reasons: 48 were not SRs (incorrect study type), 129 did not focus on children or adolescents with GD, 87 did not address the treatment of interest, and 5 were excluded due to duplicate reporting (See Figure 1.1). After screening, 17 SRs met the inclusion criteria, examining the effects of psychotherapy (n = 5),[11] social transition (n = 2),[12] PBs (n = 9),[13] CSH (n = 8),[14] and surgeries (n = 3)[15] among children or adolescents with GD.

2.1 Risk of bias assessment in included SRs

Of the 17 included SRs, ten were rated as having a low risk of bias (see Table 2.1).[16]

The low risk of bias SRs could be organized into five groups:

1. The SRs by scholars from McMaster University in Canada on PBs (Miroshnychenko 2025a[17]), CSH (Miroshnychenko 2025b[18]), and mastectomy (Miroshnychenko 2024[19]).

[11] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[12] Dopp et al. (2024); Hall et al. (2024).
[13] Chew et al. (2018); Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Ramos et al. (2021); Rew et al. (2021); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[14] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[15] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[16] Dopp et al. (2024); Hall et al. (2024); Heathcote et al. (2024); Ludvigsson et al. (2023); Miroshnychenko et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024); Zepf et al. (2024).
[17] Miroshnychenko, Roldan, et al. (2025).
[18] Miroshnychenko, Ibrahim, et al. (2025).
[19] Miroshnychenko et al. (2024).

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2. The SRs conducted by scholars from University of York to inform the Cass Review, comprising the reviews of PBs (Taylor 2024a[20]), CSH (Taylor 2024b[21]), psychotherapy (Heathcote 2024[22]), and social transition (Hall 2024[23]).
3. The systematic review by researchers from Rand Corporation on all treatment strategies (Dopp 2024[24]).
4. The systematic review by Swedish Agency for Health Technology Assessment and Assessment of Social Services on hormone therapies (Ludvigsson 2023[25]).
5. The systematic review by Zepf et al., which was an update and followed the same methodology of the two SRs published in German.

SRs within each group generally followed the same methodological approach. The three SRs by McMaster University scored as having a low risk of bias across all four domains, as well as low risk of bias overall.[26] Other SRs rated at low risk of bias had limitations in one or more domains. For instance, though published in 2024, the literature search for the University of York SRs was conducted in April 2022. Additionally, there were concerns regarding the risk of bias assessment. Though the Newcastle-Ottawa Scale is an appropriate tool for the study types included in the systematic reviews, the high quality studies (for example, high quality cross-sectional or retrospective studies) are not adequate to provide high certainty evidence on the treatment effect.[27] While narrative descriptors such as “very uncertain” and “no conclusions can be drawn” correspond to the rating of “low/very low certainty” using GRADE, no formal GRADE assessment was performed. The Dopp et al. (2024)[28] review had limitations in the domain of study eligibility criteria as it included case reports and qualitative studies for

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[20] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[21] Taylor, Mitchell, Hall, Langton, et al. (2024).
[22] Heathcote et al. (2024).
[23] Hall et al. (2024).
[24] Dopp et al. (2024).
[25] Ludvigsson et al. (2023).
[26] Hall et al. (2024); Heathcote et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).
[27] van der Miesen 2020 was the only high-quality study in the systematic review on PBs, though it is a cross-sectional study and not adequate to assess treatment effect. Jensen 2019 was assessed as the only high-quality study in the systematic review on CSH, and it was a retrospective chart review and only reported side-effects, not treatment effects.
[28] Dopp et al. (2024).

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estimating treatment effects, and in the domain of identification and selection of studies was limited by searching in only one database.

A total of seven SRs[29] were rated at high risk of bias overall, often due to limited or poorly defined research questions and eligibility criteria, lack of risk of bias assessments, and inadequate synthesis of findings. This appendix includes a detailed summary of study characteristics and risk of bias considerations for all included SRs. The variation in methodological rigor highlights the need for cautious interpretation of findings, especially from reviews rated at high risk of bias.

[29] Chew et al. (2018); Expósito-Campos et al. (2023); Karalexi et al. (2020); Malpas et al. (2022); Ramos et al. (2021); Rew et al. (2021); Thompson et al. (2023).

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Table 2.1. Scope of included SRs

Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Chew 2018[30]	Y	Y				High risk of bias	Low risk of bias	High risk of bias	High risk of bias	High risk of bias
Dopp 2024[31]	Y	Y	Y	Y	Y	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Expósito-Campos 2023[32]				Y		High risk of bias	High risk of bias	Low risk of bias	High risk of bias	High risk of bias
Hall 2024[33]					Y	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Heathcote 2024[34]				Y		Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Karalexi 2020[35]		Y				High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Ludvigsson 2023[36]	Y	Y				Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	**Low risk of bias**

[30] Chew et al. (2018).
[31] Dopp et al. (2024).
[32] Expósito-Campos et al. (2023).
[33] Hall et al. (2024).
[34] Heathcote et al. (2024).
[35] Karalexi et al. (2020).
[36] Ludvigsson et al. (2023).

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Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Malpas 2022[37]				Y		High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Miroshnychenko 2025a[38]	Y					Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2025b[39]		Y				Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2024[40]			Y			Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Ramos 2021[41]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Rew 2021[42]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Taylor 2024a[43]	Y					Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**

[37] Malpas et al. (2022).
[38] Miroshnychenko, Roldan, et al. (2025).
[39] Miroshnychenko, Ibrahim, et al. (2025).
[40] Miroshnychenko et al. (2024).
[41] Ramos et al. (2021).
[42] Rew et al. (2021).
[43] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Taylor 2024b[44]		Y				Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Thompson 2023[45]	Y	Y	Y	Y		Low risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Zepf 2024[46]	Y	Y				Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	**Low risk of bias**

[44] Taylor, Mitchell, Hall, Langton, et al. (2024).
[45] Thompson et al. (2023).
[46] Zepf et al. (2024).

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2.2 Excluded SRs

Box 2.1 provides examples of excluded SRs due to focusing on a mixed population, or interventions not relevant to this overview.

Box 2.1 Examples of excluded SRs

SRs that were a mixed population (with more than 25% included studies on mature adults):

Baker 2021

Baker, K. E., Wilson, L. M., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2021). Hormone therapy, mental health, and quality of life among transgender people: A systematic review. Journal of the Endocrine Society, 5(4), 1-16.

Doyle 2023

Doyle, D. M., Lewis, T. O. G., & Barreto, M. (2023). A systematic review of psychosocial functioning changes after gender-affirming hormone therapy among transgender people. Nature Human Behaviour.

Dunford 2021

Dunford, C., Bell, K., & Rashid, T. (2021). Genital reconstructive surgery in male to female transgender patients: A systematic review of primary surgical techniques, complication profiles, and functional outcomes from 1950 to present day. European Urology Focus, 7(2), 464-471.

Haupt 2020

Haupt, C., Henke, M., Kutschmar, A., Hauser, B., Baldinger, S., Saenz, S. R., . . . Schreiber, G. (2020). Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. Cochrane Database of Systematic Reviews(11).

Javier 2022

Javier, C., Crimston, C. R., & Barlow, F. K. (2022). Surgical satisfaction and quality of life outcomes reported by transgender men and women at least one year post

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gender-affirming surgery: A systematic literature review. International Journal of Transgender Health, 23(3), 255-273.

Kloer 2021

Kloer, C., Parker, A., Blasdel, G., Kaplan, S., Zhao, L., & Bluebond-Langner, R. (2021). Sexual health after vaginoplasty: A systematic review. Andrology, andr.13022.

Kotamari 2021

Kotamarti, V. S., Greige, N., Heiman, A. J., Patel, A., & Ricci, J. A. (2021). Risk for venous thromboembolism in transgender patients undergoing cross-sex hormone treatment: A systematic review. The Journal of Sexual Medicine, 18(7), 1280-1291.

Thornton 2024

Thornton, S. M., Edalatpour, A., & Gast, K. M. (2024). A systematic review of patient regret after surgery- a common phenomenon in many specialties but rare within gender-affirmation surgery. The American Journal of Surgery.

van Leerdam 2021

van Leerdam, T. R., Zajac, J. D., & Cheung, A. S. (2021). The effect of gender-affirming hormones on gender dysphoria, quality of life, and psychological functioning in transgender individuals: A systematic review. Transgender Health, trgh.2020.0094.

Wilson 2020

Wilson, L. M., Baker, K. E., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2020). Effects of antiandrogens on prolactin levels among transgender women on estrogen therapy: A systematic review. *International journal of transgender health*, *21*(4), 391–402.

SRs that were not on the interventions of interest:

Diana 2024

Diana, P., Belluzzi, B., Corona, F., Barbi, E., & Tornese, G. (2024). Nonmedical gender-affirming practices in transgender and gender diverse adolescents: A narrative review. Transgender Health.

di Giacomo 2018

di Giacomo, E., Krausz, M., Colmegna, F., Aspesi, F., & Clerici, M. (2018). Estimating the Risk of Attempted Suicide Among Sexual Minority Youths: A Systematic Review and Meta-analysis. *JAMA pediatrics*, *172*(12), 1145–1152.

Notably, this overview excluded two SRs by National Institute for Health and Care Excellence (NICE) in October 2020.[47] This was because these two SRs were commissioned by NHS England to inform Dr Hilary Cass' independent review. In 2024, several SRs funded and commissioned by NHS England to inform the Cass review were published and were more comprehensive and updated than the two NICE SRs.

2.3 Baker et al. 2021

This overview also excluded the SR by Baker and colleagues,[48] which was funded by the World Professional Association for Transgender Health (WPATH), because it predominantly included studies on mature adults and was therefore too indirect to inform the healthcare of children or adolescents with GD. However, since the Baker et al. review supported the recommendations in the Adolescent chapter of WPATH SOC-8 it was subjected to a separate ROBIS analysis and was found to be at "high risk of bias" due to limitations in data collection and risk of bias assessment, and synthesis of results.

Study eligibility criteria: Low risk of bias.

The systematic review authors registered a protocol and had explicit and appropriate eligibility criteria. The systematic review excluded studies with follow up less than 3 months and studies that did not provide sufficient information about regimen of intervention.

Identification and selection of studies: Low risk of bias.

The authors searched in several databases and other resources. The authors also reported duplicate screening process.

[47] National Institute for Health and Care Excellence (2020b, 2020a).
[48] Baker et al. (2021).

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Data collection and study appraisal: High risk of bias.

The authors reported using a standardized form and they performed screening and risk of bias assessment in duplicate, suggesting that data collection was also done in duplicate. The authors described the most important characteristics of the included studies. The results collected, however, are not standardized across studies. For some studies, authors reported magnitudes of effect and confidence intervals, whereas for others they reported only that "no changes were observed."[49] Although the authors aimed to use the correct tools, when assessing risk of bias they did not consider that the design of the studies was not the same for the researchers of the primary studies versus the systematic review's question, leading the authors to assess studies using an inappropriate tool: for example, the systematic review authors assessed a primary study as a trial while it should have been assessed as a case series for the review purposes.

Synthesis and findings: High risk of bias.

Although reported per outcome, Baker et al. describe the results at the study level instead of across studies without justifying why they did not conduct a meta-analysis or reporting whether they planned to do so. Therefore, it is challenging for readers to draw any conclusions at the outcome level. While the review used the AHRQ guidelines for assessing strength of evidence, the authors did not comment on a formal assessment of heterogeneity, regardless of apparent between-study variation. The AHRQ guidelines do not consider publication bias. The authors did comment on risk of bias at the outcome level.

Risk of bias in the review: High risk of bias.

While the authors mention some limitations of the evidence, they did not comment on applicability or address all concerns identified with the evidence.

3 Synopses of SRs assessed at low risk of bias

Dopp et al. 2024:[50] This RAND SR examined evidence on interventions for GD and related health problems in youth with GD. The SR applied a strategy of combining

[49] Baker et al. (2021).
[50] Dopp et al. (2024).

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targeted search from existing clinical guidelines, reviews, and legal proceedings, and a broad search from PubMed. It included 105 studies and organized them into seven categories of interventions: psychosocial interventions, PBs, CSH, surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, and other treatments described as "gender identity and expression change efforts." Although this systematic review is comprehensive (49 studies for PBs, 56 studies for CSH, and 18 studies for surgery), a notable limitation is the inclusion of case reports. Case reports are inherently limited in their ability to establish treatment effects due to the lack of control groups and high risk of bias. The inclusion of case reports inflated the number of included studies but provided no additional benefits in informing about treatment effectiveness, which was reflected by the very low certainty of evidence despite a large number of eligible studies. This SR is limited by having systematically searched PubMed but no other databases. Compared with other low risk of bias SRs on hormonal and surgical treatment (Miroshnychenko 2024, Miroshnychenko 2025a,[51] Miroshnychenko 2025b,[52] Taylor 2024a,[53] Taylor 2024b[54]), the Dopp et al. 2024 review missed more case series and before-after studies while including more case reports. It summarized effect estimates by reviewing all reports of outcomes across studies and applied the GRADE methodology to assess the certainty of evidence. This SR reported that the evidence was limited by lack of long-term outcomes, lack of randomized controlled trials, and inconsistent measurement of outcomes, concluding that the certainty of evidence was frequently low or very low. For interventions including PBs, CSH, and surgeries, the certainty of evidence was very low for GD and mental health outcomes.

Hall et al. 2024:[55] This SR is part of the systematic review effort commissioned by the Cass Review. It assessed the effects of social transition (e.g., name/pronoun use, clothing changes) in patients under 18 with GD/incongruence. The authors included 11

[51] Miroshnychenko, Roldan, et al. (2025).
[52] Miroshnychenko, Ibrahim, et al. (2025).
[53] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[54] Taylor, Mitchell, Hall, Langton, et al. (2024).
[55] Hall et al. (2024).

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studies, most from the US and of low quality, using cross-sectional and cohort designs. The literature search was conducted in April 2022. The authors used an adapted version of the Newcastle-Ottawa Scale for cohort studies. Notably, the Newcastle-Ottawa Scale is suitable for the study type, but a high-quality study as assessed by this tool may be assessed as having high risk of bias according to other tools such as ROBINS-I, which has been developed to consider both the study design and the appropriateness of a study for answering questions about treatment effects. This SR did not conduct meta-analysis to synthesize evidence quantitatively; instead, it narratively summarized the effect estimates by outcomes. The review authors interpreted the evidence with caution, considering the limitations of the evidence (small sample sizes, lack of longitudinal or controlled designs, and heterogeneous outcomes across included studies), but did not use GRADE methodology to explicitly assess the certainty of evidence. The authors concluded that there is insufficient evidence to determine benefits or harms of social transition.

Heathcote et al. 2024:[56] This SR is part of the systematic review effort commissioned by the Cass Review. It evaluated psychosocial support interventions for children and adolescents experiencing GD. Ten studies with diverse designs (cohort, pre–post, mixed methods) were included. The literature search was conducted in April 2022. This SR used the Mixed Methods Appraisal Tool for quality assessment. Although the review followed systematic methods and focused on interventions beyond medical or surgical treatments, the evidence base was limited by the small number of studies, low quality, lack of comparators, and heterogeneity in interventions and outcomes. According to the authors, conclusions were limited due to poor reporting and inconsistent measurement. The authors called for clarity in intervention description and core outcome sets to enhance future research synthesis.

[56] Heathcote et al. (2024).

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Ludvigsson et al. 2023:[57] This systematic review by the Swedish National Board of Health and Welfare synthesized evidence on hormonal and surgical interventions in adolescents with GD. The review conducted a literature search in 2022 and included 24 studies (eight studies on GnRH alone, 13 studies on GnRH and CSH, and three studies on CSH alone). The review applied the GRADE methodology and downgraded the evidence due to concerns related to risk of bias and imprecise outcome measurement. However, the review authors mistakenly concluded that the certainty of evidence "cannot be assessed." Based on the authors' assessment to downgrade the evidence, the certainty of evidence should be "very low" for all outcomes assessed, including global function, suicidal ideation, GD, depression, anxiety, and quality of life. The SR concluded that evidence for benefits and harms of hormonal and surgical interventions remains insufficient for routine clinical use in adolescents.

Miroshnychenko et al. 2024:[58] This systematic review and meta-analysis examined the psychological and physical effects of mastectomy in birth-registered females under 26 years with GD. The search included databases through June 2023, yielding 39 studies (3 comparative observational, 2 before–after, and 34 case series). Outcomes included mental health measures, GD, body satisfaction, and surgical complications. The review used ROBINS-I for risk of bias assessment, conducted meta-analyses for evidence synthesis, and applied the GRADE methodology for certainty of evidence assessments. Comprehensive and methodologically sound, the SR found the certainty of evidence was limited by a predominance of case series, lack of prospective comparative studies, and other risk of bias concerns in the included studies, as well as small sample sizes. Indirectness was also a concern when participants' age at surgery was above the eligibility threshold. The authors found very low to low certainty evidence regarding mental health outcomes including global functioning, suicide attempt, and non-suicidal self-injuries.

[57] Ludvigsson et al. (2023).
[58] Miroshnychenko et al. (2024).

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Miroshnychenko et al. 2025a:[59] This SR evaluated the effects of PBs in individuals under 26 years with GD. The authors searched ten databases up to September 2023 and included studies employing observational and interventional designs. Outcomes assessed included psychological functioning, bone health, growth, and progression to CSH. The methodology of this systematic review was the same as that of another systematic review on mastectomy by the same group of researchers (Miroshnychenko 2024). The SR included 10 studies, including 3 comparative observational studies and 7 before-after studies. The review authors concluded that the certainty of evidence for psychological and physical health is very low. This SR found that 92% of individuals who received PBs progressed to receiving CSH, though the evidence on the impact of PBs on this outcome is very uncertain (very low certainty of evidence).

Miroshnychenko et al. 2025b:[60] This SR and meta-analysis assessed the effects of cross-sex hormone therapy in individuals with GD aged under 26 years. The authors searched ten databases through September 2023 and included 24 studies (9 comparative observational, 13 before–after, and 2 case series). Outcomes assessed included psychological (e.g., depression, global function) and physical effects (e.g., bone mineral density, cardiovascular events). The review followed the same methodology as two other SRs (on PBs and surgery) by the same group of researchers (Miroshnychenko 2024, Miroshnychenko 2025a[61]). The review found very low to low certainty evidence for psychological outcomes, and very low certainty evidence on bone mineral density. This SR found high certainty evidence on the proportion of natal females experiencing cardiovascular events during a 7 to 109 months of follow-up, which was 40 per 1000 following CSH use.

[59] Miroshnychenko, Roldan, et al. (2025).
[60] Miroshnychenko, Ibrahim, et al. (2025).
[61] Miroshnychenko, Roldan, et al. (2025).

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Taylor et al. 2024a:[62] This SR is part of the systematic review effort commissioned by the Cass Review. It focused on the outcomes of puberty blocker treatment in adolescents with GD or gender incongruence. The authors searched the literature through April 2022 and narratively synthesized studies on psychological, physical, and developmental effects. The SR followed the same methodology as the other reviews by the same research group (Hall 2024), including using the Newcastle-Ottawa scale to assess the risk of bias for included studies. This SR included 50 studies, including one high quality cross-sectional study and 25 moderate-quality observational studies. Notably, "moderate-quality observational studies" is not equivalent to "moderate-quality evidence." Moderate-quality observational studies or high-quality cross-sectional studies are inherently limited in evaluating treatment effects. Moreover, most included studies were observational with small sample sizes and varying outcome definitions. The review employed a narrative synthesis, including only moderate- and high-quality studies but did not explicitly assess the certainty of evidence using the GRADE methodology. The review findings were inconclusive, with inconsistent evidence on psychological benefits and concerns about effects on bone health and growth.

Taylor et al. 2024b:[63] This SR is part of the systematic review effort commissioned by the Cass Review. It synthesized studies on the outcomes of masculinising and feminising hormone therapy in adolescents with GD. It included 53 studies (12 cohort, 9 cross-sectional, 32 pre–post) identified through a search conducted in April 2022. Of all included studies, there was only one high-quality cohort study, which measured adverse outcomes only. The other included studies were moderate-quality studies. The review employed a narrative synthesis, which was limited by heterogeneity in study designs and outcome measures. Compared with other low risk of bias reviews, not using GRADE methodology to explicitly assess the certainty of evidence is a limitation and creates confusion among users: the review authors discuss "moderate quality" studies, rather than moderate certainty of evidence. The authors found inconsistent or insufficient evidence for the effect of CSH on GD, body satisfaction, psychosocial,

[62] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[63] Taylor, Mitchell, Hall, Langton, et al. (2024).

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cognitive, and physical health outcomes and concluded that robust evidence is lacking. This conclusion is consistent with other SRs of similar scope (Dopp 2024,[64] Miroshnychenko 2025b[65]), which suggested very low certainty of benefits.

[64] Dopp et al. (2024).
[65] Miroshnychenko, Ibrahim, et al. (2025).

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4 Summary of all included SRs

Chew et al. 2018[66]	
Study population description	Young people with gender dysphoria
Intervention	Hormonal treatment including PBs and CSH
Outcomes	Physical effects (including physical sex characteristics, side effects, bone mineral density, etc.), psychological effects, cognitive effects
Included studies	13 studies including 9 on GnRHas, 3 on estrogen, 5 on testosterone, 1 on antiandrogen (cyproterone acetate), and 1 on progestin (lynestrenol). There were no randomized trials included, and only 2 studies included control groups.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol available, though the authors describe the eligibility criteria with details for the population (age and diagnosis) and intervention, which seem appropriate for the question and are clear and unambiguous. Identification and selection of studies: The authors searched in the largest electronic databases, and although they did not use a formal search strategy, their search terms were broad enough to have likely captured all relevant studies. They also searched the reference list of relevant studies. Data collection and study appraisal: Data extraction captured relevant outcomes including mental health and physical parameters. The authors describe the most important characteristics of the included studies. The results collected, however, are not standardized across studies. Although the authors reported that two reviewers performed risk of bias assessments, they used a tool not designed for these types of study. Synthesis and findings: Only narrative synthesis was used. Although reported per outcome, the authors describe the results at the study level. For some outcomes, they provide a summary that focuses on counting the number of studies with statistically significant results. Risk of bias in the review: The authors mentioned some of the limitations of the evidence; however, they ignored these when interpreting the results and made claims about the presence of associations.
Results	Most of the included studies were assessed as studies with high risk of bias. This systematic review did not conduct evidence synthesis and instead relied on narrative description of individual studies. There was no formal assessment of the certainty of evidence. Nevertheless, the review authors concluded that hormonal treatments effectively achieved their intended physical effects, with GnRHas and cyproterone acetate suppressing sex hormones, and estrogen or testosterone promoting the development of feminized or masculinized secondary sex characteristics. GnRHa treatment was associated with improvements in several domains of psychological functioning, though not in gender dysphoria itself.

[66] Chew et al. (2018).

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Dopp et al. 2024[67]	
Study population description	Transgender and gender-expansive youth
Intervention	A health intervention related to recipients' transgender and gender-expansive identity (i.e., targeting gender dysphoria, related health problems, or both): psychosocial interventions, puberty-suppressing hormones, CSH, and surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, other treatments described as "gender identity and expression change efforts."
Outcomes	Psychosocial interventions: suicidality, mental health outcomes (including both depression or mood symptoms, and functioning), regret or dissatisfaction, family support. Puberty-suppressing hormones: decrease in pubertal changes targeted for suppression, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. CSH: increase in pubertal changes targeted for initiation, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Surgeries: gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Reproductive health interventions: successful cryopreservation of oocytes and embryos, successful cryopreservation of semen. Treatment of co-occurring mental health or developmental disorders: eating disorder symptoms co-occurring with gender dysphoria, depression and/or anxiety symptom co-occurring with gender dysphoria, gender dysphoria co-occurring with autism spectrum disorder. "Gender identity and expression change efforts": suicidality, mental health symptoms.
Included studies	Psychosocial interventions: 22 studies, including 1 randomized controlled trial (intervention as video narratives of lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities of overcoming coming-out-related difficulties),[68] 2 cohort studies, 6 quasi-experimental studies, 9 cross-sectional studies, 3 case reports, and 1 qualitative study. Puberty-suppressing hormones: 49 studies, including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study. CSH: 56 studies, including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study. Surgeries: 18 studies, including 6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study. Reproductive health interventions: 9 studies, using cross-sectional or case report designs with small samples (one to 20 transgender youth per sample). Treatment of co-occurring mental health or developmental disorders: 7 studies, all studies using case report design. "Gender identity and expression change efforts": 4 studies, including 3 using retrospective survey designs with community samples, and 1 case report.

[67] Dopp et al. (2024).
[68] This randomized controlled trial compared "coping-oriented brief videos" as an intervention for suicidality among sexual or gender minority. It was not a trial comparing psychotherapy with no psychotherapy for youth with gender dysphoria.

AMERICAN OVERSIGHT

Dopp et al. 2024[67]	
Risk of bias assessment consideration	Study eligibility criteria: The review did not include a preregistered protocol. The eligibility criteria focused on youth with gender dysphoria under 26 years old and required post-intervention outcomes. However, case reports and qualitative studies were included, which may be limited in estimating the treatment effects. Identification and selection of studies: There were two phases of literature search, and a comprehensive search was conducted in PubMed. However, other databases were not searched. Data collection and study appraisal: Data collection followed a structured form with critical appraisal procedures. Reviewers conducted risk of bias assessments using the JBI critical appraisal checklist. The tool was appropriate for the study research design. The reviewers discussed disagreements for consensus. Synthesis and findings: The review synthesized all identified studies for each intervention into a summary of effect estimates for each outcome that had been studied. Results for all prespecified outcomes reported and summarized. However, this review only narratively described the results for each outcome, without details on the evidence synthesis strategy or rationale. The interpretation of review findings were based on study quality and the limitations of included studies. Applicability of evidence was discussed, including study demographics, and statistical results were not overemphasized.
Results	Psychosocial interventions: very low certainty evidence for all outcomes. Puberty-suppressing hormones: low certainty evidence for decrease in pubertal changes targeted for suppression, very low certainty evidence for all the other outcomes. CSH: low certainty evidence for increase in pubertal changes targeted for initiation, very low certainty evidence for all the other outcomes. Surgeries: low certainty evidence for decrease in gender dysphoria after mastectomy, very low certainty evidence for decrease in gender dysphoria after other surgeries and other outcomes. Reproductive health interventions: very low certainty evidence for two outcomes. Treatment of co-occurring mental health or developmental disorders: very low certainty for all outcomes. “Gender identity and expression change efforts”: low certainty evidence in increases in suicidality, very low certainty for mental health symptoms.

AMERICAN OVERSIGHT

Expósito-Campos et al. 2023[69]	
Study population description	Transgender and non-binary youth and adults
Intervention	Empirically supported affirmative psychological intervention.
Outcomes	Mental health outcomes including anxiety, depression, trauma, suicidality, substance abuse, etc.
Included studies	22 studies, with 10 studies reporting outcome information for transgender and non-binary people (3 randomized controlled trials and 7 uncontrolled before-after studies), while 12 studies reporting mixed outcome information for transgender and non-binary and non-transgender populations.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were vague, for example, "well-described psychological interventions" introduces subjectivity. It is unclear whether studies following up parallel groups of study participants were considered as "quasi-experimental designs" and included or not. Identification and selection of studies: The search strategy combined five blocks with Boolean logic "AND", including "transgender" "distress" "affirming" "psychotherapy" and "intervention". This strategy was narrow. Data collection and study appraisal: Duplicate efforts and consensus process were reported. Synthesis and findings: The planned meta-analysis was not feasible. However, the narrative synthesis was reported inappropriately. The synthesis was by studies, according to the study population, types of study design, and interventions, while preferably it should be by outcomes and types of interventions. Risk of bias in the review: The interpretation of evidence did not address the concerns in the systematic review process.
Results	This systematic review did not conduct evidence synthesis by outcome, and there was no formal certainty of evidence assessment. The review authors concluded found “improvements in psychological distress, depression, anxiety, suicidality, substance-related risk behaviors, coping skills/emotion regulation, stress appraisal, self-esteem, self-acceptance, social support, minority stress, resilience, hope, positive identity, and identity acceptance” but also noted that conclusions are limited by moderate-to-high risk of bias.

[69] Expósito-Campos et al. (2023).

AMERICAN OVERSIGHT

Hall et al. 2024[70]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Social transition
Outcomes	Mental health outcomes including depression, anxiety, substance use, and suicidality, gender identity outcomes (e.g., persistence of gender dysphoria/incongruence)
Included studies	11 studies including 8 cross-sectional studies, 1 reanalysis of previously published cross-sectional data, 1 prospective longitudinal study, and 1 retrospective cohort study
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in July 2023, and published in April 2024. Databases were searched comprehensively and search dates accurately reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	No prospective longitudinal studies with suitable comparator groups have evaluated the effects of social transition on mental health or gender-related outcomes in children and adolescents. Existing studies consistently found no significant differences in mental health outcomes among children who had socially transitioned. For adolescents, the findings were mixed.

[70] Hall et al. (2024).

AMERICAN OVERSIGHT

Heathcote et al. 2024[71]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Psychosocial support
Outcomes	Mental health outcomes (including depression, anxiety, combined outcome measurement, emotional dysregulation, suicidality), psychological change (including relationship, resilience, self-compassion, self-care, coping, and problem solving, anger, life satisfaction), psychosocial change (including quality of life, well-being).
Included studies	10 studies including 4 cohort studies, 2 pre–post studies, 3 mixed methods, and 1 was a secondary analysis of intervention group data from four randomised controlled trials (these trials were not eligible).
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that the literature search was updated until April 2022, while the review was submitted for publication in September 2023, and published in April 2024. Databases searched comprehensively and search dates were reported. Though one overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool was Mixed Methods Appraisal Tool. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	Research on the outcomes of psychosocial interventions for children and adolescents with gender dysphoria or incongruence is limited. The risk of bias and poor reporting of the 10 included studies limited the conclusions about the effectiveness of psychosocial support.

[71] Heathcote et al. (2024).

AMERICAN OVERSIGHT

Karalexi et al. 2020[72]	
Study population description	Transgender young adults
Intervention	Hormone therapy
Outcomes	Cognitive outcomes including visuospatial ability, verbal memory, verbal reasoning, verbal working memory, computation, motor coordination.
Included studies	10 studies, including 6 cohort studies, 3 cross-sectional studies, and 1 with both longitudinal and cross-sectional analysis.
Risk of bias assessment consideration	Study eligibility criteria: The review included cohorts and cross-sectional studies. It is unclear whether a single group of participants with before-after study design but not labeled as "cohort" would be included or not. Identification and selection of studies: Literature search was conducted only in one database, MEDLINE. The search strategy included terms for "outcome", which may exclude records that are eligible but not indexed by reported outcomes. The number of records was low compared with other reviews. Data collection and study appraisal: Data collection seemed to be appropriate. Risk of bias was assessed using Newcastle-Ottawa Scale; However, the description of how the assessment was done suggested that the assessment may not be properly done. For example, all cohort studies were awarded with two stars in the ''Comparability'' section. Synthesis and findings: Meta-analysis was conducted where appropriate; but the review also conducted narrative synthesis elsewhere. Sources of heterogeneity was assessed using I^2 and this review briefly described the heterogeneity was not evident. No certainty of evidence assessed. Risk of bias in the review: No discussion or interpretation was included considering the risk of bias of included studies, and the limitation of the evidence.
Results	The review included meta-analyses on the cognitive functions, but did not formally assess the certainty of evidence. The systematic review did not identify evidence on adverse impact of hormone therapy on cognitive function.

[72] Karalexi et al. (2020).

AMERICAN OVERSIGHT

Ludvigsson et al. 2023[73]	
Study population description	Children with gender dysphoria
Intervention	Hormone therapy
Outcomes	Psychosocial and mental health outcomes (including gender dysphoria, depression, anxiety), cognitive outcomes, bone health outcomes, body composition and metabolic markers.
Included studies	24 studies, all observational studies, including 8 studies on GnRH alone, 13 studies on GnRH and CSH, and 3 studies on cross-sex hormone alone.
Risk of bias assessment consideration	Study eligibility criteria: This review followed PRISMA and internally register the protocol in the Swedish health technology assessment agency- However, the original protocol was not accessible. Identification and selection of studies: The literature search was comprehensive and reported in detail. However, the search may be outdated when the report was submitted for publication. Data collection and study appraisal: Two independent reviewers extracted data and conducted risk of bias assessment. Synthesis and findings: Narrative synthesis by outcome groups was justified given heterogeneity in studies. Robustness of results was considered through methodological description and bias discussion. Risk of bias in the review: The interpretation of review findings considered study quality and limitations of included studies. Conclusions aligned with evidence and noted significant research gaps. Though the GRADE assessment was labelled as "cannot be assessed", when four or more levels of downgrading happened. It should be very low.
Results	This systematic review did not identify any randomized control trails. The limited number of longitudinal observational studies were constrained by small sample sizes and high dropout rates. The evidence of long-term psychosocial effects of hormone therapy was limited. Treatment with GnRHas was found to delay bone maturation and the accrual of bone mineral density; however, partial recovery was observed during cross-sex hormone therapy when assessed at age 22.

[73] Ludvigsson et al. (2023).

AMERICAN OVERSIGHT

Malpas et al. 2022[74]	
Study population description	Transgender and gender expansive youth
Intervention	Family-based interventions: (1) providing psychoeducation, (2) allowing space for families to express reactions to their child's gender, (3) emphasizing the protective power of family acceptance, (4) utilizing multiple modalities of support, (5) giving families opportunities for allyship and advocacy, (6)connecting families to transgender and gender expansive youth community resources, and (7) centering intersectional approaches and concerns.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol. This review included three review processes, and the inclusion criteria were vague. For example, for Review 1, the inclusion criteria were: "(1) the article was published in English, and (2) the article provided treatment strategies, best practices, clinical recommendations, or outcome data related to family therapy or interventions to increase family engagement with transgender and gender expansive (TGE) youth." Identification and selection of studies: This review included three stages of search. Review 1 was the part that best met the scope of this overview. However, the number of results was low compared with other reviews. Separating Review 1 and Review 2 may have introduced bias in the review process. Though the search was updated until 2018, while the review was published in 2022. Data collection and study appraisal: No details were reported other than only "Relevant information was then coded ...". There was very brief information for included studies. No formal risk of bias assessment was applied. Synthesis and findings: The review did not identify quantitative outcome information; thus, this review narratively describe the qualitative results. The themes identified through this review included "(1) the change of clinical stance on families of youth with gender dysphoria over time, (2) the theoretical models often cited and used, (3) the most frequently recommended best clinical practices when working with youth with gender dysphoria and their families, and (4) the commonalities of these best practices with outcome data on family therapy with lesbian, gay, and bisexual youth." The review results and analyses deviated from the purpose of summarizing the evidence on family-based intervention. Risk of bias in the review: The concerns identified were not addressed in the interpretation of evidence.
Outcomes	No quantitative outcome for effectiveness. This systematic review identified four themes related to family-based intervention.
Included studies	32 studies on clinical practice recommendations for family-based interventions for transgender and gender expansive youth.
Results	This systematic review found that clinical strategies have moved from pathologizing to affirming of transgender and gender expansive youths' gender journey.

[74] Malpas et al. (2022).

AMERICAN OVERSIGHT

Miroshnychenko et al. 2024[75]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	Mastectomy
Outcomes	Mental health measures (including distress, suicide), gender dysphoria, body satisfaction, and surgical complications (including death, necrosis, and scarring).
Included studies	39 studies, including 3 comparative observational studies, 2 before–after, and 34 case series.
Risk of bias assessment consideration	Study eligibility criteria: The protocol was registered, and the eligibility criteria were clear. Identification and selection of studies: The literature search covered multiple databases with support from an information specialist. The authors described their duplicate screening and consensus processes. Data collection and study appraisal: Standardized data extraction form and duplicate extraction efforts were used; and a third reviewer was available for consensus. The risk of bias tool was appropriate for the review purpose. Synthesis and findings: Meta-analyses were conducted. When meta-analyses were not feasible, narrative syntheses were conducted. Certainty of evidence was rated using GRADE and considered the heterogeneity and risk of bias in included studies. Risk of bias in the review: The interpretation of evidence was appropriately cautious given very low to low certainty of much of the evidence.
Results	The authors found low certainty evidence on non-suicidal self-injuries, and very low certainty evidence regarding gender dysphoria and other psychological outcomes such as global functioning and suicide attempt. The review also identified high certainty evidence for outcomes of death, necrosis, and excessive scarring after surgery. The numbers of events after mastectomy were estimated to be 0, 10 to 30, and 50 per 1,000 persons for death, necrosis, and excessive scarring, respectively.

[75] Miroshnychenko et al. (2024).

AMERICAN OVERSIGHT

Miroshnychenko et al. 2025a[76]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	PBs
Outcomes	Gender dysphoria, global function, depression, bone mineral density, progression to CSH.
Included studies	10 studies, 3 comparative observational studies, and 7 before–after design studies.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[77]
Results	The systematic review identified very low certainty of evidence on the outcomes of gender dysphoria, global function, depression, and bone mineral density. There remains considerable uncertainty regarding the effects of PBs in individuals experiencing gender dysphoria.

[76] Miroshnychenko, Roldan, et al. (2025).
[77] Miroshnychenko et al. (2024).

AMERICAN OVERSIGHT

Miroshnychenko et al. 2025b[78]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	CSH
Outcomes	Gender dysphoria, global function, depression, death by suicide, bone mineral density, sexual dysfunction, cardiovascular events.
Included studies	24 studies, including 9 comparative observational studies, 13 before–after studies, and 2 case series.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[79]
Results	This systematic review found very low to low certainty evidence about depression, very low certainty evidence on gender dysphoria, global function, and bone mineral density. The systematic review found moderate to high certainty evidence on the incidence of cardiovascular events after receiving CSH.

[78] Miroshnychenko, Ibrahim, et al. (2025).
[79] Miroshnychenko et al. (2024).

AMERICAN OVERSIGHT

Ramos et al. 2021[80]	
Study population description	Adolescents with gender incongruity
Intervention	PBs
Outcomes	Gender dysphoria, bone mineral density, side effects.
Included studies	11 studies including 9 observational studies and 2 qualitative studies.
Risk of bias assessment consideration	Study eligibility criteria: The authors used study design as a reason for exclusion (e.g. literature reviews, systematic reviews, reports and case series, guidelines, summaries and comments). "Theme" was described as an exclusion reason at full-text screening, but the associated eligibility criterion was not clear. Identification and selection of studies: Search terms, filters, and strategies were reported. However, search strategy included restrictive terms including "NOT" operators that could be related to outcomes of interest (e.g. depressive disorder), which was probably not appropriate as psychosocial functioning is one of the outcomes summarized. The literature search only identified 108 records, which was low compared to other included reviews. Data collection and study appraisal: The study characteristics were not systematically reported. The authors noted using "Cochrane risk of bias assessment for observational and intervention studies", assessing, "bias of selection, performance, selective reporting, detection, attrition, and other (e.g., inadequate control for key confounders)...", and provided an alphanumeric rating at the study level in Table 1 (e.g. 2B, 2C, 4). There was no legend provided for the meaning of these ratings. It was not clear whether the Cochrane risk of bias tool is referring to ROBINS-I, which does not have these rating categories. At least one of the studies included is a qualitative study, and it was not clear how the risk of bias tool for observational and intervention studies would apply to the qualitative study. There was no mention of whether the assessment was conducted independently, in duplicate. Synthesis and findings: The authors included a narrative synthesis at the study-level highlighting results or conclusions from individual studies. The synthesis was not organized by outcome, and there was high risk of bias for selectively including study results in the narrative synthesis. The authors did not address heterogeneity in the synthesis, rather in the limitations it was noted, "Studies found are heterogeneous (different definitions, population and evaluation techniques) and sometimes based on small sample size, restricting statistical power." Risk of bias in the review: The concerns identified were not addressed.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results by individual studies. There was no certainty of evidence assessment, but according to the review authors, the use of GnRHa seems to be well tolerated by the studied population, prevent the irreversible phenotypic changes, and “contribute to the mental health.”

[80] Ramos et al. (2021).

AMERICAN OVERSIGHT

Rew et al. 2021[81]	
Study population description	Transgender and gender diverse youth
Intervention	PBs
Outcomes	Anthropomorphic measurements, sexual characteristics, mental health functioning, depression, emotional and behaviour problems, suicide, and side effects.
Included studies	9 studies including 6 observational studies, 1 cross-sectional study, and 2 case reports.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criterion for outcomes was vague by being specified as studies needing to "identify risks and/or benefits associated with the use of these medications." Identification and selection of studies: The literature search only identified 151 records after de-duplication, which was low compared to other included reviews. The study selection approach was not described. Screening involved multiple reviewers but there was no detailed reporting of calibration or adjudication. Data collection and study appraisal: A data extraction form was developed, but approach to data extraction was not described. Synthesis and findings: Narrative synthesis was justified due to design heterogeneity. Some of the included studies reported the same outcomes (e.g., body composition), but the synthesis (Table 2) was presented at the study-level instead of at the outcome-level, and the summary in the main text was collated under 'risks/adverse outcomes' and 'positive outcomes'. Risk of bias in the review: The interpretation of findings did not address the concerns identified in the process. While the risk of bias was described for the studies, it was not described in relation to the outcomes and findings.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results. This systematic review listed studies reporting positive outcomes and adverse effects. For example, “positive outcomes were decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life. Adverse factors associated with use were changes in body composition, slow growth, decreased height velocity, decreased bone turnover, cost of drugs, and lack of insurance coverage.” There was no certainty of evidence assessment, and the interpretation did not take into consideration of the strengths and limitations of the evidence.

[81] Rew et al. (2021).

AMERICAN OVERSIGHT

Taylor et al. 2024a[82]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	PBs
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including puberty progression, hormone levels, menstrual suppression, height/growth, body composition, bone geometry, etc.).
Included studies	50 studies, including 11 cohorts, 8 cross-sectional and 31 before-after studies. The descriptive evidence synthesis included 1 high quality cross-sectional study, and 25 moderate observational studies.
Risk of bias assessment consideration	Study eligibility criteria: There was a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in November 2023, and published in April 2024. Databases searched comprehensively and search dates reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality were discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	This systematic review did not identify high-quality studies with appropriate designs (only 1 “high-quality” cross-sectional study). Of the 11 cohort studies, only five were rated as moderate in quality. The evidence on the effects of PBs in adolescents with gender dysphoria or incongruence regarding its impact on gender dysphoria, mental or psychosocial health, or cognitive development was limited. Evidence also suggests that bone health and height may be adversely affected during treatment. Recently published studies which were not included in this systematic review align with the findings of this systematic review.

[82] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

AMERICAN OVERSIGHT

Taylor et al. 2024b[83]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	CSH
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including induced puberty progression, hormone levels, menstrual suppression, height/growth, body composition/shape, bone geometry, etc.), and fertility.
Included studies	53 studies including 12 cohort, 9 cross-sectional, 32 pre–post studies. This systematic review included 1 high quality cohort study.
Risk of bias assessment consideration	Same as Taylor 2024a.[84]
Results	High-quality research on the outcomes of hormone interventions in adolescents with gender dysphoria or incongruence is lacking, and few studies include long-term follow-up. There is uncertainty regarding their effects on gender-related outcomes, body satisfaction, psychosocial health, cognitive development, or fertility, and the impacts on height, growth, cardiometabolic health, and bone health. The review authors identified "moderate quality" studies[85] mental health may be improved during treatment.

[83] Taylor, Mitchell, Hall, Langton, et al. (2024).
[84] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[85] This review had identified "moderate quality" observational studies. Including "moderate-quality observational studies" is not equivalent to "moderate quality (certainty) evidence." According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).

AMERICAN OVERSIGHT

Thompson et al. 2023[86]	
Study population description	Adolescents with gender dysphoria
Intervention	Psychosocial only PBs CSH Surgeries
Outcomes	Psychosocial only: mental health. PBs: blood pressure, biochemistry and hematological measurements, anthropometric, bone density and physical changes, mental health. CSH: biochemical and hematological, anthropometric, bone density and physical changes, and mental health. Surgeries: mental health.
Included studies	19 studies, including 13 retrospective studies and no randomized controlled trial.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: There was no literature search for unpublished literature. Reference list of included studies was checked. But the inclusion criteria also excluded the possibility of searching grey literature. Data collection and study appraisal: Data were comprehensive and tabulated; overlapping samples were identified. All outcome domains from included studies were described, but synthesis was limited to narrative integration. Risk of bias was assessed using Crowe Critical Appraisal Tool, this tool may lack specificity. For example, with this tool, many papers scored lower on was the issue of consent— but many studies were retrospective in nature and the consent process was waived. Synthesis and findings: Narrative synthesis was used by outcomes. However, the syntheses for outcomes were conducted combining both puberty blockers and cross-sex hormones, which may not be appropriate. Heterogeneity was discussed narratively but no subgroup or sensitivity analysis was performed. This review described risk of bias, however, did not account for the limitations of studies in the synthesis. Risk of bias in the review: The interpretation of evidence did not address the concerns identified.
Results	No certainty of evidence assessment was conducted. Most changes to health parameters were inconclusive, “except an observed decrease in bone density z-scores with PBs.” “Some improvements were observed in global functioning and depressive symptoms once treatment was started.”

[86] Thompson et al. (2023).

AMERICAN OVERSIGHT

Zepf et al. 2024[87]	
Study population description	Children/adolescents with gender dysphoria
Intervention	PBs CSH
Outcomes	PBs: gender dysphoria, mental health, quality of life, body image, psychosocial effects, health care utilization, satisfaction with surgery following PBs, and treatment discontinuation. Cross-sex hormone: body image, psychosocial outcomes, treatment discontinuation, and bone metabolism.
Included studies	This systematic review was an update on the systematic review efforts by NICE (National Institute for Health and Care Excellence) – which aimed to "inform Dr Hilary Cass' independent review into gender identity services for children and young people." This updated further included two observational studies on CSH.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: Five databases were searched; strategy was comprehensive. Screening process was not fully described. Data collection and study appraisal: It is unclear if a structured risk of bias tool was applied. Synthesis and findings: The authors synthesize the results from all studies. They do not describe methods for data analysis. The studies seemed heterogeneous enough that summarizing them narratively is appropriate. Limitations were discussed in detail, including inconsistency and weak study designs. Risk of bias in the review: The authors considered the limitations of the evidence when interpreting the results.
Results	This systematic review concluded that the evidence on the effectiveness of PBs and/or CSH in children and adolescents with gender dysphoria remains inadequate.

[87] Zepf et al. (2024).

AMERICAN OVERSIGHT

5 Evidence synthesis: Puberty Blockers

This overview identified nine SRs on the treatment effects of PBs. Across all primary studies included in these SRs, there were no eligible randomized controlled trials. These SRs frequently used the labels based on study design, such as “cohort,” to describe the study design for included studies. However, these labels may be confusing due to the variations in study design with the same label. To address this concern, the researchers from McMaster University used labels such as “comparative observational studies” and “before-after study.” This overview found that across all primary studies in the nine SRs on PBs, only six were observational studies with parallel control groups comparing PBs with no PBs among children or adolescents with GD.[88] The sample sizes in these studies were small: three studies included fewer than 100 participants, ranging from 60 to 438 across these six comparative observational studies. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of PBs.

5.1 Included SRs on PBs

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria

[88] Becker-Hebly et al. (2021); Costa et al. (2015); Grimstad et al. (2021); Jensen et al. (2019); McGregor et al. (2024); Tordoff et al. (2022).

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and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025a

Miroshnychenko, A., Roldan, Y., Ibrahim, S., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Puberty blockers for gender dysphoria in youth: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327909

Ramos 2021

Ramos, G. G. F., Mengai, A. C. S., Daltro, C. A. T., Cutrim, P. T., Zlotnik, E., & Beck, A. P. A. (2021). Systematic review: Puberty suppression with gnrh analogues in adolescents with gender incongruity. *Journal of endocrinological investigation*, *44*(6), 1151-1158.

Rew 2021

Rew, L., Young, C. C., Monge, M., & Bogucka, R. (2021). Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. *Child and adolescent mental health*, *26*(1), 3-14.

Taylor 2024a

Taylor, J., Mitchell, A., Hall, R., Heathcote, C., Langton, T., Fraser, L., . . . Hewitt, C. E. (2024). Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s33-s47.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

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Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

5.2 Low risk of bias SRs

Four English language SRs were classified at low risk of bias.[89] Only SRs with low risk of bias were summarized to assess outcomes.

Of the four low risk of bias SRs, the eligibility criteria and number of included studies varied. Notably, the systematic review by Taylor and colleagues[90] included most studies: 50 studies including 11 cohorts, 8 cross-sectional, and 31 before-after studies. This SR synthesized only study results from high or moderate quality studies. Dopp 2024[91] included 49 studies including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study (case reports and qualitative studies are inadequate to provide quantitative information on treatment effects). In contrast, Ludvigsson 2023[92] included 21 studies, and Miroshnychenko 2025a[93] included 10 studies (including 3 comparative observational studies and 7 before–after design).

[89] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[90] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[91] Dopp et al. (2024).
[92] Ludvigsson et al. (2023).
[93] Miroshnychenko, Roldan, et al. (2025).

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Only seven studies were included in all four low risk of bias SRs, including two comparative cohorts (one in Germany,[94] one in the UK[95]), as well as the five before-after studies reported in Canada,[96] Netherlands,[97] and UK.[98])

5.3 Outcome 1. Gender dysphoria

A total of four low risk of bias SRs assessed the impact of PBs on GD.[99] Dopp 2024[100] included the most studies, though these included case reports and a qualitative study, which have limited value in estimating treatment effects. This systematic review narratively described that PBs lead to improved GD, without details on its methods for evidence synthesis. In contrast, the other three SRs reported no change in GD associated with PBs.

The interpretation of these results requires caution regarding the certainty of evidence. All three SRs using the GRADE methodology to assess certainty of evidence concluded the certainty of evidence was very low.[101] Taylor 2024a did not formally assess the certainty of evidence but found that "no high-quality studies using an appropriate design were identified, … no conclusions can be drawn," [102] which is equivalent to very low certainty evidence.

In summary, this overview concludes that the certainty of evidence is very low, and no conclusion could be drawn on the impact of PBs on GD.

5.4 Outcome 2. Mental health and wellbeing

A total of four SRs assessed the impact of PBs on mental health, using varying measures of mental health such as global function, suicidality, depression, anxiety, and

[94] Becker-Hebly et al. (2021).
[95] Costa et al. (2015).
[96] Navabi et al. (2021).
[97] Klink et al. (2015); Schagen et al. (2016).
[98] Carmichael et al. (2021); Joseph et al. (2019).
[99] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[100] Dopp et al. (2024).
[101] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025).
[102] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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quality of life.[103] Similar to the reviews on the GD outcome, Dopp 2024[104] included more studies than the three other SRs because it included case reports and a qualitative study. It narratively described that PBs lead to improved mental health, though the certainty of evidence was assessed as very low. The remaining three SRs reported either no change or small changes in mental health associated with PBs. The certainty of evidence was very low or "uncertain."

In summary, this overview concludes that no conclusion could be drawn on the impact of PBs on mental health due to very low certainty evidence.

5.5 Outcome 3. Pubertal development

Two SRs assessed the impact of PBs on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[105] SRs showed that the use of PBs is consistently associated with reductions in pubertal development. This overview assessed the certainty of evidence as high due to the observed very large effects.[106]

In summary, this overview finds high certainty evidence showing PBs lead to expected physiological effects on pubertal development.

5.6 Outcome 4. Need for or progression to further treatment

Only one systematic review assessed the impact of PBs on proceeding with CSH. Miroshnychenko and colleagues[107] included 2 case series and estimated that 92% of children or adolescents with GD proceeded with CSH, suggesting a high proportion of adolescents receiving PBs proceed to CSH. However, due to concerns related to risk of bias, the certainty of evidence regarding the causal role that PBs play in this progression is very low.

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[103] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[104] Dopp et al. (2024).
[105] Dopp et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[106] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to the very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011).
[107] Miroshnychenko, Roldan, et al. (2025).

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5.7 Outcome 5. Safety

A total of four low risk of bias SRs reported the safety outcomes for PBs in children or adolescents with GD.[108] Outcomes included overall risk of adverse events, bone health, fertility, anthropometric measures, body composition, growth, and other measures. Dopp 2024[109] included the largest number of eligible studies. The SRs reported side effects including mild headaches or hot flushes, moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems. The certainty of evidence on the overall risk of adverse events was very low.

The SRs found no evidence on the long-term safety of PBs.

All four SRs assessed bone health, and the evidence was based primarily on before-after studies. The most frequently reported outcome for bone health was bone mineral density decreases relative to reference values (z score). All SRs reported that bone density is compromised during puberty blocker treatment. Specifically, Miroshnycheko and colleagues[110] reported decreases in bone mineral density for hip, lumbar spine, and femoral neck. There was disagreement across SRs on certainty of evidence assessment, which was low according to Ludvigsson 2023[111] (due to risk of bias and imprecision concerns) but very low according to Dopp 2024[112] and Miroshnycheko 2025a.[113] Taylor 2024a[114] did not formally assess the certainty of evidence but concluded that multiple studies found that bone density is compromised. This overview of SRs assessed the certainty of evidence on bone health as low. This was due to the risk of bias in evidence based on observational studies.[115] In summary, this overview concludes there is low certainty evidence that PBs lead to compromised bone density.

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[108] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[109] Dopp et al. (2024).
[110] Miroshnychenko, Roldan, et al. (2025).
[111] Ludvigsson et al. (2023).
[112] Dopp et al. (2024).
[113] Miroshnychenko, Roldan, et al. (2025).
[114] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[115] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty, due to risk of bias concerns arising from unbalanced prognostic factors and uncontrolled confounding (lack of randomization). There is no further downgrade of evidence by this overview. The certainty of evidence is low.

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Only one systematic review reported on fertility outcomes. Based on two case reports of fertility preservation, Dopp et al[116] concluded that there was very low certainty evidence on the risk of infertility after PBs. This overview has not identified empirical evidence on fertility outcomes from included SRs. However, based on high certainty evidence in this overview on PBs' effects on pubertal development and the consideration of fertility preservation in clinical practice, adolescents receiving PBs who then proceed with CSH probably experience infertility, though the impact may depend on natal sex and stage of pubertal development when starting PBs.

Two SRs[117] reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low, or uncertain. This overview concludes that the certainty of evidence for these outcomes is very low.

5.8 Outcome 6. Regret

Only one SR assessed regret after PBs and reported high satisfaction ratings and low rates of regret. The certainty of evidence was very low, and no conclusions can be reached on the regret rate after PBs.

5.9 Evidence gap

Important gaps remain in both the range and quality of outcomes assessed across the existing literature. Many primary studies were not designed to adequately measure or report on outcomes related to puberty blocker use. For example, only a small number of primary studies included in the SRs assessed the impact of PBs on outcomes such as GD or mental health. Although PBs are frequently described as a "pause button," no studies have systematically examined their role in the decision-making process or the outcomes of those who discontinue treatment.

When outcomes were assessed, the primary focus was on short term psychological or physiological changes, or surrogate outcomes—such as suicidal ideation or bone mineral density—rather than clinically important endpoints like suicide or fractures.

[116] Dopp et al. (2024).
[117] Ludvigsson et al. (2023); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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There is particularly limited evidence on long-term outcomes related to fertility, growth, and cognitive development.

While studies suggest that a high proportion of youth proceed to cross-sex hormones after puberty suppression,[118] there is minimal evidence on the impact of this combined pathway compared to CSH alone, on long-term outcomes such as surgical outcomes, or on the need for future surgery. Furthermore, no studies have clearly examined the physical or psychosocial trajectories of those who stop PBs without transitioning to CSH. As a result, there is little data on what happens after treatment ends, and the assumption of reversibility of all puberty blocker effects remains largely untested. A further important limitation is that most primary studies did not consider the effects of PBs on males versus females. Overall, the absence of long-term, high-certainty evidence on these critical outcomes (including suicide, fractures, fertility, growth, and cognitive development) leaves substantial uncertainty about the effects of PBs.

5.10 Summary

In summary, this overview identified nine SRs addressing the effects of PBs on GD, mental health, safety, pubertal development, and further treatment decisions. There is high certainty evidence that PBs exert physiological effects such as puberty suppression, and that they probably lead to infertility when adolescents receiving PBs go on to receive CSH. PBs may compromise bone health. A high proportion of youth proceed to CSH from PBs. The evidence is very uncertain regarding the effect on GD, improvement in mental health, and safety.

[118] Miroshnychenko, Roldan, et al. (2025).

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5.11 Evidence mapping: SRs on PBs

Table 5.1. Evidence mapping of the SRs on PBs and the primary studies that these SRs included

	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Achille 2020		Y		Y			Y		
Akgul 2019		Y					Y		
Arcelus 2016							Y		
Arnoldussen 2022		Y							
Barnard 2019		Y							
Becker-Hebly 2021		Y	Y	Y			Y	Y	
Brik 2020		Y							Y
Burke 2020	Y						Y		
Caanen 2017		Y							
Cantu 2020			Y						
Carmichael 2021		Y[128]	Y	Y			Y		
Chen 2016								Y	
Chiniara 2018							Y		

[119] Chew et al. (2018).
[120] Dopp et al. (2024).
[121] Ludvigsson et al. (2023).
[122] Miroshnychenko, Roldan, et al. (2025).
[123] Ramos et al. (2021).
[124] Rew et al. (2021).
[125] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[126] Thompson et al. (2023).
[127] Zepf et al. (2024).
[128] Another citation, McPherson 2023 was provided for this study. This report was a re-analysis of the data collected by the previous report. However, this citation was not included by any other SRs on PBs or CSH.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Cohen-Kettenis 2011[129]		Y				Y			
Costa 2015	Y	Y	Y	Y	Y		Y	Y	Y
de Nie 2022							Y		
de Vries 2014	Y		Y		Y		Y		
de Vries 2011	Y	Y		Y	Y	Y	Y	Y	Y
Delemarre-van de Waal 2006	Y	Y					Y		
Donaldson 2018		Y							
Ewan 2014		Y							
Fontanari 2020							Y		
Ghelani 2020							Y		
Giovanardi 2019					Y				
Grannis 2021, Grannis 2023, and Olsavsky 2023		Y[130]							
Grimstad 2021a							Y		
Hisle-Gorman 2021		Y	Y				Y		
Jensen 2019								Y	
Joseph 2019		Y	Y	Y			Y	Y	Y
Karakılıç Özturan 2023				Y					
Khatchadourian 2014		Y			Y	Y	Y		Y
Klaver 2020		Y	Y				Y	Y	
Klaver 2018			Y		Y	Y	Y	Y	

[129] Another citation (Cohen-Kettenis, 1998) was provided for this study. However, this citation was not included by any other SRs on PBs or CSH, although it was included by Dopp et al. (2024) for CSH and surgeries.
[130] Dopp et al. (2024) included three citations for one study.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Klink 2015	Y	Y	Y	Y	Y		Y		Y
Klink 2013					Y				
Kuper 2020		Y					Y	Y	
Lavender 2023		Y							
Lee 2020			Y					Y	
Lee 2024		Y							
Littman 2021		Y							
Lopez 2018					Y			Y	
López de Lara 2020		Y							
Lynch 2015							Y		
Martin 2021		Y							
McGregor 2024		Y							
Mejia-Otero 2021							Y		
Moussaoui 2023		Y							
Nahata 2017						Y		Y	
Navabi 2021		Y	Y	Y			Y		
Neyman 2019		Y					Y		
Nokoff 2021			Y				Y		
Olson 2022		Y							
Olson-Kennedy 2021							Y		
Pang 2020		Y							

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Perl 2021[131]		Y					Y		
Perl 2020[132]		Y	Y				Y	Y	
Pine-Twaddell 2023							Y		
Ristori 2019		Y							
Russell 2021							Y	Y	
Schagen 2016	Y	Y	Y		Y	Y	Y		Y
Schagen 2018							Y		
Schagen 2020		Y	Y	Y			Y	Y	
Schneider 2017		Y				Y			
Schulmeister 2022			Y				Y		
Schwartz 2023		Y							
Segev-Becker 2020							Y		
Staphorsius 2015	Y		Y				Y		Y
Stoffers 2019			Y				Y	Y	
Strang 2022							Y		
Tack 2016		Y					Y	Y	
Tack 2018		Y					Y	Y	
Tack 2017		Y					Y	Y	
Tordoff 2022		Y					Y		
Turban 2020		Y				Y	Y		

[131] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024a included the two citations as two moderate quality before-after studies.
[132] See above note.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
van de Grift 2020		Y					Y		
van der Loos 2022		Y							
van der Loos 2023		Y							
van der Loos 2021			Y				Y		
van der Miesen 2020		Y					Y		
Vlot 2017	Y	Y	Y		Y	Y	Y		Y
Vrouenraets 2016		Y			Y				
Waldner 2023							Y		

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5.12 Evidence tables on outcomes for PBs in youth with gender dysphoria

Table 5.2. Summary of evidence on gender dysphoria after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[133]	11 studies	-[134]	PBs lead to improved gender dysphoria. However, reductions in gender dysphoria were measured less consistently than pubertal changes, and almost never in the same study as pubertal changes	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Ludvigsson 2023[135]	2 prospective observational cohort studies	145 participants on hormones, 49 were evaluated	Two of these studies observed no statistically significant change in gender dysphoria	Very low certainty due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[136]	2 before-after studies	59 participants	Standardised mean change: -0.1 (95% confidence interval: -0.4 to 0.19) (higher score indicating greater gender dysphoria)	Very low certainty due to serious inconsistency and very serious imprecision
Taylor 2024a[137]	2 before-after studies[138]	114 participants were treated	Two before-after studies measured gender dysphoria and reported no change before and after receiving treatment	No high-quality studies using an appropriate design were identified, and only four measured gender dysphoria as an outcome. No conclusions can be drawn
Evidence synthesis			No conclusion can be drawn on the impact of PBs on gender dysphoria.	The certainty of evidence is very low.

[133] Dopp et al. (2024).
[134] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[135] Ludvigsson et al. (2023).
[136] Miroshnychenko, Roldan, et al. (2025).
[137] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review only synthesized excluded low quality.
[138] Though four studies reported gender dysphoria, only two moderate quality before-after studies were included in evidence synthesis.

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Table 5.3. Summary of evidence on mental health and well-being after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[139]	21 studies	-[140]	Receipt of PBs was sometimes associated with improvements in mental health symptoms (depression, anxiety, quality of life, general functioning). In samples that started psychosocial supports prior to starting PBs, however, there were generally no changes in mental health outcomes after PBs began. Effects were also found less consistently for decreases in suicidality, potentially due to the outcome being relatively rare (which makes finding effects more difficult), especially in the younger age range seen in many of these studies.	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Ludvigsson 2023[141]	4 observational cohort studies: 1 prospective and 3 retrospective	254 participants on hormones,[142] 113 were evaluated	Improved global function as assessed with the Children's Global Assessment Scale	Very low certainty[143] due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[144]	2 comparative observational studies, and 2 before-after studies	103 participants from 2 comparative observational studies, and 53 participants from 2 before-after studies	Difference in mean change from baseline 7.67 (95% confidence interval: -2 to 17.34) in PBs group compared with no PBs group from comparative observational studies; and Mean change 3.63 (95% confidence interval: 3.17 to 4.09) from before-after studies (higher score indicating greater global function)	Very low certainty due to serious risk of bias, inconsistency and imprecision

[139] Dopp et al. (2024).
[140] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020). One study included by this review, Grannis 2023, was about CSH not PBs.
[141] Ludvigsson et al. (2023).
[142] In two studies, the participants had also received CSH.
[143] Ludvigsson et al. concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[144] Miroshnychenko, Roldan, et al. (2025).

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Taylor 2024a[145]	1 cohort and 2 before-after studies	174 participants were treated	Three before-after studies reported no clinically significant change	No conclusions can be drawn.
Suicidality				
Ludvigsson 2023[146]	1 prospective observational cohort study with mixed treatment (38 subjects with no pharmacological treatment)	42 participants on hormones, 28 were evaluated	No change in suicide ideation	Very low certainty[147] due to very serious risk of bias and very serious imprecision
Taylor 2024a[148]	1 cross-sectional study and 1 before-after study	222 participants were treated	The cross-sectional study reported less self-harm/ suicidality in those treated, although similar to group with no gender dysphoria. The before-after study did not report change over time.	No conclusions can be drawn.
Depression				
Ludvigsson 2023[149]	2 prospective observational cohort studies of which one included mixed treatment	97 participants on hormones, 60 were evaluated	No change in depression	Very low certainty[150] due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[151]	1 comparative observational study, and 1 before-after study	26 participants from 1 comparative observational study, and 41 participants from 2 before-after study	The comparative observational study with 26 participants (88% using PBs) reported that PBs did not result in a statistically significant decrease in scores in female to male participants; but resulted in a statistically significant decrease in score in male to female	Very low certainty due to very serious risk of bias, and serious imprecision

[145] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[146] Ludvigsson et al. (2023).
[147] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[148] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[149] Ludvigsson et al. (2023).
[150] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[151] Miroshnychenko, Roldan, et al. (2025).

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			participants; and Mean change -3.36 (95% confidence interval: -3.69 to -3.03) from 1 before-after study (higher score indicating greater depression)	
Taylor 2024a[152]	1 before-after study	70 participants were treated	Reduction in depressive symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Anxiety				
Ludvigsson 2023[153]	2 prospective observational cohort studies	97 participants on hormones, 60 were evaluated	No change in anxiety	Very low certainty[154] due to very serious risk of bias and very serious imprecision
Taylor 2024a[155]	1 before-after study	70 participants were treated	No change in anxiety symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Quality of life				
Ludvigsson 2023[156]	2 prospective observational cohort studies, including one retrospective	98 participants on hormones, 46 were evaluated	One study reported improvement in quality of life most pronounced in subjects receiving puberty-blocking hormones, followed by CSH treatment. A second study reported some improvement in quality of life.	Very low certainty[157] due to very serious risk of bias and very serious imprecision.
Taylor 2024a[158]	1 before-after study	44 participants were treated	No change in quality of life	A single study, reporting no improvement. No conclusion can be drawn.

[152] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[153] Ludvigsson et al. (2023).
[154] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[155] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[156] Ludvigsson et al. (2023).
[157] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[158] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Internalising problems				
Taylor 2024a[159]	1 cross-sectional study, and 2 before-after studies	292 participants were treated	No change to small decrease in internalising problems	No high certainty evidence was identified. No conclusion can be drawn.
Externalising problems				
Taylor 2024a[160]	1 cross-sectional study, and 2 before-after studies	292 participants were treated	No change to small decrease in externalising problems	No conclusion can be drawn.
Psychological functioning/psychopathology				
Taylor 2024a[161]	2 before-after studies	114 participants were treated	Two before-after studies reported no change to a small change	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of mental health outcomes by PBs.	The certainty of evidence is very low.

[159] See above note,
[160] See above note.
[161] See above note.

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Table 5.4. Summary of evidence on pubertal development after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Pubertal progression				
Dopp 2024[162]	20 studies	-[163]	Receipt of PBs was consistently associated with reductions in pubertal changes (which were targeted for suppression due to being inconsistent with the youth's gender identity), compared to expected pubertal progress and/or developmental control participants. Various physical and hormonal changes were documented over time, including reductions in endogenous sex-linked hormones, decreased progression (and sometimes regression) of physical sex characteristic development, changes in body hair, changes in height/growth and body fat composition congruent with youths' gender identities, grip strength, vocal register, and cessation of menstruation (both from menstrual suppression treatments and other forms of PBs).	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024a[164]	4 studies including 2 cohort studies and 2 before-after studies	385 participants	In one cohort study, clinical pubertal escape was reported in 2/21 participants. Another cohort study reported that Tanner stage 2/3 treatment resulted in smaller breast size in birth registered females and lower average penile length and fewer testes descended in birth registered males, compared with Tanner stage 4/5 or no GnRH-a.	Four studies showed that PBs exert its expected physiological effects
Hormone level				
Taylor 2024a[165]	9 studies including two cohort studies and seven before-after studies	606 participants were treated	Studies reported decreases in luteinising hormone, follicle-stimulating hormone, oestradiol and testosterone after receiving GnRH-a	Multiple mainly before-after studies showed that PBs exerts its expected physiological effects

[162] Dopp et al. (2024).
[163] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[164] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[165] See note above.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Menstrual suppression				
Taylor 2024a[166]	3 studies including 1 cohort study and 2 before-after studies	202 participants	All studies reported menstrual suppression	Three studies showed that exert its expected physiological effects
Evidence synthesis			PBs lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of PBs).[167]

[166] See note above.

[167] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011). These very large effects on pubertal development would otherwise not have been observed without PBs.

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Table 5.5. Summary of evidence on progression to further treatment after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[168]	2 case series	65 participants	Proportion 0.92 (95% confidence interval: 0.53 to 0.99)	Very low certainty due to risk of bias concern (rating down by three levels)
Evidence synthesis			A high proportion of adolescents receiving PBs proceed with cross-sex hormone therapy.	The certainty of evidence is very low.

[168] Miroshnychenko, Roldan, et al. (2025).

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Table 5.6. Summary of evidence on safety outcomes after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Overall risk of adverse events				
Dopp 2024[169]	18 studies	-[170]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication). Over time, few statistically significant changes were observed in a variety of parameters for cardiovascular health (cholesterol, blood pressure, glucose, lipid levels) and liver enzymes; for the parameters that did show some changes (e.g., body mass index, creatinine levels, hemoglobin/hematocrit levels), values typically remained within the expected or healthy range and thus were not clinically significant. Other minor and infrequent side effects or complications included sterile abscess, headaches, mood changes, hot flashes, decreased libido, and breakthrough menstruation.	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024a[171]	3 before-after studies	109 participants	A cohort study of GnRH-a reported side effects including mild headaches or hot flushes (~20%) and moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems (<10%). Two other studies assessed other medications and reported headaches and hot flushes as common and an increase in acne in a sample of birth-registered females receiving lynestrenol, and complaints of fatigue in birth-registered males receiving cyproterone acetate	No conclusions can be drawn.

[169] Dopp et al. (2024).
[170] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis 2011, Ristori 2019).
[171] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of PBs.	The certainty of evidence is very low.
Bone density				
Dopp 2024[172]	10 studies		The primary concern noted during treatment with PBs was decreases in bone health metrics (e.g., bone mineral density, bone growth markers). These metrics tended to remain stable during PBs treatment but showed decreases relative to age-based reference ranges; as growth rates are slowed during PBs treatment, age-based reference ranges become less relevant, and the clinical significance of these effects is unclear. Bone mineral density generally showed improvement after youth started CSH and initiated puberty consistent with their gender identity; however, it is unclear what the long-term effects on bone health and related functional outcomes (e.g., risk of fracture) would be when a patient desires long-term PBs treatment without future interventions that would enable its discontinuation.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[173]				
• **Bone density during PBs treatment (g/cm2, g/cm3)**	5 observational cohort studies (4 retrospective and 1 prospective)	363 participants on hormones, 297 were evaluated	Unchanged bone density (Dual-Energy X-ray Absorptiometry measurement)	Low certainty due to serious risk of bias and serious imprecision
• **Bone density during PBs treatment in relation to reference data in the literature (z-score)**	5 observational cohort studies (4 retrospective and 1 prospective)	408 participants on hormones, 292 were evaluated	Decreased increase in bone density over time	Low certainty due to serious risk of bias and serious imprecision

[172] Dopp et al. (2024).
[173] Ludvigsson et al. (2023); This review also assessed the effect on bone density when treatment with PBs was followed by CSH.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[174]				
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	2 before-after studies	128 participants	Mean change: -0.71 (95% confidence interval: -1.09 to -0.33)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	5 before-after studies	222 participants	Mean change: -0.72 (95% confidence interval: -0.91 to -0.54)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 20–24 months**	1 before-after study	9 participants	Mean change: -1.3 (95% confidence interval: -1.57 to -1.03)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, short term follow-up assessed with: DXA, z scores scale (−3 to 3).**	2 before-after studies	93 participants	Mean change: -0.7 (95% confidence interval: -1.11 to -0.29)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)

[174] Miroshnychenko, Roldan, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Follow-up: 6 months				
Taylor 2024a	5 before-after studies	331 participants	Five studies found decreases in bone mineral apparent density and z-scores before-after treatment; however, absolute measures generally remained stable or increased/decreased slightly	Multiple studies found that bone density is compromised during PBs treatment
Evidence synthesis			PBs may lead to decreases in bone mineral density (BMD)accumulation that normally occurs during puberty, lowering Z-scores.	The certainty of evidence is low due to evidence based on only observational studies (risk of bias).[175]
Fertility				
Dopp 2024[176]	2 studies	12 participants[177]	Case reports documented healthy, viable oocyte cryopreservation after taking PBs and pausing for at least 3 months	Very low certainty due to very serious risk of bias and very serious indirectness
Evidence synthesis			It is uncertain of PBs alone will result in impaired fertility once PBs are discontinued and puberty resumes. PBs probably lead to infertility if followed by CSH.	No empirical evidence. Inferred based on high certainty evidence on PBs effects on puberty progression.
Anthropometric measures				
Ludvigsson 2023[178]	1 retrospective observational cohort	192 participants on hormones, 192 were evaluated	Increased weight and body mass index	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision

[175] This overview re-evaluates the certainty of evidence because there was disagreement across the SRs. This overview concludes that the certainty of evidence is low because only evidence based on observational studies is available. Evidence based on observational studies without additional risk of bias concerns is assessed as low certainty of evidence, if there is no sufficient justification to upgrade the certainty of evidence.
[176] Dopp et al. (2024).
[177] This systematic review by Dopp et al reported fertility preservation based on case reports, not fertility outcomes.
[178] Ludvigsson et al. (2023).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Ludvigsson 2023[179]	2 prospective observational cohort studies and 1 controlled cross-sectional study	325 participants on hormones, 286 were evaluated	Decreased lean body mass	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[180]	2 before-after studies	152 participants	In both sexes, lean body mass percentage or SD score decreased while fat percentage increased	No conclusions can be drawn.
Blood pressure				
Ludvigsson 2023[181]	1 retrospective observational cohort	15 participants on hormones, 15 were evaluated	Change in blood pressure	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[182]	3 before-after studies	96 participants	Three studies reported no change or small, non-clinically significant change in blood pressure	No conclusions can be drawn.
Metabolic measures				
Ludvigsson 2023[183]	1 retrospective observational cohort study and 1 controlled cross-sectional study	209 participants on hormones, 209 were evaluated	No change in serum lipids or blood pressure Increased insulin level in natal males Decreased insulin sensitivity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[184]	3 before-after studies	127 participants	Three studies reported no change or small change in metabolic measures.	No conclusions can be drawn.
Growth (cm/year)				

[179] Ludvigsson et al. (2023).
[180] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[181] Ludvigsson et al. (2023).
[182] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[183] Ludvigsson et al. (2023).
[184] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Ludvigsson 2023[185]	1 prospective multicentre observational study	55 participants on hormones, 55 were evaluated	Reduced growth velocity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[186]	11 studies, including 1 cohort study, and 10 before-after studies	925 participants	The cohort study found a similar height velocity between the GnRH-a group and adolescent controls. Other studies reported no change or small decrease	No high-quality studies using an appropriate design were identified. No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on anthropometric measures, body composition, blood pressure, and growth.	The certainty of evidence is very low for outcomes such as body composition, anthropometric measures, blood pressure, metabolic measures, and growth.
Cognition				
Ludvigsson 2023[187]	1 cross-sectional study	20 participants on hormones, 20 were evaluated	No change in cognition compared with matched controls	Very low certainty due to very serious risk of bias and very serious imprecision
Taylor 2024a[188]	1 cross-sectional study, and 1 before-after study	109 participants	One cross-sectional study measured executive functioning and found no difference between adolescents who were treated for <1 year compared with those not treated, but worse executive functioning in those treated for >1 year compared with those not treated. A before-after study found no differences in features typically associated with autism spectrum condition after treatment	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on cognitive outcomes.	The certainty of evidence is very low.

[185] Ludvigsson et al. (2023).
[186] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[187] Ludvigsson et al. (2023).
[188] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Table 5.7. Summary of evidence on regret after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[189]	14 studies	-[190]	High satisfaction ratings and low rates of regret (3.5% or lower) were documented, and most youth who received that intervention progressed to CSH.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after PBs.	The certainty of evidence is very low.

[189] Dopp et al. (2024).
[190] The number of participants is not calculated because this review included heterogeneous types of studies, including that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis et al. 2011), qualitative studies (e.g., Vrouenraets et al. 2022).

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6 Evidence synthesis: Cross-sex hormones

This overview identified eight SRs on the treatment effects of CSH.[191] Across all primary studies included in the eight SRs, there were no eligible randomized controlled trials. Furthermore, this overview found only eight observational studies with parallel comparison groups comparing CSH to no CSH among children or adolescents GD.[192] Generally, the sample size of these studies was small: five studies included fewer than 100 participants. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of CSH.

6.1 Included SRs on CSH

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Karalexi 2020

Karalexi, M. A., Georgakis, M. K., Dimitriou, N. G., Vichos, T., Katsimpris, A., Petridou, E. T., . . . Papadopoulos, F. C. (2020). Gender-affirming hormone treatment and cognitive function in transgender young adults: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *119*, 104721.

[191] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[192] Becker-Hebly et al. (2021); Filipov et al. (2023); Grannis et al. (2021), (2023); Grimstad et al. (2021); Hisle-Gorman et al. (2021); Jensen et al. (2019); Tordoff et al. (2022).

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Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025b

Miroshnychenko, A., Ibrahim, S., Roldan, Y., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327921

Taylor 2024b

Taylor, J., Mitchell, A., Hall, R., Langton, T., Fraser, L., & Hewitt, C. E. (2024). Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s48-s56.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

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6.2 Low risk of bias systematic reviews

Four English SRs were classified at low risk of bias.[193] Of these reviews, the eligibility criteria and number of included studies varied. Dopp 2024[194] included 56 studies including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study. The SR by Taylor and colleagues[195] included 53 studies including 12 cohort, 9 cross-sectional, 32 pre–post studies. This SR excluded results from low quality studies in the evidence synthesis. Ludvigsson 2023[196] included 16 studies and Miroshnychenko 2025b[197] included 24 studies (including 9 comparative observational studies, 13 before–after design, and 2 case series) on CSH. Only four primary studies were included in all four low risk of bias SRs, including one comparative cohort study in Germany,[198] and three before-after studies reported in the US[199] and Netherlands.[200]

6.3 Outcome 1. Gender dysphoria

A total of three SRs assessed the impact of CSH on GD.[201] Dopp 2024[202] included a greater number of studies than three other SRs, though it included case reports and a qualitative study, which inflated the overall number of studies. This systematic review narratively described that therapy with CSH was associated with improved GD and body satisfaction, despite concluding that the certainty of evidence was very low. The other two SRs, based on evidence from observational studies, concluded that the evidence on the effect of CSH on GD and body satisfaction was very uncertain.

In summary, the certainty of evidence is very low, and no conclusion can be drawn on the impact of CSH on GD.

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[193] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[194] Dopp et al. (2024).
[195] Taylor, Mitchell, Hall, Langton, et al. (2024).
[196] Ludvigsson et al. (2023).
[197] Miroshnychenko, Ibrahim, et al. (2025).
[198] Becker-Hebly et al. (2021).
[199] Cantu et al. (2020).
[200] Schagen et al. (2020); Vlot et al. (2017).
[201] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[202] Dopp et al. (2024).

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6.4 Outcome 2. Mental health and well-being

Three SRs assessed the impact of CSH on mental health, including global function, suicidality, depression, anxiety, and other symptoms.[203] Like the SRs on GD, Dopp 2024[204] included more studies than the other SRs because it included case reports and a qualitative study. This systematic review narratively described that CSH leads to improved mental health, though the certainty of evidence was assessed as very low. Three SRs reported either no change or small changes in mental health associated with CSH. The certainty of evidence was very low or uncertain. In summary, no conclusion could be drawn on the impact of CSH on mental health due to very low certainty evidence.

For suicidality, the risk of death by suicide among hormonally-treated youth was estimated to be 6 per 1,000 according to Miroshnychenko and colleagues,[205] though the certainty of evidence was very low. According to the review by Taylor and colleagues,[206] two before-after studies reported reduced treatment needs or lower levels of suicidality and self-harm. Two other cross-sectional studies reported mixed findings: one found that adolescents receiving hormones were less likely to have seriously considered or attempted suicide compared to those not receiving hormones, while another found no difference between groups among birth-registered females. It is uncertain whether CSH leads to lower risk of suicide.

In summary, this overview finds the certainty of evidence on mental health and well-being is very low, and no conclusions can be drawn.

6.5 Outcome 3. Pubertal development

Two SRs assessed the impact of CSH on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[207] SRs showed that the use of cross-sex hormone is consistently associated with physical changes. This overview

[203] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[204] Dopp et al. (2024).
[205] Miroshnychenko, Ibrahim, et al. (2025).
[206] Taylor, Mitchell, Hall, Langton, et al. (2024).
[207] Dopp et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).

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assessed the certainty of evidence as high due to the observed very large effects.[208] One example of a very large effect pertains to menstrual suppression, which is expected to be rare without CSH. Taylor and colleagues[209] reported that menstrual suppression occurred in most participants on the basis of three before-after studies. In summary, there is high certainty evidence that CSH exerts physiological effects.

6.6 Outcome 4. Safety

Four SRs reported on safety outcomes for CSH in children or adolescents with GD. These included overall risk of adverse events, cardiovascular events, bone health, fertility, sexual dysfunction, body composition, growth, and other measures.[210] Dopp 2024[211] reported that side effects and complications were limited, and these side effects did not have a major impact on treatment. Taylor 2024b[212] listed adverse event types. In birth-registered females, reported adverse events included acne, mood changes, elevated red blood markers, increased appetite, headaches, hot flashes, fatigue, hair loss, and a slight increase in metrorrhagia. In birth-registered males, adverse events included breast tenderness, elevated liver enzymes, mood swings, and increased appetite. The certainty of evidence on the overall risk of adverse events was very low.

There is limited evidence on the long-term safety of CSH among children or adolescents with GD. Based on evidence from retrospective case series, Miroshnychenko 2025b[213] reported that the risk of cardiovascular events after CSH was estimated to be 0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months. The certainty of evidence was estimated to be moderate to high, because the SR authors contemplated that a comparison group was not needed to estimate the risk of cardiovascular events following cross-sex hormone.

All four SRs assessed bone health. The evidence was primarily based on before-after studies. The most frequently reported outcome for bone health was bone mineral

[208] Guyatt, Oxman, Sultan, et al. (2011).
[209] Taylor, Mitchell, Hall, Langton, et al. (2024).
[210] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[211] Dopp et al. (2024).
[212] Taylor, Mitchell, Hall, Langton, et al. (2024).
[213] Miroshnychenko, Ibrahim, et al. (2025).

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density decreases relative to reference values (z score). Dopp 2024[214] and Ludvigsson 2023[215] reported that bone density may recover after discontinuation of PBs and initiation of CSH. Miroshnycheko and colleagues[216] reported no changes in bone mineral density for hip, lumbar spine, and femoral neck. Taylor 2024b[217] reported conflicting results from four before-after studies: two studies reported an increase in absolute bone density measures and standard deviation (SD) scores at follow-up, with one focusing exclusively on birth-registered females. In contrast, two other studies found no change in bone density or bone biomarkers, though these involved small sample sizes. There was disagreement across SRs on certainty of evidence assessment, which was very low according to Dopp 2024[218] and Miroshnycheko 2025b,[219] but low according to Ludvigsson 2023.[220] Taylor 2024b[221] did not formally assess the certainty of evidence but concluded the evidence was very uncertain. This overview assessed the certainty of evidence for bone health as very low, considering serious risk of bias in included studies, inconsistent findings in included primary studies, and imprecision of evidence (it is unclear whether the difference in bone density is clinically meaningful).

Two SRs reported on fertility outcomes. Dopp et al[222] reported cases describing successful cryopreservation of healthy, viable oocytes, embryos, and semen, often after pausing hormone therapy. According to Taylor et al,[223] 1 cohort study reported mature spermatozoa observed in patients starting treatment at Tanner stage 4 or higher, but immature germ cells present in all patients treated earlier in puberty. This overview concludes that the evidence is very low for the impact of CSH on fertility.

[214] Dopp et al. (2024).
[215] Ludvigsson et al. (2023).
[216] Miroshnychenko, Ibrahim, et al. (2025).
[217] Taylor, Mitchell, Hall, Langton, et al. (2024).
[218] Dopp et al. (2024).
[219] Miroshnychenko, Ibrahim, et al. (2025).
[220] Ludvigsson et al. (2023).
[221] Taylor, Mitchell, Hall, Langton, et al. (2024).
[222] Dopp et al. (2024).
[223] Taylor, Mitchell, Hall, Langton, et al. (2024).

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Miroshnychenko 2025b[224] included 1 before-after study, reporting no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at 6 months or 12 months of follow-up. The certainty of evidence on sexual dysfunction was assessed as very low.

Taylor 2024b[225] also reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low or uncertain. Similarly, Ludvigsson et al[226] included three retrospective longitudinal studies assessing CSH in children without prior PBs treatment. Due to small sample sizes and differing outcomes measured (e.g., lipid levels, hemoglobin, blood pressure, metrorrhagia), the studies had low external validity. No overall conclusions could be drawn.

In summary, this overview concludes that the certainty of evidence for these outcomes is very low.

6.7 Outcome 5. Regret

Only one review assessed regret after CSH and reported high satisfaction ratings and low rates of regret.[227] The certainty of evidence was very low. This overview concludes that the evidence is uncertain, and no conclusion can be drawn on regret rate.

6.8 Evidence gap

Important evidence gaps exist for the effects of CSH. Many studies were not specifically designed to capture the full range of long-term outcomes and have largely concentrated on short-term psychological or physiological changes. Key outcomes such as GD, mental health, and quality of life have been inconsistently measured and, when reported, often are derived from small, observational studies with limited follow-up periods. Critically important long-term outcomes remain poorly understood. Sexual dysfunction, despite being highly relevant to long-term well-being, has been infrequently

[224] Miroshnychenko, Ibrahim, et al. (2025).
[225] Taylor, Mitchell, Hall, Langton, et al. (2024).
[226] Ludvigsson et al. (2023).
[227] Dopp et al. (2024).

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assessed. Although a few studies have reported cardiovascular event rates, long-term follow-up is still needed to evaluate cumulative risk.

Evidence on fertility is also sparse, with little data on whether reproductive effects vary by age at treatment initiation and whether these effects are reversible. Furthermore, the compounded effects of sequential treatment with PBs followed by CSH—such as their impact on bone health recovery, final adult height, or likelihood of requiring surgical interventions—have not been investigated adequately. A lack of primary studies that separately evaluate the effects of estrogen in males and testosterone in females is a significant limitation, as hormone-sex interactions may meaningfully influence outcomes.

6.9 Summary

In summary, this overview identified eight SRs addressing the effects of CSH among children or adolescents with GD. There is high certainty evidence that CSH exerts physiological effects. The evidence is very uncertain regarding effects on GD, mental health, or safety (such as impacts on fertility and bone health).

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KS-AG-26-1037-A-000495

6.10 Evidence mapping: SRs on CSH

Table 6.1. Evidence mapping of the SRs on CSHs and the primary studies that these SRs included

	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Achille 2020		Y			Y	Y		Y
Aldridge 2021					Y			
Allen 2019		Y				Y		Y
Amir 2020		Y						
Arcelus 2016						Y		
Arnoldussen 2022		Y						
Ascha 2022					Y			
Barnard 2019		Y						
Becker-Hebly 2021		Y		Y	Y	Y	Y	
Beking 2020						Y		
Bodlund 1996		Y						
Burke 2016	Y	Y	Y			Y		
Burke 2020						Y		
Caanen 2017		Y						
Campbell 2023		Y						

[228] Chew et al. (2018).
[229] Dopp et al. (2024).
[230] Ludvigsson et al. (2023)
[231] Miroshnychenko, Ibrahim, et al. (2025).
[232] Taylor, Mitchell, Hall, Langton, et al. (2024).
[233] Thompson et al. (2023).
[234] Zepf et al. (2024).

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Cantu 2020		Y		Y	Y	Y		
Chen 2023		Y			Y			
Chen 2016							Y	
Chiniara 2018						Y		
Cohen-Kettenis 2011[235]		Y						
de Nie 2022		Y				Y		
de Vries 2014	Y	Y		Y		Y		
de Vries 2011							Y	
Delemarre-van de Waal 2006		Y				Y		
Donaldson 2018		Y						
Filipov 2023					Y			
Fontanari 2020					Y	Y		
Foster 2021					Y			
Friedman 2000			Y					
Gale 2021		Y						
Gómez-Gil 2009			Y					
Grannis 2021[236]		Y				Y		Y
Grannis 2023[237]		Y			Y			

[235] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and surgeries.
[236] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 42 for Grannis 2021. The study population may overlap.
[237] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 82 for Grannis 2023. This report was an update to Grannis 2021. The study population may overlap.

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Green 2022		Y			Y	Y		
Grimstad 2021a		Y				Y		
Grimstad 2021b						Y		
Gupta 2023		Y						
Hannema 2017						Y		
Haraldsen 2005			Y		Y			
Hisle-Gorman 2021		Y		Y		Y		
Insogna 2020		Y						
Jarin 2017	Y	Y		Y		Y		
Jensen 2019						Y	Y	
Kaltiala 2020		Y			Y	Y		Y
Khatchadourian 2014		Y				Y		Y
Klaver 2020		Y		Y		Y	Y	Y
Klaver 2018				Y		Y	Y	
Klink 2015	Y	Y		Y		Y		Y
Kuper 2020		Y				Y	Y	Y
Laurenzano 2021		Y				Y		
Lavender 2023		Y						
Lee 2024		Y						
Lierman 2017		Y						
Littman 2021		Y						
López de Lara 2020		Y				Y		Y
Madsen 2021						Y		

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Martin 2021		Y						
Mehringer 2021		Y						
Miles 2006			Y					
Miles 1998			Y					
Millington 2022						Y		
Millington 2021						Y		
Millington 2019						Y		
Morningstar 2023								Y
Mullins 2021		Y		Y		Y		
Nokoff 2020						Y		
Nota 2019					Y			
Olsavsky 2023		Y[238]			Y			
Olson 2014	Y	Y				Y		
Olson 2022		Y						
Olson-Kennedy 2018a		Y				Y		
Perl 2021[239]		Y				Y		
Perl 2020[240]		Y		Y		Y	Y	
Pyra 2020					Y			
Ristori 2019		Y						

[238] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 75 for Olsavsky 2023. This report was a cross-sectional analysis of recruited participants.
[239] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024b included the two citations as two moderate quality before-after studies.
[240] See above note.

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Schagen 2016		Y						
Schagen 2018						Y		
Schagen 2020		Y		Y	Y	Y	Y	
Schöning 2010			Y					
Segev-Becker 2020						Y		
Sequeira 2019						Y		
Slabbekoorn 1999			Y					
Stanley 2018		Y						
Stoffers 2019		Y		Y		Y	Y	Y
Strang 2022						Y		
Tack 2016	Y	Y		Y		Y	Y	
Tack 2017	Y	Y				Y	Y	
Tordoff 2022		Y			Y	Y		
Turan 2018					Y			
Turban 2018		Y						
Turban 2022		Y				Y		
Valentine 2021						Y		
van de Grift 2020						Y		
van der Loos 2022		Y						
van der Loos 2023		Y						
van der Loos 2021				Y		Y		
van Dijk 2019					Y			
van Goozen 2002			Y					

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
van Goozen 1994			Y					
van Kesteren 1996					Y			
Vlot 2017	Y	Y		Y	Y	Y		Y
Wiepjes 2019					Y			
Wiepjes 2017					Y			

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6.11 Evidence tables on outcomes for CSH in youth with gender dysphoria

Table 6.2. Summary of evidence on gender dysphoria after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[241]	8 studies	-[242]	CSH was associated with reduced gender dysphoria and improved body satisfaction in adolescents and young adults with gender dysphoria. Effect sizes for gender dysphoria and body dissatisfaction were the largest observed for any intervention.	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Miroshnychenko 2025b[243]	1 comparative observational study and 1 before-after study	146 participants from 1 comparative study and 36 from 1 before-after study	Mean difference: -0.4 (95% confidence interval: -0.24 to 0.16) from 1 comparative study and Standardised mean change 0.26 lower (1.64 lower to 1.13 higher) from 1 before-after study (higher score indicating higher levels of gender dysphoria)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision
Taylor 2024b[244]	1 before-after study	23 participants from the before-after study	The pre–post study reported a reduction in dysphoria with no participants in clinical range at follow-up.	There was insufficient evidence regarding changes to gender dysphoria
Evidence synthesis			No conclusion can be drawn on the impact of gender dysphoria by CSH.	The certainty of evidence is very low.

[241] Dopp et al. (2024).
[242] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Ristori et al, 2019).
[243] Miroshnychenko, Ibrahim, et al. (2025).
[244] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Table 6.3. Summary of evidence on mental health and well-being after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[245]	21 studies	-[246]	CSH was associated with improved mental health outcomes in adolescents and young adults with gender dysphoria. The majority of reported outcomes showed statistical significance, and nearly all of those indicated clinical significance as well (measured by effect size or compared to norms). Benefits were most consistent for depression and general functioning or well-being, and sometimes also seen for reductions in outcomes like suicidality, anxiety, and substance use (although these less consistently showed statistically significant changes).	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Miroshnychenko 2025b[247]	2 prospective observational cohort studies; 2 before-after studies	125 from 2 prospective observational cohort studies; 73 participants from 2 before-after studies	Standardised mean difference: 0.87 higher (95% confidence interval: 0.25 lower to 2 higher) from 2 prospective observational cohort studies; Standardised mean change 0.25 higher (0.09 higher to 0.4 higher) from 2 before-after studies (higher score indicating better global function)	Very low certainty due to very serious risk of bias, serious imprecision and indirectness

[245] Dopp et al. (2024)

[246] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. For this outcome of mental health, this systematic review included two reports on the same large cross-sectional study (2015 US Transgender Survey, Lee et al. (2024); Turban et al. (2022)). Cross-sectional studies were of limited value in assessing treatment effects, while the reviewers should not include two studies on the same survey.

[247] Miroshnychenko, Ibrahim, et al. (2025)

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2025b[248]	1 case series study	315 participants	6 per 1000 (1 to 18)	Very low certainty due to very serious risk of bias (rating down by three levels)
Self-harm and suicide				
Taylor 2024b[249]	2 before-after, and 2 cross-sectional studies	99 participants from 2 before-after studies, and 293 participants from 2 cross-sectional studies	Two before-after studies found a reduction in treatment needs for (or lower levels of) suicidality/self-harm, while two cross-sectional studies found conflicting results: those receiving hormones were less likely to have seriously considered/attempted suicide compared with adolescents not receiving hormones, and in birth-registered females there was no difference between groups	Hormone treatment may in the short-term improve psychological health.[250]
Depression				
Miroshnychenko 2025b[251]	2 prospective observational cohort studies; 2 before-after studies	154 from 2 prospective observational cohort studies; 389 participants from 2 before-after studies	Standardised mean difference: 0.3 lower (95% confidence interval: 0.85 lower to 0.25 higher) from 2 prospective observational cohort studies; Standardised mean change 0.41 lower (0.65 lower to 0.17 lower) from 2 before-after studies (higher score indicating worse depression)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision

[248] Miroshnychenko, Ibrahim, et al. (2025)
[249] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[250] This systematic review concluded that there is “moderate-quality evidence from mainly pre–post studies that hormone treatment may in the short-term improve psychological health”. This review had identified “moderate quality” observational studies. Including “moderate-quality observational studies” is not equivalent to “moderate quality (certainty) evidence.” According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).
[251] Miroshnychenko, Ibrahim, et al. (2025)

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Taylor 2024b[252]	1 cohort, 1 before-after, and 2 cross-sectional studies	23 participants from 1 cohort, 52 participants from 1 before-after, and 293 participants from 2 cross-sectional studies	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study. A cross-sectional study reported lower levels of depression in adolescents who had received hormones compared with those who had wanted hormones but had not received them.	Hormone treatment may in the short-term improve psychological health.
Anxiety				
Taylor 2024b[253]	1 cohort, 1 before-after, and 1 cross-sectional study	23 participants from 1 cohort, 52 participants from 1 before-after, and 19 participants from 1 cross-sectional study	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study.	Hormone treatment may in the short-term improve psychological health.
Internalising problems				
Taylor 2024b[254]	1 cohort study	23 participants	Emotional symptoms decreased at follow-up and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.

[252] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[253] See above note.
[254] See above note.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Externalising problems				
Taylor 2024b[255]	1 cohort study	23 participants	Conduct problems and hyperactivity decreased and were lower at follow-up compared to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Psychological difficulties				
Taylor 2024b[256]	1 cohort study	23 participants	Difficulties decreased with fewer in borderline/abnormal range at follow-up, and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by CSH.	The certainty of evidence is very low.[257]

[255] See above note.

[256] See above note.

[257] Two systematic reviews assessed reported very low certainty evidence, while another claimed that there was “moderate quality evidence.” This overview assesses the certainty of evidence as very low.

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Table 6.4. Summary of evidence on pubertal development after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Induced physical changes				
Dopp 2024[258]	14 studies	-[259]	CSH was associated with physical changes resulting from increased levels of masculinizing hormones (e.g., deeper voice, increased body hair, changes in muscle mass, menstrual suppression) or feminizing hormones (e.g., decreased body hair, changes in body fat distribution, breast growth), which were targeted for initiation due to being consistent with the gender identity of youth with gender dysphoria.	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024b[260]	4 before-after studies	187 participants were treated	Two observed an increase in breast volume in birth-registered males after hormones, although objectively breast volume was small, and another reported no change in breast volume in birth-registered females. One study of birth-registered females reported an increase in facial, abdominal, chest and extremities hair, and voice deepening in all participants at follow-up. Another reported no change in Tanner genital stage in birth-registered males, and no change in Tanner pubic hair stage for both	Exogenous hormones increase hormone levels and to varying degrees of induced physical changes, with potential differences depending on birth-registered sex and timing of treatment

[258] Dopp et al. (2024).
[259] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[260] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Hormone level				
Taylor 2024b[261]	15 studies including 2 cohort studies, 12 before-after studies, and 1 cross-sectional study	1519 participants were treated	All pre–post studies and a cohort reporting pre–post data found increased/heightened testosterone and oestradiol in birth-registered females and males	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Menstrual suppression				
Taylor 2024b[262]	3 before-after studies	387 participants were treated	Three pre–post studies reported suppression in most participants	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Evidence synthesis			CSH lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of CSH).[263]

[261] See note above.
[262] Taylor, Mitchell, Hall, Langton, et al. (2024).
[263] According to the GRADE methods, evidence based on observational studies can be upgraded. See Guyatt, Oxman, Sultan, et al. (2011); This overview assessed the certainty of evidence as high, upgraded by two levels due to very large effects on physical changes, hormone level, and menstrual suppression that would otherwise not be observed without CSH.

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Table 6.5. Summary of evidence on safety outcomes after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[264]	19 studies	-[265]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication).[266]	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024b[267]	4 studies, including 1 cohort, and 3 before-after studies	17 participants from 1 cohort, and 184 participants from 3 before-after studies	In birth-registered females, three studies noted increased acne; one also reported mood changes, elevated red blood markers, increased appetite, and less commonly, headaches, hot flashes, fatigue, and hair loss. Another study found a slight rise in metrorrhagia after adding testosterone to <6 months of lynestrenol. In birth-registered males, two studies commonly reported breast tenderness. Less common effects included elevated liver enzymes and high oestradiol levels, while mood swings and increased appetite were frequent.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of CSH.	The certainty of evidence is very low.
Cardiovascular events				
Miroshnychenko 2025b[268]	2 case series studies	5768 participants	0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months	Moderate to high certainty

[264] Dopp et al. (2024).
[265] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[266] This systematic review qualitatively described the types of side effects, such as parameters for cardiovascular health, liver enzyme, etc., but did not provide detailed, separate description for these outcomes.
[267] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[268] Miroshnychenko, Ibrahim, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body mass index				
Taylor 2024b[269]	16 studies (1 cohort, 14 before-after studies, and 1 cross-sectional study)	1275 participants	No change overall but some inconsistencies	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			For every 1,000 young people receiving CSH, 40 may experience cardiovascular events in 9 years.	The certainty of evidence is moderate to high.
Bone health				
Dopp 2024[270]	7 studies	-[271]	CSH was associated with improved bone density in adolescents and young adults who experienced decreases in bone density during PBs treatment. Bone density values after CSH returned to pre-treatment levels or fell within the age-based reference range for some participants.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[272]	3 observational cohort studies (2 retrospective and 1 prospective)	268 participants on hormones, 165 were evaluated	Bone density after 1–3 years (up to 22 years of age) of CSH, which had been preceded by puberty-blocking hormonal treatment in relation to reference data in the literature: After group median five years with CSH, bone density recovered in hip but not in lumbar spine compared to data at start of treatment (z-score)	Low certainty due to serious risk of bias and serious imprecision

[269] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[270] Dopp et al. (2024).
[271] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[272] Ludvigsson et al. (2023).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025b273				
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12 months**	1 before-after study	199 participants	Mean change: 0 (0.01 lower to 0)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	1 before-after study	199 participants	Mean change: 0.01 higher (0.01 higher to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	2 before-after studies	234 participants	Mean change: 0.01 higher (0 to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
Taylor 2024b[274]	4 before-after studies	244 participants from 4 before-after studies	Two studies reported increased bone density and SD scores at follow-up (one study included birth-registered females only), while two others found no change in bone density or biomarkers, though sample sizes were small.	There is insufficient evidence about the risks of hormone interventions

[273] Miroshnychenko, Ibrahim, et al. (2025).
[274] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the impact of CSH on bone health.	The certainty of evidence is very low.
Fertility				
Dopp 2024[275]	7 studies	-[276]	Studies documented healthy, viable oocyte or embryo cryopreservation after taking CSH and pausing for at least 3 months; a case report documented that a transgender young adult man cryopreserved viable oocytes without pausing CSH, and two other case reports documented viable semen cryopreservation after pausing CSH.	Very low certainty due to very serious risk of bias, serious imprecision, and very serious indirectness
Taylor 2024b[277]	1 cohort study	78 participants	Mature spermatozoa only observed in those starting treatment at Tanner stage 4 or higher. Immature germ cells present in all treated in early puberty.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on fertility.	The certainty of evidence is very low.
Sexual dysfunction[278]				
Miroshnychenko 2025b[279]	1 before-after study	193 participants	A linear regression analysis showed no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at 6 months or 12 months of follow up.	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
Evidence synthesis			No conclusion can be drawn on the impact of CSH on sexual dysfunction.	The certainty of evidence is very low.

[275] Dopp et al. (2024).
[276] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. This review assessed fertility preservation outcomes, not fertility outcome.
[277] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[278] Evidence only on natal females.
[279] Miroshnychenko, Ibrahim, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Cognitive				
Taylor 2024b[280]	4 studies including 2 cohort studies and 2 cross-sectional studies	42 participants from 2 cohort studies and 71 participants from 2 cross-sectional studies	Two cohort studies of birth-registered females explored testosterone's impact on brain activity. One found no performance differences in visuospatial working memory across groups but noted stronger frontal and parietal activation in treated individuals and male controls. The other observed slightly more rightward amygdala lateralisation post-treatment, aligning with patterns in male and female controls. A cross-sectional study also found greater amygdala activation and stronger amygdala–prefrontal connectivity in those on hormones. Another study reported better executive function, cognitive flexibility, and working memory in hormone-treated individuals.	There was insufficient evidence regarding changes to cognitive outcomes
Evidence synthesis			No conclusion can be drawn on the impact of CSH on cognitive outcomes.	The certainty of evidence is very low.
Height/growth				
Taylor 2024b[281]	7 studies including 1 cohort study and 6 before-after studies	43 participants from 1 cohort study and 563 participants from 6 before-after studies	For birth-registered males, two studies reported an increase in height SD score and one no change. Three studies reported an increase in absolute height. For birth-registered females, two studies reported no change in height SD score, and three reported an increase in absolute height. One study reported that birth-registered females who received hormones earlier and for longer, were taller than those who started treatment later.	There is insufficient evidence about the risks of hormone interventions

[280] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[281] See note above.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Taylor 2024b[282]	2 studies including 1 cohort study and 1 cross-sectional study	28 participants from 1 cohort study and 35 participants from 1 cross-sectional study	Birth-registered females on testosterone had lower body fat and higher lean mass than female controls. Birth-registered males had higher body fat and lower lean mass after hormone treatment than male controls. A pre–post study in birth-registered males found no fat mass change at 2 years, but an increase at 3 years. Fat percentage and lean mass percentage remained stable.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on height/growth or body composition.	The certainty of evidence is very low.

[282] See above note.

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Table 6.6. Summary of evidence on regret after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[283]	13 studies	-[284]	Findings suggest high levels of satisfaction and low rates of regret with CSH, and most youth who received that intervention did not discontinue it.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after CSH.	The certainty of evidence is very low.

[283] Dopp et al. (2024).
[284] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

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7 Evidence synthesis: surgeries

This overview identified three SRs on surgeries for children or adolescents with GD[285], with most of the evidence considering mastectomy only. Across all primary studies included in the three SRs, there were no eligible randomized controlled trials. Furthermore, this overview found that only two observational studies with parallel control groups comparing surgery with no surgery among youth with GD.[286] Generally, the sample size of these studies was small: one study included 75 participants and another included 136 participants.

7.1 Included SRs on surgeries

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Miroshnychenko 2024

Miroshnychenko, A., Roldan, Y. M., Ibrahim, S., Kulatunga-Moruzi, C., Dahlin, K., Montante, S., . . . Brignardello-Petersen, R. (2024). "Mastectomy for individuals with gender dysphoria below 26 years of age: A systematic review and meta-analysis". *Plast Reconstr Surg*. https://doi.org/10.1097/prs.0000000000011734

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

[285] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[286] Becker-Hebly et al. (2021); Olson-Kennedy et al. (2018).

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7.2 Low risk of bias systematic reviews

Of the two low risk of bias SRs,[287] Dopp 2024[288] included 18 studies (6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study), and included all types of surgeries, though most of the included studies were on mastectomy. Miroshnychenko 2024[289] included 39 studies (3 comparative observational, 2 before–after, and 34 case series), and only assessed the effects of mastectomy. Three studies were included by both reviews.[290]

7.3 Outcome 1. Gender dysphoria

Two SRs assessed the impact of surgery on GD. Dopp 2024[291] narratively described that according to 10 studies mastectomy was associated with reduced GD. The certainty of evidence was low. Miroshnychenko and colleagues included 1 comparative observational study with 136 participants and 1 before-after study with 35 participants and concluded that the certainty of evidence was very low. The authors concluded that no conclusion could be drawn on the effect of surgery in improving GD.

In conclusion, this overview finds that the certainty of evidence is very low.

7.4 Outcome 2. Mental health and well-being

The SRs assessed the impact of surgery on mental health, including global functioning, suicidality, non-suicidal self-harm, depression, and quality of life.[292] Dopp 2024[293] reported that adolescents and young adults generally showed improved mental health after surgery, with about half the outcomes showing clinically significant gains (e.g., self-perception, distress, functioning, quality of life). This systematic review acknowledged that most patients had prior interventions or were already high functioning, making it hard to isolate the effects of surgery. The other systematic review[294] reported a lower level of distress measured by Kessler Psychological Distress from one comparative

[287] Dopp et al. (2024); Miroshnychenko et al. (2024).
[288] Dopp et al. (2024).
[289] Miroshnychenko et al. (2024).
[290] Ascha et al. (2022); Marinkovic & Newfield (2017); Tang et al. (2022).
[291] Dopp et al. (2024).
[292] Dopp et al. (2024); Miroshnychenko et al. (2024).
[293] Dopp et al. (2024).
[294] Miroshnychenko et al. (2024).

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observational study. However, both SRs assessed the certainty of evidence as very low. In summary, no conclusion could be drawn on the impact of surgery on global function due to very low certainty evidence.

Miroshnychenko et al[295] reported very low certainty evidence for the effect of mastectomy on outcomes such as quality of life, depression, suicide attempts and death by suicide compared with no mastectomy. Low certainty evidence suggested that mastectomy may be associated with a lower risk of non-suicidal self-injury.

In summary, this overview suggests that it is unclear whether mastectomy leads to benefits in mental health due to very low certainty evidence.

7.5 Outcome 3. Safety

Dopp 2024[296] concluded that side effects after surgeries, such as scarring or issues with function/appearance, were generally limited. Most complications (e.g., fluid buildup, pain, bruising, infection) were minor and resolved naturally or with simple follow-up care. Miroshnychenko and colleagues[297] found high certainty evidence showing no increased risk of death following the surgery as well as high-certainty evidence for necrosis and excessive scarring after surgery.

7.6 Outcome 4. Regret

Both SRs reported a low level of regret,[298] albeit both reviews found the certainty of evidence was very low. The current evidence basis is not sufficient to reach a conclusion on the regret rate after surgery.

7.7 Evidence gap

There are substantial gaps in the evidence on surgeries for adolescents with GD. Most existing studies are case series or small observational designs, with limited or no comparator groups, and thus are unable to isolate the effects of surgery from prior

[295] Miroshnychenko et al. (2024).
[296] Dopp et al. (2024).
[297] Miroshnychenko et al. (2024).
[298] Dopp et al. (2024); Miroshnychenko et al. (2024).

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medical or psychosocial interventions. Outcomes such as GD, mental health, and quality of life are inconsistently reported and often lack validated measures.

Long-term outcomes, including the durability of psychological benefits, sexual function, need for revision surgeries, and satisfaction and well-being into adulthood, remain poorly characterized. Furthermore, while regret is a frequent topic of public discussion, existing studies do not provide robust data on the factors influencing regret. There are also knowledge gaps for other types of surgeries, including genital surgeries

7.8 Summary

In summary, this overview identified three systematic reviews addressing the effects of surgeries among children or adolescents with GD. There is high certainty evidence that mastectomy is associated with predictable surgical complications such as necrosis and scarring. The evidence is very uncertain regarding the effect of surgery on GD, improvement in mental health including suicidality, depression, and long-term outcomes such as sexual function, quality of life, and regret.

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7.9 Evidence mapping: SRs on surgeries

Table 7.1. Evidence mapping of the SRs on surgeries and the primary studies that these SRs included

	Dopp 2024[299]	Miroshnychenko 2024[300]	Thompson 2023[301]
Arnoldussen 2022	Y		
Ascha 2022	Y	Y	
Ayyala 2020		Y	
Becker-Hebly 2021	Y		Y
Berry 2012		Y	
Bodlund 1996	Y		
Boskey 2023	Y		
Bungener 2020	Y		
Bustos 2020		Y	
Caro 2024		Y	
Cohen-Kettenis 2011[302]	Y		
Cohen-Kettenis 1997[303]	Y		
Cuccolo 2019		Y	
de Vries 2014	Y		
Donaldson 2018	Y		
Donato 2017		Y	
Ederer 2023		Y	
Elfering 2020		Y	
Frederick 2017		Y	
Gold 2021		Y	
Jolly 2023		Y	
Junn 2021		Y	
Kääriäinen 2017		Y	

[299] Dopp et al. (2024).
[300] Miroshnychenko et al. (2024).
[301] Thompson et al. (2023).
[302] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and CSH.
[303] Two other citations were included for this study, Smith 2021 and Smith 2022. Neither citation was included by other reviews on PBs, CSH, or surgeries.

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	Dopp 2024[299]	Miroshnychenko 2024[300]	Thompson 2023[301]
Kamali 2021		Y	
Kaur 2023		Y	
Kelly-Schuette 2022		Y	
Kuper 2020	Y		Y
Lane 2023		Y	
Lang 2021		Y	
Lee 2024	Y		
Littman 2021	Y		
Marinkovic 2017	Y	Y	
McEvenue 2017		Y	
Mehringer 2021	Y		
Naides 2021		Y	
Namba 2009		Y	
Olson-Kennedy 2018a	Y		
Olson-Kennedy 2018b		Y	
Perez-Alvarez 2021		Y	
Robinson 2023		Y	
Rothenberg 2021		Y	
Rothenberg 2018		Y	
Sır 2022		Y	
Skorochod 2023	Y		
Stein 2021		Y	
Stojanovic 2017		Y	
Tan 2023		Y	
Tang 2022	Y	Y	
Top 2017		Y	
van de Grift 2017		Y	
van de Grift 2018		Y	
van de Grift 2016		Y	
Wolf 2021		Y	
Wolter 2018		Y	

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7.10 Evidence tables on outcomes for surgeries in youth with gender dysphoria

Table 7.2. Summary of evidence on gender dysphoria after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Mastectomy				
Dopp 2024[304]	10 studies	-[305]	Mastectomy was associated with reduced gender dysphoria (including specifically chest dysphoria), and related improvements with body satisfaction for primary and sometimes secondary sex characteristics, in natal female adolescents and young adults with gender.	Low certainty due to serious risk of bias and serious indirectness
Miroshnychenko 2024[306]	1 comparative observational study and 1 before-after study	136 participants from 1 comparative observational study and 35 participants from 1 before-after study	Mean difference 26.3 lower (28.84 lower to 23.76 lower) from the comparative observational study; mean change 28 lower (28.33 lower to 27.67 lower) for gender dysphoria related to chest, and mean change 9.1 higher (8.74 higher to 9.46 higher) according to participant reported transgender congruence scale from the before-after study (higher score indicating greater gender dysphoria)	Very low certainty due to serious risk of bias, imprecision, and indirectness
Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty				
Dopp 2024[307]	4 studies	-[308]	Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal female young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness

[304] Dopp et al. (2024).
[305] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[306] Miroshnychenko et al. (2024).
[307] Dopp et al. (2024).
[308] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Vaginoplasty and/or mammaplasty				
Dopp 2024[309]	5 studies	-[310]	Vaginoplasty "bottom surgery" and/or mammaplasty "top surgery" was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal male adolescents and young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of surgeries on gender dysphoria.	The certainty of evidence is very low.

[309] Dopp et al. (2024).
[310] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

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Table 7.3. Summary of evidence on mental health and well-being after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[311]	10 studies	-[312]	Across surgeries, adolescents and young adults with gender dysphoria generally showed improvement in mental health outcomes, with clinically significant effect sizes for about half of reported outcomes; examples of outcomes measured include self-perception, psychological distress, mental health symptoms, global functioning, and quality of life. In cases where improvement was not found, average scores on outcomes were maintained at the same level as pre-surgery. No evidence of mental health harms was found. In most studies, patients had received numerous interventions and/or been required to demonstrate high levels of functioning prior to receiving surgery, which made it difficult to assess mental health outcomes of surgery, and they are considered secondary intervention benefits.	Very low certainty due to very serious risk of bias, very serious imprecision, serious inconsistency and indirectness
Miroshnychenko 2024[313]	1 comparative observational study	299	16.39% participants had mastectomy. A multivariate analysis showed that those who received mastectomy (chest reconstruction surgery) scored an average of -7.13 (CI= -10.25 to -4.02) points lower on the Kessler Psychological Distress.	Very low certainty due to very serious risk of bias and serious indirectness

[311] Dopp et al. (2024).
[312] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), or cross-sectional study (Lee 2024).
[313] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Depression				
Miroshnychenko 2024[314]	1 before-after study[315]	68	mean change 3.16 lower (3.35 lower to 2.97 lower) (higher score indicating greater depression)	Very low certainty due to very serious risk of bias and serious indirectness and imprecision
Suicide attempts				
Miroshnychenko 2024[316]	1 comparative observational study	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.39 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.39 [95% confidence interval 0.11 to 1.45]).	Very low certainty due to very serious risk of bias and serious imprecision
Non-suicidal Self-harm				
Miroshnychenko 2024[317]	1 comparative observational study[318]	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.47 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.47 [95% confidence interval 0.22 to 0.97])	Low certainty due to very serious risk of bias
Quality of life				
Miroshnychenko 2024[319]	1 before-after study and 1 case series	80 participants from the before-after study and 34 participants from the case series	mean change 5.74 higher (5.29 higher to 6.19 higher lower) (higher score indicating better quality of life)	Very low certainty due to serious risk of bias, indirectness, and imprecision

[314] Miroshnychenko et al. (2024).
[315] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[316] Miroshnychenko et al. (2024).
[317] Miroshnychenko et al. (2024).
[318] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[319] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2024[320]	1 case series	464 participants from the case series	10 per 1,000 (0 to 20)	Very low certainty due to serious very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by surgeries.	The certainty of evidence is very low.

[320] Miroshnychenko et al. (2024).

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Table 7.4. Summary of evidence on safety after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[321]	10 studies	-[322]	Across types of surgery, side effects (e.g., scarring, issues with functioning and/or appearance) were limited and primarily would be resolved through improved surgical techniques; concerns about sexual functioning were often noted, but overall sexual functioning tended to improve from pre-surgery. Complications were also generally minor (e.g., blood fluid collection, pain, bruising, infection) and resolved through natural healing or non-invasive follow-up procedures.	Very low certainty due to very serious risk of bias and serious indirectness
Death as a postoperative complication of mastectomy				
Miroshnychenko 2024[323]	5 case series studies	3673	0 per 1,000 (0 to 0)	High certainty evidence
Necrosis (complete and partial nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[324]	8 case series studies	1998	30 per 1,000 (10 to 70)	High certainty evidence
Necrosis (complete nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[325]	13 case series studies	2236	20 per 1,000 (10 to 30)	High certainty evidence

[321] Dopp et al. (2024).
[322] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that are not typically included a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[323] Miroshnychenko et al. (2024).
[324] Miroshnychenko et al. (2024).
[325] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Excessive Scarring				
Miroshnychenko 2024[326]	12 case series studies	2405	50 per 1,000 (30 to 80)	High certainty evidence
Evidence synthesis			Surgery is generally safe and the risk of dying from surgery is low. There are risks of complications such as necrosis, scarring, sexual function impairment, and other functional impairment.	The evidence for mastectomy is high certainty. The evidence for other surgeries is very low certainty.

[326] Miroshnychenko et al. (2024).

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Table 7.5. Summary of evidence on regret after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[327]	9 studies	-[328]	Across types of surgeries, high satisfaction ratings and low rates of regret (<2%) were documented. Comparisons between adolescents and young adults with gender dysphoria suggested rates of regret and satisfaction that were equal or better in youth younger than 18.	Very low certainty due to very serious risk of bias and serious indirectness
Miroshnychenko 2024[329]	4 case series studies	775	10 per 1,000 (0 to 20)	Very low certainty due to very serious risk of bias (rating down for three levels) and serious indirectness
Evidence synthesis			There are cases of regret after surgeries. No conclusion can be drawn on the regret rate after surgery.	The certainty of evidence on regret rate is very low.

[327] Dopp et al. (2024).
[328] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), and qualitative studies (Mehringer 2021).
[329] Miroshnychenko et al. (2024).

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8 Evidence synthesis: psychotherapy

There are five SRs assessing psychotherapy among children or adolescents with GD.[330] Only two were assessed at low risk of bias in the systematic review process.[331]

8.1 Included SRs on psychotherapy

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Expósito-Campos 2023

Expósito-Campos, P., Pérez-Fernández, J. I., & Salaberria, K. (2023). Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: A systematic review. *Clinical Psychology Review*, *100*, 102229.

Heathcote 2024

Heathcote, C., Taylor, J., Hall, R., Jarvis, S. W., Langton, T., Hewitt, C. E., . . . Fraser, L. (2024). Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s19-s32.

Malpas 2022 – family-based intervention (social and psychological)

Malpas, J., Pellicane, M. J., & Glaeser, E. (2022). Family-based interventions with transgender and gender expansive youth: Systematic review and best practice recommendations. *Transgend Health*, *7*(1), 7-29.

[330] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[331] Dopp et al. (2024); Heathcote et al. (2024).

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Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

8.2 Low risk of bias systematic reviews

Evidence on the effects of psychotherapy is limited. Dopp 2024[332] included one randomized controlled trial evaluating the effects of "coping-oriented brief videos" on suicidality. There are no other randomized controlled trials. Both SRs found that psychotherapy interventions were delivered through a range of formats, highlighting considerable heterogeneity in delivery. Most were conducted face-to-face or online. Formats for both face-to-face and online interventions varied widely, including individual, group, family-based, and combined approaches. Face-to-face interventions took place in diverse settings, such as specialist gender services, community programs, community mental health clinics, a weekend retreat, and an acute residential treatment program. These heterogeneities limit the generalizability of evidence.

8.3 Outcome 1. Gender dysphoria

There was no evidence on the impact of psychotherapy on GD.

8.4 Outcome 2. Mental health and well-being

Dopp and colleagues[333] reported that peer group interventions were associated with improvements in general mental health functioning, but professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning. The certainty of evidence was very low. Heathcote and colleagues included 10 studies and found that research on psychosocial interventions for children and adolescents with GD is limited. The 10 included studies were generally low in quality and poorly reported. Most lacked clear participant selection criteria, used varied interventions, applied inconsistent outcome measures, and did not include appropriate comparators. This

[332] Dopp et al. (2024).
[333] Dopp et al. (2024).

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systematic review by Heathcote and colleagues[334] underscored a lack of robust research and the use of inadequate methodologies. In summary, the certainty of evidence for benefits of psychotherapy is very low.

8.5 Outcome 3. Safety

Neither systematic review found any indication of harm from psychotherapy.

8.6 Evidence gap

The evidence base for psychotherapy in children and adolescents with GD is marked by substantial gaps. This may be due to the inappropriate conflation of psychotherapy with "conversion therapy." As noted by the Cass Review, "[the] role of psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an unhelpfully polarised debate around conversion practices."[35] There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with GD,[36] including depression, anxiety, eating disorders, self-harm, and suicidality. Studies often did not isolate the effects of psychotherapy from those of other concurrent interventions such as social transition, PBs, or CSH, making it difficult to attribute observed outcomes to psychotherapy alone. There is little understanding of which therapeutic approaches may be more effective for specific subgroups. The lack of robust research was acknowledged by the Cass Review, which noted that "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[37]

8.7 Summary

In summary, this overview identified five systematic reviews assessing the effects of psychotherapy among children or adolescents with GD. Only two reviews were rated at low risk of bias. The available evidence on psychotherapy is limited and highly heterogeneous in terms of intervention format, delivery setting, and target population. This overview finds no evidence on the impact of psychotherapy on GD from the SRs.

[334] Heathcote et al. (2024).

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For mental health outcomes, the certainty of evidence is very low. No harms were reported.

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8.8 Evidence tables on outcomes for psychotherapy in youth with gender dysphoria

Table 8.1. Summary of evidence on mental health and well-being after psychotherapy

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Peer group intervention				
Dopp 2024[335]	4 studies	-[336]	Peer group interventions were associated with improvements in general mental health functioning in adolescents and young adults with gender dysphoria; examples of outcomes studied include mental health symptoms, well-being / quality of life, and self-esteem. All studies showed benefits on some reported outcomes, but about half of the reported outcomes did not show significant changes, and in one case the effect was not clinically significant (Austin, Craig, and D'Souza, 2018). Furthermore, a group intervention for youth with autism spectrum disorder and gender dysphoria (Brandsma et al., 2022) was associated with increases in gender dysphoria and showed benefits on only one-third of reported outcomes.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness and inconsistency

[335] Dopp et al. (2024).
[336] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Professional psychological support as a precondition for additional interventions for gender dysphoria				
Dopp 2024[337]	2 studies	135 participants	Professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning in adolescents with gender dysphoria who have started puberty. Youth remained in the clinical range on mental health symptom measures post-intervention (compared to norms) and did not show statistically or clinically significant changes over time.	Very low certainty due to very serious risk of bias, and serious indirectness
Depression				
Heathcote 2024[338]	6 studies	n = 226	Four studies found significant reductions in depression levels post-intervention and/or at a later timepoint. Two studies found non-significant differences in depression levels during mid-treatment and/or post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[337] Dopp et al. (2024).
[338] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Anxiety				
Heathcote 2024[339]	3 studies	n = 218	All three studies found significant reductions in anxiety levels post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Depression and anxiety combined				
Heathcote 2024[340]	1 study	n = 17	no significant, although marginal, difference from baseline to 6 months	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[339] Heathcote et al. (2024).
[340] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Internalising and externalising symptoms				
Heathcote 2024[341]	1 study	n = 64	Improvement in internalising and externalising symptoms	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Emotional dysregulation				
Heathcote 2024[342]	1 study	n = 35	significant reductions post-intervention and at a later timepoint (1 month)	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[341] Heathcote et al. (2024).
[342] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Suicidality				
Dopp 2024[343]	1 randomized controlled trial	483 LGBTQ+ youth (“lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities”)	A randomized controlled trial found that coping-oriented brief videos ("It Gets Better" project) led to short-term decreases in suicidality and increases in help-seeking intentions with personal contacts in young adults with gender dysphoria, but these benefits were not maintained at 4 weeks post-intervention and were not large enough to represent clinically significant effects.	Very low certainty due to serious risk of bias and indirectness
Heathcote 2024[344]	3 studies	n = 193	Two studies found significant decreases in suicidality scores from baseline to mid-treatment and/or post-intervention, and/or at a later timepoint. One study found no difference in the proportion of patients at high suicide risk before and after the intervention.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[343] Dopp et al. (2024).
[344] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Family support				
Dopp 2024[345]	2 studies	-[346]	Professional psychosocial support in the form of family and/or caregiver therapy was associated with increased family support for youth with gender dysphoria, with small but clinically significant effect sizes; similar effects were also described in one case report.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness
Psychological change				
Heathcote 2024[347]	5 studies	n = 219	For resilience, self-compassion and self-acceptance, there were significant increases in scores between baseline and post-intervention, and between baseline and 3 months for self-compassion and 6 months for self-acceptance, but the difference was no longer observed for resilience at 3-month follow-up. Participants reported more positive coping and problem-solving and increased confidence. Participants also talked about being more comfortable and accepting of their identity, having a better sense of self and self-worth, and reduced feelings of isolation and distrust towards others.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[345] Dopp et al. (2024).
[346] The sample size was not calculated because one study was an individual case report, and another was a report on parental rating.
[347] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychosocial change				
Heathcote 2024[348]	5 studies	n = 412	Three studies found significant improvements in quality of life/global functioning/well-being post-intervention and/or at later timepoints. Participants reported having better peer relationships and increased acceptance and/or support from peers (from meeting and forging relationships with others in the same situation).	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by psychotherapy.	The certainty of evidence is very low.

[348] Heathcote et al. (2024).

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9 Evidence synthesis: social transition

Two SRs assessed the impact of social transition. Both are assessed at low risk of bias.[349]

9.1 Included SRs on social transition

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Hall 2024

Hall, R., Taylor, J., Hewitt, C. E., Heathcote, C., Jarvis, S. W., Langton, T., . . . Fraser, L. (2024). Impact of social transition in relation to gender for children and adolescents: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s12-s18.

9.2 Outcome 1. Gender dysphoria

Hall 2024[350] reported the impact of social transition on GD based on two observational studies. One study found that children who had socially transitioned were more likely to experience persistence of GD into adolescence compared to those who had not. Another study reported that 92.7% of children who socially transitioned between ages 3 and 12 continued to experience GD an average of 5.4 years later. The systematic review authors did not assess the certainty of evidence, though reported a "lack of robust evidence."

This overview finds the certainty of evidence for effects of social transition on GD is very low.

[349] Dopp et al. (2024); Hall et al. (2024).
[350] Hall et al. (2024).

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9.3 Outcome 2. Mental health and wellbeing

As for mental health outcomes, Dopp 2024[351] reported that social transition among children or adolescents with GD was associated with reduced suicidality and mixed outcomes for depression or mood symptoms. However, associations with other mental health symptoms (e.g., anxiety, substance use, or overall functioning) were inconsistent. The certainty of evidence was very low. The systematic review by Hall 2024[352] highlighted that the evidence on the impact of social transition for children and adolescents with GD is limited and low in quality. Most studies are cross-sectional, US-based, use non-representative samples, and lack appropriate comparator groups. No prospective studies with suitable comparators exist. Furthermore, findings are inconsistent and should be interpreted with caution. For example, some studies suggest benefits from using a chosen name in adolescence, while another found higher rates of suicide attempts and ideation among those who socially transitioned during adolescence compared to those who socially transitioned in adulthood.

In summary, this overview concludes that the certainty of evidence for effects of social transition on mental health and well-being is very low.

9.4 Outcome 3. Regret

There was no evidence on side effects, and Dopp 2024[353] was the only review reporting the regret outcome. Though this systematic review found a low level of regret, the certainty of evidence was assessed as very low.

In conclusion, the evidence is uncertain to determine the regret rate associated with social transition.

9.5 Evidence gap

The impact of social transition on long-term GD, psychological outcomes and well-being, and future treatment decisions such as CSH or surgeries remains poorly understood. Evidence on regret is extremely limited.

[351] Dopp et al. (2024).
[352] Hall et al. (2024).
[353] Dopp et al. (2024).

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Significant evidence gaps remain in the evaluation of social transition as an intervention for children and adolescents with GD. Most available studies are cross-sectional and there are no prospective longitudinal studies with appropriate comparison groups, making it unclear whether observed associations reflect the effects of social transition or other underlying factors. Additionally, studies often did not disentangle the effects of social transition from concurrent interventions such as psychotherapy or medical treatments, further complicating interpretation.

9.6 Summary

In summary, this overview identified two systematic reviews addressing the effects of social transition among children or adolescents with GD. Both reviews were assessed at low risk of bias. The studies reviewed were largely cross-sectional and no high-quality prospective studies with appropriate comparators were identified. This overview finds that the overall certainty of evidence for effects of social transition on children and adolescents with GD is very low, and no reliable conclusions could be drawn regarding the benefits or risks of this intervention.

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9.7 Evidence tables on outcomes for social transition in youth with gender dysphoria

Table 9.1. Summary of evidence on gender dysphoria after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Hall 2024[354]				
Children	2 studies	n = 444	One study found a higher odd of persistence of gender dysphoria/incongruence in adolescence for children who had socially transitioned compared with those who had not socially transitioned. Another study found that 92.7% of those who socially transitioned between ages 3 and 12 continued to experience gender dysphoria/incongruence at the end of the study (on average, 5.4 years after socially transitioning).	There is little evidence of the benefits or harms of social transition in children and adolescents.
Adolescents	1 study	350 participants	Adolescents who preferred to be called by another name compared with no preferred name use reported higher levels of gender distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Evidence synthesis			No conclusion can be drawn on the impact of social transition on gender dysphoria.	The certainty of evidence is very low.[355]

[354] Hall et al. (2024).
[355] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

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Table 9.2. Summary of evidence on mental health and well-being after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Suicidality		
Dopp 2024[356]	5 studies	-[357]	Social transition was associated with decreased suicidality in children, adolescents, and young adults with gender dysphoria. The extent to which youth in a sample or subsample were in supportive environments moderated suicidality outcomes in several studies (Campbell, Mann, Rodgers, and Tran, 2023; Turban et al., 2021), such that social transition was associated with greater decreases in suicidality in less supportive environments. An effect size metric was available for about half of reported outcomes, all of which were clinically significant except for the impacts on suicidality in adulthood (Turban et al., 2021) which were statistically but not clinically significant.	Very low certainty due to serious risk of bias, inconsistency, and indirectness
Hall 2024[358]	2 studies	n = 9,840	A cross-sectional study reported that using a chosen name in more contexts was associated with lower suicidal thoughts and behaviors. However, another cross-sectional study[359] found that social transition during adolescence was tied to higher odds of past-year suicidal ideation and lifetime suicide attempts compared to adulthood.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[356] Dopp et al. (2024).
[357] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional studies.
[358] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with those who have not.
[359] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological functioning				
Hall 2024[360]	3 studies	n = 10,077[361]	The studies comparing children experiencing gender dysphoria/incongruence who have socially transitioned with who have not socially transitioned found that the social transition status was not associated with psychological functioning or self-perception.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Non-clinical depression or mood symptoms				
Dopp 2024[362]	6 studies	-[363]	Social transition was associated with a mix of depression or mood symptom outcomes that showed clinically significant decreases and/or showed a lack of statistically significant effects in children, adolescents, and young adults with gender dysphoria. An effect size metric was available for the majority of reported outcomes, all of which were clinically significant or in the nonclinical range (compared to norms or matched samples of cisgender youth) post-intervention.	Very low certainty due to very serious risk of bias and serious indirectness
Depressive and anxiety symptoms				
Hall 2024[364]	2 studies	n = 479	A cross-sectional study reported that adolescents using a preferred name reported fewer depressive symptoms, with no significant difference in anxiety. Another cross-sectional study found that using a chosen name in more social settings was linked to lower depression levels.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[360] Hall et al. (2024); Evidence comparing children with gender dysphoria who have socially-transitioned with those who have not.
[361] One study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 165 socially-transitioned as children.
[362] Dopp et al. (2024).
[363] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[364] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with who have not

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological distress				
Hall 2024[365]	1 study	n = 9,711[366]	A cross-sectional study found no significant link between social transition timing (adolescence vs. adulthood) and severe psychological distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Other mental health outcomes				
Dopp 2024[367]	7 studies	-[368]	Social transition did not show consistent associations with other mental health symptoms (beyond depression or mood)—such as anxiety, substance use, or broad measures of mental health symptoms or functioning—in children, adolescents, and young adults with gender dysphoria. Some measures showed a lack of statistically significant change or scores that remained elevated (compared to norms or matched samples of cisgender youth) post-intervention, and/or clinically significant improvements or scores in the nonclinical range. The high level of inconsistency suggests that these outcomes are not a core benefit of social transition. No evidence of mental health harms (e.g., increased symptoms) was found.	Very low certainty due to very serious risk of bias, and serious inconsistency and indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by social transition.	The certainty of evidence is very low. [369]

[365] See above note.
[366] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.
[367] Dopp et al. (2024).
[368] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[369] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

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Table 9.3. Summary of evidence on regret after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[370]	3 studies	-[371] ,	Social transition was found to have a very low rate of detransition to a cisgender identity (3.5%) in children with gender dysphoria, suggesting low rates of regret; data were not available for detransition rates in adolescents or young adults, but rates were lower in older children (Olson et al., 2022). Perspectives among youth who detransitioned were variable, and they did not necessarily regret the transition or reverse all social transition steps (Littman, 2021; Turban, Carswell, and Keuroghlian, 2018).	Very low certainty due to very serious risk of bias, and serious indirectness
Evidence synthesis			There are cases of regret. No conclusion can be drawn on the regret rate after social transition.	The certainty of evidence on regret rate is very low.

[370] Dopp et al. (2024).
[371] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case report.

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10 Citations for the primary studies included in the SRs on PBs, CSH, and surgeries

Achille 2020

Achille, C., Taggart, T., Eaton, N. R., Osipoff, J., Tafuri, K., Lane, A., . . . Wilson, T. A. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology, 2020(1), 8. https://doi.org/10.1186/s13633-020-00078-2

Akgul 2019

Akgul, S., Bonny, A. E., Ford, N., Holland-Hall, C., & Chelvakumar, G. (2019). Experiences of gender minority youth with the intrauterine system. J Adolesc Health, 65(1), 32-38. https://doi.org/10.1016/j.jadohealth.2018.11.010

Aldridge 2021

Aldridge, Z., Patel, S., Guo, B., Nixon, E., Pierre Bouman, W., Witcomb, G. L., . . . Arcelus, J. (2021). Long-term effect of gender-affirming hormone treatment on depression and anxiety symptoms in transgender people: A prospective cohort study. Andrology, 9(6), 1808-1816. https://doi.org/https://doi.org/10.1111/andr.12884

Allen 2019

Allen, L. R., Waston, L. B., Egan, A. M., & Moser, C. N. (2019). Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology, 7(3), 302-311. https://doi.org/https://doi.org/10.1037/cpp0000288

Amir 2020

Amir, H., Yaish, I., Samara, N., Hasson, J., Groutz, A., & Azem, F. (2020). Ovarian stimulation outcomes among transgender men compared with fertile cisgender women. J Assist Reprod Genet, 37(10), 2463-2472. https://doi.org/10.1007/s10815-020-01902-7

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Arcelus 2016

Arcelus, J., Claes, L., Witcomb, G. L., Marshall, E., & Bouman, W. P. (2016). Risk factors for non-suicidal self-injury among trans youth. J Sex Med, 13(3), 402-412. https://doi.org/10.1016/j.jsxm.2016.01.003

Arnoldussen 2022

Arnoldussen, M., van der Miesen, A. I. R., Elzinga, W. S., Alberse, A. E., Popma, A., Steensma, T. D., . . . de Vries, A. L. C. (2022). Self-perception of transgender adolescents after gender-affirming treatment: A follow-up study into young adulthood. LGBT Health, 9(4), 238-246. https://doi.org/10.1089/lgbt.2020.0494

Ascha 2022

Ascha, M., Sasson, D. C., Sood, R., Cornelius, J. W., Schauer, J. M., Runge, A., . . . Jordan, S. W. (2022). Top surgery and chest dysphoria among transmasculine and nonbinary adolescents and young adults. JAMA Pediatr, 176(11), 1115-1122. https://doi.org/10.1001/jamapediatrics.2022.3424

Ayyala 2020

Ayyala, H. S., Mukherjee, T. J., Le, T. M., Cohen, W. A., Luthringer, M., & Keith, J. D. (2020). A three-step technique for optimal nipple position in transgender chest masculinization. Aesthet Surg J, 40(11), Np619-np625. https://doi.org/10.1093/asj/sjaa150

Barnard 2019

Barnard, E. P., Dhar, C. P., Rothenberg, S. S., Menke, M. N., Witchel, S. F., Montano, G. T., . . . Valli-Pulaski, H. (2019). Fertility preservation outcomes in adolescent and young adult feminizing transgender patients. Pediatrics, 144(3). https://doi.org/10.1542/peds.2018-3943

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Becker-Hebly 2021

Becker-Hebly, I., Fahrenkrug, S., Campion, F., Richter-Appelt, H., Schulte-Markwort, M., & Barkmann, C. (2021). Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: A descriptive study from the hamburg gender identity service. Eur Child Adolesc Psychiatry, 30(11), 1755-1767. https://doi.org/10.1007/s00787-020-01640-2

Beking 2020

Beking, T., Burke, S. M., Geuze, R. H., Staphorsius, A. S., Bakker, J., Groothuis, A. G. G., . . . Kreukels, B. P. C. (2020). Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. Psychoneuroendocrinology, 111, 104461. https://doi.org/https://doi.org/10.1016/j.psyneuen.2019.104461

Berry 2012

Berry, M. G., Curtis, R., & Davies, D. (2012). Female-to-male transgender chest reconstruction: A large consecutive, single-surgeon experience. J Plast Reconstr Aesthet Surg, 65(6), 711-719. https://doi.org/10.1016/j.bjps.2011.11.053

Bodlund 1996

Bodlund, O., & Kullgren, G. (1996). Transsexualism--general outcome and prognostic factors: A five-year follow-up study of nineteen transsexuals in the process of changing sex. Arch Sex Behav, 25(3), 303-316. https://doi.org/10.1007/bf02438167

Boskey 2023

Boskey, E. R., Jolly, D., Kant, J. D., & Ganor, O. (2023). Prospective evaluation of psychosocial changes after chest reconstruction in transmasculine and non-binary youth. J Adolesc Health, 73(3), 503-509. https://doi.org/10.1016/j.jadohealth.2023.04.029

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Brik 2020

Brik, T., Vrouenraets, L. J. J. J., de Vries, M. C., & Hannema, S. E. (2020). Trajectories of adolescents treated with gonadotropin-releasing hormone analogues for gender dysphoria. Archives of Sexual Behavior, 49(7), 2611-2618. https://doi.org/10.1007/s10508-020-01660-8

Bungener 2020

Bungener, S. L., de Vries, A. L. C., Popma, A., & Steensma, T. D. (2020). Sexual experiences of young transgender persons during and after gender-affirmative treatment. Pediatrics, 146(6). https://doi.org/10.1542/peds.2019-1411

Burke 2016

Burke, S. M., Kreukels, B. P., Cohen-Kettenis, P. T., Veltman, D. J., Klink, D. T., & Bakker, J. (2016). Male-typical visuospatial functioning in gynephilic girls with gender dysphoria - organizational and activational effects of testosterone. J Psychiatry Neurosci, 41(6), 395-404. https://doi.org/10.1503/jpn.150147

Burke 2020

Burke, S. M., van Heesewijk, J. O., Menks, W. M., Klink, D. T., Kreukels, B. P. C., Cohen-Kettenis, P. T., . . . Bakker, J. (2020). Postnatal effects of sex hormones on click-evoked otoacoustic emissions: A study of adolescents with gender dysphoria. Arch Sex Behav, 49(2), 455-465. https://doi.org/10.1007/s10508-020-01652-8

Bustos 2020

Bustos, S. S., Forte, A. J., Ciudad, P., & Manrique, O. J. (2020). The nipple split sharing vs. Conventional nipple graft technique in chest wall masculinization surgery: Can we improve patient satisfaction and aesthetic outcomes? Aesthetic Plast Surg, 44(5), 1478-1486. https://doi.org/10.1007/s00266-020-01803-1

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Caanen 2017

Caanen, M. R., Schouten, N. E., Kuijper, E. A. M., van Rijswijk, J., van den Berg, M. H., van Dulmen-den Broeder, E., . . . Lambalk, C. B. (2017). Effects of long-term exogenous testosterone administration on ovarian morphology, determined by transvaginal (3d) ultrasound in female-to-male transsexuals. Hum Reprod, 32(7), 1457-1464. https://doi.org/10.1093/humrep/dex098

Campbell 2023

Campbell, T., Mann, S., Nguyen, D. H., & Rodgers, Y. v. d. M. (2023). Hormone therapy, suicidal risk, and transgender youth in the united states. AEA Papers and Proceedings, 113, 551–555. https://doi.org/10.1257/pandp.20231057

Cantu 2020

Cantu, A. L., Moyer, D. N., Connelly, K. J., & Holley, A. L. (2020). Changes in anxiety and depression from intake to first follow-up among transgender youth in a pediatric endocrinology clinic. Transgend Health, 5(3), 196-200. https://doi.org/10.1089/trgh.2019.0077

Carmichael 2021

Carmichael, P., Butler, G., Masic, U., Cole, T. J., De Stavola, B. L., Davidson, S., . . . Viner, R. M. (2021). Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. PLoS ONE, 16(2), e0243894. https://doi.org/10.1371/journal.pone.0243894

Caro 2024

Caro, C., Florek, A., Hahn, M., & Marx, M. (2024). Color doppler sonography assisted subcutaneous mastectomy with inferior pedicled nipple-areola complex in female-to-male transsexuals: A retrospective cohort analysis. Aesthetic Plast Surg, 48(6), 1126-1132. https://doi.org/10.1007/s00266-022-02945-0

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Chen 2016

Chen, M., Fuqua, J., & Eugster, E. A. (2016). Characteristics of referrals for gender dysphoria over a 13-year period. J Adolesc Health, 58(3), 369-371. https://doi.org/10.1016/j.jadohealth.2015.11.010

Chen 2023

Chen, D., Berona, J., Chan, Y. M., Ehrensaft, D., Garofalo, R., Hidalgo, M. A., . . . Olson-Kennedy, J. (2023). Psychosocial functioning in transgender youth after 2 years of hormones. N Engl J Med, 388(3), 240-250. https://doi.org/10.1056/NEJMoa2206297

Chiniara 2018

Chiniara, L. N., Bonifacio, H. J., & Palmert, M. R. (2018). Characteristics of adolescents referred to a gender clinic: Are youth seen now different from those in initial reports? Horm Res Paediatr, 89(6), 434-441. https://doi.org/10.1159/000489608

Cohen-Kettenis 1997 (three citations)

- Cohen-Kettenis, P. T., & van Goozen, S. H. (1997). Sex reassignment of adolescent transsexuals: A follow-up study. J Am Acad Child Adolesc Psychiatry, 36(2), 263-271.
- Smith, Y. L., Cohen, L., & Cohen-Kettenis, P. T. (2002). Postoperative psychological functioning of adolescent transsexuals: a Rorschach study. *Archives of sexual behavior*, *31*(3), 255–261.
- Smith, Y. L., van Goozen, S. H., & Cohen-Kettenis, P. T. (2001). Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *Journal of the American Academy of Child and Adolescent Psychiatry*, *40*(4), 472–481.

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Cohen-Kettenis 2011 (two citations)

- Cohen-Kettenis, P. T., Schagen, S. E. E., Steensma, T. D., de Vries, A. L. C., & Delemarre-van de Waal, H. A. (2011). Puberty suppression in a gender-dysphoric adolescent: A 22-year follow-up. Archives of Sexual Behavior, 40(4), 843-847.
- Cohen-Kettenis, P. T., & van Goozen, S. H. (1998). Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent. *European child & adolescent psychiatry*, *7*(4), 246–248.

Costa 2015

Costa, R., Dunsford, M., Skagerberg, E., Holt, V., Carmichael, P., & Colizzi, M. (2015). Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. J Sex Med, 12(11), 2206-2214. https://doi.org/10.1111/jsm.13034

Cuccolo 2019

Cuccolo, N. G., Kang, C. O., Boskey, E. R., Ibrahim, A. M. S., Blankensteijn, L. L., Taghinia, A., . . . Ganor, O. (2019). Mastectomy in transgender and cisgender patients: A comparative analysis of epidemiology and postoperative outcomes. Plast Reconstr Surg Glob Open, 7(6), e2316. https://doi.org/10.1097/gox.0000000000002316

de Nie 2022

de Nie, I., Mulder, C. L., Meißner, A., Schut, Y., Holleman, E. M., van der Sluis, W. B., . . . van Mello, N. M. (2022). Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. Hum Reprod, 37(2), 297-308. https://doi.org/10.1093/humrep/deab240

de Vries 2011

de Vries, A. L., Steensma, T. D., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2011). Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. J Sex Med, 8(8), 2276-2283. https://doi.org/10.1111/j.1743-6109.2010.01943.x

de Vries 2014

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de Vries, A. L., McGuire, J. K., Steensma, T. D., Wagenaar, E. C., Doreleijers, T. A., & Cohen-Kettenis, P. T. (2014). Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics, 134(4), 696-704. https://doi.org/10.1542/peds.2013-2958

Delemarre-van de Waal 2006

Delemarre-van de Waal, H. A., & Cohen-Kettenis, P. T. (2006). Clinical management of gender identity disorder in adolescents: A protocol on psychological and paediatric endocrinology aspectsthis paper was presented at the 4th ferring pharmaceuticals international paediatric endocrinology symposium, paris (2006). Ferring pharmaceuticals has supported the publication of these proceedings. European Journal of Endocrinology, 155(Supplement_1), S131-S137. https://doi.org/10.1530/eje.1.02231

Donaldson 2018

Donaldson, A. A., Hall, A., Neukirch, J., Kasper, V., Simones, S., Gagnon, S., . . . Forcier, M. (2018). Multidisciplinary care considerations for gender nonconforming adolescents with eating disorders: A case series. Int J Eat Disord, 51(5), 475-479. https://doi.org/10.1002/eat.22868

Donato 2017

Donato, D. P., Walzer, N. K., Rivera, A., Wright, L., & Agarwal, C. A. (2017). Female-to-male chest reconstruction: A review of technique and outcomes. Ann Plast Surg, 79(3), 259-263. https://doi.org/10.1097/sap.0000000000001099

Ederer 2023

Ederer, I. A., Spennato, S., Nguyen, C. T., Wehle, A., Wachtel, C., Kiehlmann, M., . . . Rieger, U. M. (2023). A single-center 10-year experience of 180 transmasculine patients undergoing gender-affirming mastectomy while continuing masculinizing hormone replacement therapy. Aesthetic Plast Surg, 47(3), 946-954. https://doi.org/10.1007/s00266-022-03213-x

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KS-AG-26-1037-A-000556

Elfering 2020

Elfering, L., van de Grift, T. C., Bouman, M. B., van Mello, N. M., Groenman, F. A., Huirne, J. A., . . . Mullender, M. G. (2020). Combining total laparoscopic hysterectomy and bilateral salpingo-oophorectomy with subcutaneous mastectomy in trans men: The effect on safety outcomes. International Journal of Transgender Health, 21(2), 138-146. https://doi.org/10.1080/26895269.2020.1751014

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Errata to *Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices*

Numerous minor editorial corrections have been made to the originally published version on May 1, 2025 to improve clarity, consistency, and formatting. These include typographical fixes, minor grammatical adjustments, missing bibliography items, and refinements to citations.

The following errata list notes the substantive corrections—that is, changes involving factual clarification, citation accuracy, or correction of misleading or incorrect statements. Page and footnote numbers refer to the current Review document and Appendix 4.

- Appendix 4, Section 1, Figure 1.1 (p. 8): The number of excluded studies was corrected from 3,200 to 3,198. This correction was also made in Section 5.1, Figure 5.1., of the main document.
- Section 4.2.1 (p. 63): The phrase: “recommended that PBs be offered only within a research context until further data are available” was replaced with: “recommended that PBs be offered only as part of a clinical trial until further data are available, and that all potential interventions should be tested within a research context.”
- Section 5.3 (p. 86): The term “irreversible” was corrected to “reversible.”
- Section 6.2.2 (p. 99): “Tordoff et al., 2023” in the section heading was corrected to 2022.
- Section 7.3.5, Footnote 47 (p. 114): The incorrect citation to Shrier (2020) was corrected to Shrier (2021b).
- Section 10.5, Footnote 133 (p. 177): The incorrect amicus curiae brief citation was corrected to Clinical Practice Guideline Experts (2024).
- Section 11.4, Footnote 58 (p. 193): The quotation was previously attributed in part to another source; attribution was corrected to show the entire quotation is from McNamara (2024).

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- Section 12.1 (p. 203): A sentence was corrected to indicate that *Gender-Affirming Psychiatric Care* is a textbook published by the American Psychiatric Association, not a clinical practice guideline.
- Section 12.1 (p. 203): The sentence “Instead, the APA reaffirmed its commitment to existing recommendations without addressing the critiques” and its associated footnote were deleted. The originally-referenced policy was issued by the American Psychological Association, not the American Psychiatric Association.
- Section 14.4, Footnotes 51 and 52 (p. 247): The national origin of treatment recommendations was corrected; the U.K.’s recommendations had been mislabeled as Finland’s, and vice versa.

May 15, 2025

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From: Dalton, Charles
To: Jorgensen, Susan
Subject: FW: Letter to Health Care Providers on HHS Gender Dysphoria Report
Date: Thursday, May 29, 2025 4:22:45 PM
Attachments: 5.28.25 Letter to Health Providers re Literature Review FINAL.pdf
Treatment for Pediatric Gender Dysphoria Review of Evidence and Best Practices.pdf

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From: Stevens, Lee (OS/IEA) <Lee.Stevens@hhs.gov>
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Dear State Partners,

Attached please find a letter from Secretary Robert F. Kennedy, Jr. and literature review of evidence and best practices associated with Treatment for Pediatric Gender Dysphoria. The Review documents the weak evidence and growing international retreat from the use of puberty blockers, cross-sex hormones, and surgeries to treat gender dysphoria in minors.

We appreciate your attention to this important information. Please do not hesitate to contact the Office of Intergovernmental and External Affairs if you have questions.

Darcie Johnston, Director

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Office of Intergovernmental and External Affairs
US Department of Health and Human Services
Washington, D.C.

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Darcie Johnston, Director

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Office of Intergovernmental and External Affairs
US Department of Health and Human Services
Washington, D.C.

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THE SECRETARY OF HEALTH AND HUMAN SERVICES

WASHINGTON, D.C. 20201

May 28, 2025

VIA ELECTRONIC MAIL

Dear Health Care Providers, Health Care Risk Managers, and State Medical Boards:

This letter advises you to read with care "Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices" (the Review) published by the U.S. Department of Health and Human Services (HHS) on May 1, 2025. The Review documents the "weak evidence and growing international retreat" (p. 205) from the use of puberty blockers, cross-sex hormones, and surgeries to treat gender dysphoria in minors and the "risk of significant harm" (p. 10). The Review explains that "many treatments (e.g., surgery, hormone therapy) can lead to relatively common and potentially serious long-term adverse effects" (p. 221). Given your "obligation to avoid serious harm" (p. 221) and the findings of the Review, HHS expects you promptly to make the necessary updates to your treatment protocols and training for care for children and adolescents with gender dysphoria to protect them from these harmful interventions.

The Review includes a methodologically rigorous assessment of evidence underpinning the use of surgical or endocrine interventions, including puberty blockers and cross-sex hormones, within the so-called "gender-affirming" model of care, while also drawing on international practice evaluations such as the U.K.'s Cass Review (April 2024). The Review documents serious concerns regarding the lack of reliable evidence of benefits and risks of significant harms for this model of care that have mounted in recent years, and points to psychotherapy (talk therapy) as a noninvasive alternative. As Sweden's national health authority has recommended, "[p]sychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures" (p. 247).

Providers should avoid relying on the World Professional Association for Transgender Health's (WPATH) *Standards of Care for the Health of Transgender and Gender Diverse People,* Version 8 (SOC-8). As the Review documents in detail, the creation of SOC-8 was fraudulent and marked "a clear departure from the principles of unbiased, evidence-driven clinical guideline development" (p. 172). To wit, in the context of developing its recommendations, WPATH suppressed systematic reviews of evidence, failed to manage conflicts of interest, and relied on legal and political considerations rather than clinical ones (p. 173). Health care risk managers should take note that a recent systematic review of international guideline quality did not recommend either the WPATH or the Endocrine Society guidelines for clinical use after determining they "lack developmental rigour and transparency" (p. 14). These and other guidelines based on the so-called "gender-affirming" model of care should not be relied upon to harm children any further (pg. 141).

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In contrast to WPATH SOC-8, the Review employs the tools of evidence-based medicine, widely recognized by health authorities worldwide as the foundation of high-quality care, and assesses the evidence underpinning the use of hormones and surgeries for minors. Specifically, it includes an "umbrella review," an overview of systematic reviews, which "found that the overall quality of evidence concerning the effects of these interventions on psychological outcomes, quality of life, regret, or long-term health, is very low" (p. 13). The Review also notes, based on what is known about human physiology and the effects and mechanisms of the pharmacological agents used, that there are risks of significant harms associated with the uses of puberty blockers, cross-sex hormones, and surgeries, including "infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret" (p. 10).

The Hippocratic Oath lays down the foundational commitment for the medical profession: "First, do no harm." The Review makes clear that "the evidence for benefit of pediatric medical transition is very uncertain, while the evidence for harm is less uncertain" (p. 15). For this reason, the Review states that when "medical interventions pose unnecessary, disproportionate risks of harm, healthcare providers should refuse to offer them even when they are preferred, requested, or demanded by patients" (ibid.).

The findings of the Review align with those of European countries, such as Sweden, Finland, and England, which have "sharply restricted" access to these interventions for minors following systematic reviews of evidence commissioned by their public health authorities, concluding that the risks outweighed the benefits (p. 246).

Health care providers are reminded, as the Centers for Medicare and Medicaid Services wrote in a Quality & Safety Special Alert memo on March 5, 2025, that "it is of utmost importance that all providers follow the highest standards of care and adhere closely to the foundational principles of medicine, especially as it comes to America's children." To this end, HHS published guidance on April 14, 2025, to protect whistleblowers who make reports concerning these harmful interventions for minors, including for waste, fraud, and abuse in HHS-funded programs, and created a portal to receive complaints at www.hhs.gov/protect-kids. HHS is committed to protecting whistleblowers to the full extent of the law. HHS may soon undertake new policies and oversight actions, consistent with applicable law, to ensure the protection of children, and to hold providers that harm children accountable.

Again, I urge you to read the Review and expect you to update your treatment protocols and training to ensure that our nation's children are protected from harm.

Sincerely,

/s/

Robert F. Kennedy, Jr.

Attachment: "Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices," U.S. Department of Health and Human Services, May 1, 2025, https://opa.hhs.gov/gender-dysphoria-report

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Treatment for Pediatric Gender Dysphoria

Review of Evidence and Best Practices



Department of Health and Human Services

May 1, 2025

KS-AG-26-1037-A-000600

Minor corrections made May 15, 2025: see Errata

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Foreword

Over the past decade, the number of children and adolescents who question their sex and identify as transgender or nonbinary has grown significantly. Many have been diagnosed with a condition known as “gender dysphoria” and offered a treatment approach known as “gender-affirming care.” This approach emphasizes social affirmation of a child’s self-reported identity; puberty suppressing drugs to prevent the onset of puberty; cross-sex hormones to spur the secondary sex characteristics of the opposite sex; and surgeries including mastectomy and (in rare cases) vaginoplasty. Thousands of American children and adolescents have received these interventions.

While sex-role nonconformity itself is not pathological and does not require treatment, the use of pharmacological and surgical interventions as treatments for pediatric gender dysphoria has been called “medically necessary” and even “lifesaving.” Motivated by a desire to ensure their children’s health and well-being, parents of transgender-identified children and adolescents often struggle with how best to support them. Many of these children and adolescents have co-occurring psychiatric or neurodevelopmental conditions, rendering them especially vulnerable. When they seek professional help, they and their families should receive compassionate, evidence-based care tailored to their specific needs.

Society has a special responsibility to safeguard the well-being of children. Given that the challenges faced by these patients intersect with deeply contested issues of moral and social significance—including social identity, sex and reproduction, bodily integrity, and sex-based norms of expression and behavior—the medical practices that have recently emerged to address their needs have become a focus of significant controversy.

This Review is published against the backdrop of growing international concern about pediatric medical transition. Having recognized the experimental nature of these medical interventions and their potential for harm, health authorities in a number of countries have imposed restrictions. For example, the U.K. has banned the routine use of puberty blockers as an intervention for pediatric gender dysphoria.

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Health authorities have also recognized the exceptional nature of this area of medicine. That exceptionalism is due to a convergence of factors. One is that the diagnosis of gender dysphoria is based entirely on subjective self-reports and behavioral observations, without any objective physical, imaging, or laboratory markers. The diagnosis centers on attitudes, feelings, and behaviors that are known to fluctuate during adolescence.

Additionally, the natural history of pediatric gender dysphoria is poorly understood, though existing research suggests it will remit without intervention in most cases. Medical professionals have no way to know which patients may continue to experience gender dysphoria and which will come to terms with their bodies.

Nevertheless, the "gender-affirming" model of care includes irreversible endocrine and surgical interventions on minors with no physical pathology. These interventions carry risk of significant harms including infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret. Meanwhile, systematic reviews of the evidence have revealed deep uncertainty about the purported benefits of these interventions.

The controversies surrounding the medical transition of minors extend beyond scientific debate; they are deeply cultural and political. Public discourse is dominated by intensely polarizing narratives. Some view the medical transition of minors as a pressing civil rights issue, while others regard it as a profound medical failure and a sobering reminder that even modern medicine is vulnerable to serious error. In the midst of this highly charged debate, children and adolescents, and their families—who seek only to support their flourishing—have found themselves caught between competing perspectives. They require, and are entitled to, accurate, evidence-based information to guide their decisions.

This Review of evidence and best practices was commissioned pursuant to Executive Order 14187, signed on January 28, 2025. It is not a clinical practice guideline, and it does not issue legislative or policy recommendations. Rather, it seeks to provide the most accurate and current information available regarding the evidence base for the

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treatment of gender dysphoria in this population, the state of the relevant medical field in the United States, and the ethical considerations associated with the treatments offered.

The Review is intended for policymakers, clinicians, therapists, medical organizations and, importantly, patients and their families. It summarizes, synthesizes, and critically evaluates the existing literature on best practices for promoting the health and well-being of children and adolescents with distress related to their sex or to social expectations associated with their sex. Treatment of adults constitutes a separate topic and is not addressed in this Review. A summary of the Review's main findings is presented below.

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Executive Summary

Part I: Background

- Gender dysphoria is a condition that involves distress regarding one's sexed body and/or associated social expectations. Increasing numbers of children and adolescents in the U.S. and other countries are diagnosed with gender dysphoria. Internationally, there is intense disagreement about how best to help them.
- The term "rapid onset gender dysphoria" (ROGD) has been suggested to describe a new clinical presentation of gender dysphoria. Despite sharp disagreement about the concept's validity, symptoms consistent with ROGD have been recorded in clinics in the U.S. and other countries.
- In the U.S., the current approach to treating pediatric gender dysphoria aligns with the "gender-affirming" model of care recommended by the World Professional Association for Transgender Health (WPATH). This model emphasizes the use of puberty blockers and cross-sex hormones, as well as surgeries, and casts suspicion on psychotherapeutic approaches for management of gender dysphoria.
- The understandable desire to avoid language that may cause discomfort to patients has, in some cases, given rise to modes of communication that lack scientific grounding, that presuppose answers to unresolved ethical controversies, and that risk misleading patients and families. This Review uses scientifically accurate and neutral terminology throughout.
- In many areas of medicine, treatments are first established as safe and effective in adults before being extended to pediatric populations. In this case, however, the opposite occurred: clinician-researchers developed the pediatric medical transition protocol in response to disappointing psychosocial outcomes in adults who underwent medical transition.
- The protocols were adopted internationally before the publication of the first outcome studies. In recent years, in response to dramatic shifts in the number

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and clinical profiles of minor patients, as well as to multiple systematic reviews of evidence, health authorities in an increasing number of countries have restricted access to puberty blockers and cross-sex hormones, and, in the rare cases where they were offered, surgeries for minors. These authorities now recommend psychosocial approaches, rather than hormonal or surgical interventions, as the primary treatment.

- There is currently no international consensus about best practices for the care of children and adolescents with gender dysphoria.

Part II: Evidence Review

- Evidence-based medicine is widely recognized by health authorities worldwide as the foundation of high-quality care. Consistent with its principles, this Review undertook a methodologically rigorous assessment of the evidence underpinning pediatric gender medicine.
- Specifically, this Review conducted an overview of systematic reviews—also known as an "umbrella review"—to evaluate the direct evidence regarding the benefits and harms of treatment for children and adolescents with gender dysphoria. Existing systematic reviews of evidence, including several that have informed health authorities in Europe, were assessed for methodological quality. The umbrella review found that the overall quality of evidence concerning the effects of any intervention on psychological outcomes, quality of life, regret, or long-term health, is very low. This indicates that the beneficial effects reported in the literature are likely to differ substantially from the true effects of the interventions.
- Evidence for harms associated with pediatric medical transition in systematic reviews is also sparse, but this finding should be interpreted with caution. Inadequate harm detection in pediatric gender medicine may reflect the relatively short period of time since the widespread adoption of the medical/surgical treatment model; the failure of existing studies to systematically track and report harms; and publication bias. Despite the lack of robust evidence from population level studies, important insights can be drawn from established knowledge about

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human physiology and the effects and mechanisms of the pharmacological agents used.

- The risks of pediatric medical transition include infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret.

Part III: Clinical Realities

- In the U.S., the most influential clinical guidelines for the treatment of pediatric gender dysphoria are published by WPATH and the Endocrine Society. A recent systematic review of international guideline quality did not recommend either guideline for clinical use after determining they "lack developmental rigour and transparency."[1]
- Problems with the development of WPATH's *Standards of Care*, Version 8 (SOC-8) extend beyond those identified in the systematic review of international guidelines. In the process of developing SOC-8, WPATH suppressed systematic reviews its leaders believed would undermine its favored treatment approach. SOC-8 developers also violated conflict of interest management requirements and eliminated nearly all recommended age minimums for medical and surgical interventions in response to political pressures.
- Although SOC-8 relaxed the eligibility criteria for access to puberty blockers, cross-sex hormones, and surgeries, there is compelling evidence that U.S. gender clinics are not adhering even to those more permissive criteria.
- The "gender-affirming" model of care, as practiced in U.S. clinics, is characterized by a child-led process in which comprehensive mental health assessments are often minimized or omitted, and the patient's "embodiment goals" serve as the primary guide for treatment decisions. In some of the nation's

[1] Taylor, Hall, Heathcote et al. (2024a, p. 7).

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leading pediatric gender clinics, assessments are conducted in a single session lasting two hours.

- The voices of whistleblowers and detransitioners have played a critical role in drawing public attention to the risks and harms associated with pediatric medical transition. Their concerns have been discounted, dismissed, or ignored by prominent advocates and practitioners of pediatric medical transition.
- U.S. medical associations played a key role in creating a perception that there is professional consensus in support of pediatric medical transition. This apparent consensus, however, is driven primarily by a small number of specialized committees, influenced by WPATH. It is not clear that the official views of these associations are shared by the wider medical community, or even by most of their members. There is evidence that some medical and mental health associations have suppressed dissent and stifled debate about this issue among their members.

Part IV: Ethical Considerations

- The principle of autonomy in medicine establishes a moral and legal right of competent patients to refuse any medical intervention. However, there is no corollary right to receive interventions that are not beneficial. Respect for patient autonomy does not negate clinicians' professional and ethical obligation to protect and promote their patients' health.
- The evidence for benefit of pediatric medical transition is very uncertain, while the evidence for harm is less uncertain. When medical interventions pose unnecessary, disproportionate risks of harm, healthcare providers should refuse to offer them even when they are preferred, requested, or demanded by patients. Failure to do so increases the risk of iatrogenic harm and reduces medicine to consumerism, threatening the integrity of the profession and undermining trust in medical authority.
- Proponents of pediatric medical transition claim that regret is vanishingly rare, while critics assert that regret is increasingly common. The true rate of regret is

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not known and better data collection is needed. That some patients report profound regret after undergoing invasive, life-changing medical interventions is clearly of importance. However, regret alone (just like satisfaction alone) is not a valid indicator of whether an intervention is medically justified. Patients may regret medically justified treatments or feel satisfied with unjustified ones.

- A natural response to the absence of credible evidence is to call for more and better research. Even if high quality research such as randomized controlled trials on pubertal suppression or hormone therapy were feasible, however, conducting it may conflict with well-established ethical standards for human subjects research.

Part V: Psychotherapy

- The rise in youth gender dysphoria and the corresponding demand for medical interventions have occurred against the backdrop of a broader mental health crisis affecting adolescents. The relationship between these two phenomena remains a subject of scientific controversy.
- Suicidal ideation and behavior are independently associated with comorbidities common among children and adolescents diagnosed with gender dysphoria. Suicidal ideation and behavior have known psychotherapeutic management strategies. No independent association between gender dysphoria and suicidality has been found, and there is no evidence that pediatric medical transition reduces the incidence of suicide, which remains, fortunately, very low.
- There is a dearth of research on psychotherapeutic approaches to managing gender dysphoria in children and adolescents. This is due in part to the mischaracterization of such approaches as “conversion therapy.” A more robust evidence base supports psychotherapeutic approaches to managing common comorbid mental health conditions. Psychotherapy is a noninvasive alternative to endocrine and surgical interventions for the treatment of pediatric gender dysphoria. Systematic reviews of evidence have found no evidence of adverse effects of psychotherapy in this context.

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PART 1

BACKGROUND

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Chapter 1 Introduction

Currently, an estimated 3.3% of adolescents in the United States identify as transgender, and an additional 2.2% question whether they might be.[1] Many have received hormonal or surgical treatment for accompanying distress. A 2023 study published in the *Journal of the American Medical Association* found that between 2016 and 2020, 3,215 patients between the ages of 12 and 18 received surgical "breast or chest procedures" relating to their transgender identity.[2] A more recent study reported that approximately 0.1% of American 17-year-olds, or one in 1,000, was receiving cross-sex hormones between 2018 and 2022.[3] A national estimate of clinics offering pediatric medical transition interventions found at least 271 such institutions in the U.S. as of March 2023.[4]

This Review assesses the existing literature on best practices for promoting the health of children and adolescents with gender dysphoria (GD; serious distress at one's sexed body and associated social expectations[5]) or milder forms of such distress. Treatment of GD in adults is a separate topic and is not covered here.

In the United States, a number of institutions follow the guidelines of the World Professional Association for Transgender Health (WPATH) and the Endocrine Society (ES) for treating gender-dysphoric children and adolescents. This approach is usually called "gender-affirming care." Diane Ehrensaft, Director of Mental Health at UCSF's Child & Adolescent Gender Center, is a leading proponent. As Ehrensaft explains,

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[1] Suarez et al. (2024, Table 2).
[2] Wright et al. (2023).
[3] Hughes et al. (2025).
[4] Borah et al. (2023, p. 375-376). Some of these clinics were closed due to state age restriction laws.
[5] As an American Psychological Association report put it, quoting the American Psychiatric Association, gender dysphoria is an "aversion to some or all of those physical characteristics or social roles that connote one's own biological sex" (Schneider et al., 2009, p. 28). As explained in Zucker et al. (2016), "gender dysphoria" is a "technical term" that refers to symptoms of distress, but is also, as of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (2013), a "diagnostic term" (p. 218). Gender Dysphoria is a formal diagnosis in the current (text revision) version of the DSM-5, the DSM-5-TR (American Psychiatric Association, 2022). For the relevant diagnostic criteria for children, adolescents, and adults in the DSM-III, IV, and 5, and in the current *International Classification of Diseases* (ICD-11), see Appendix 2 of this Review. The term "gender dysphoria" is used throughout this Review to refer to sex-related distress or discomfort, unless the context makes clear that the formal diagnosis is the topic.

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> [gender-affirming care] is defined as a method of therapeutic care that includes allowing children to speak for themselves about their self-experienced gender identity and expressions and providing support for them to evolve into their authentic gender selves, no matter at what age. Interventions include social transition from one gender to another and/or evolving gender nonconforming expressions and presentations, as well as later gender-affirming medical interventions (puberty blockers, cross-sex hormones, surgeries).[6]

This Review is needed because—as later chapters will detail—the emphasis on medicalization makes the field of pediatric gender medicine (PGM) highly controversial. WPATH and ES guidelines recommend commencement of puberty blockers (drugs that halt pubertal development) at the earliest signs of puberty (i.e. Tanner Stage 2), which may begin as early as age 8 in girls and 9 in boys. According to these guidelines,[7] cross-sex hormones (CSH; estrogen for boys and testosterone for girls) are started sometime thereafter; surgeries (e.g., breast removal for girls) are also recommended for some adolescents.[8] All these interventions are associated with significant risks, and most cause irreversible physical or physiological effects.[9]

Do PBs, CSH, and surgeries constitute best practice for this population? Guidelines and policies promulgated by professional medical societies in the U.S. differ from some European guidelines that recommend psychotherapy, *not* hormones or surgeries, for children and adolescents with GD. This Review, then, is written against a backdrop of intense disagreement in the international medical community. The number of young people with GD has surged, and many are suffering, as are their families. The question of how to best help these patients hinges on a comprehensive assessment of the evidence base for different treatment approaches, together with ethical considerations. Bringing ethical principles to bear on the evidence is one goal of this Review. While the need for respect and compassion resonates with all reasonable Americans, an invasive

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[6] Ehrensaft (2017a, p. 62). The gender-affirming approach can be applied to adults too; this Review is entirely focused on the pediatric variety.
[7] Coleman et al. (2022); Hembree et al. (2017).
[8] The latest version of WPATH's clinical practice guideline has no recommended age limits for surgical procedures, with the exception of 18 years old for phalloplasty (the construction of a neophallus in females with skin taken from the patient's arm or leg).
[9] See Chapter 7.

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treatment with lifelong ramifications deserves the highest level of dispassionate scrutiny.[10]

The diagnostic description of GD has changed since the condition appeared in the third edition (1980) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), as has the terminology used to name it. But one thing has not changed. The DSM-III was clear that "Gender Identity Disorder of Childhood" was "not merely the rejection of stereotypical sex role behavior as, for example, in 'tomboyishness' in girls or 'sissyish' behavior in boys"[11]; the current DSM has a similar emphasis: "The diagnosis is not meant to merely describe nonconformity to stereotypical gender role behavior (e.g., "tomboyism" in girls, "girly-boy" behavior in boys, occasional cross-dressing in adult men)."[12] Non-conformity to sex-role stereotypes is as old as history, and present to some degree in every known culture.[13] This feature of the human experience is not pathological and needs no treatment. What may require treatment is the suffering experienced by those alienated from their sexed bodies.

PGM is a complex topic. This Review, therefore, will cover the field's history and evolution in some detail, from the inception of the medicalized approach in the Netherlands (Chapter 3)[14] to current treatment practices in the U.S. and other countries (Chapter 4, Chapter 9). The Review describes an international trend of retreat from the present "gender affirming" approach and reviews the reasons underlying it.

This Review finds that clinical practice in this field of medicine is exceptional and concerning (Chapter 11). The influential PGM guidelines followed in the U.S. are especially problematic. They were developed in ways that contravene best practices for

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[10] The U.K.'s Cass Review pointed out that although some conceptualize controversies about pediatric gender medicine primarily from political/social standpoints, healthcare guidance should "[work] in an evidence-based way" (Cass, 2024a, p. 20).
[11] American Psychiatric Association (1980, p. 264).
[12] American Psychiatric Association (2013, p. 458).
[13] See Chapter 3, Note 1.
[14] The general treatment paradigm of puberty blockers, cross-sex hormones, and surgeries originated in the Netherlands in the 1990s as an experimental research protocol, and, based on one small study that claimed to demonstrate significant benefits to mental health, was rapidly incorporated internationally into standard practice. As described in the Cass Review's interim report, the "affirmative model" is a "model of gender healthcare that originated in the USA which affirms a young person's subjective gender experience while remaining open to fluidity … This approach is used in some key child and adolescent clinics across the Western world" (Cass, 2022a, p. 78).

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guideline development (Chapter 9, Chapter 10). This Review also finds evidence of extreme toxicity and polarization surrounding this field of medicine. ("There are few other areas of healthcare where professionals are so afraid to openly discuss their views … where name-calling echoes the worst bullying behaviour."[15]) Additionally, this Review describes the inadequate response of professional medical and mental health associations to new evidence and controversies (Chapter 12).

Section 1.1 of this opening chapter emphasizes the exceptional nature of PGM. Section 1.2 outlines the role that evidence-based medicine (EBM) plays in the Review; Section 1.3 does the same for medical ethics.

1.1 Exceptionalism

The field of PGM is exceptional due to the convergence of several distinct features.

First, the *diagnostic criteria* for GD are based solely on subjective reports and behavioral observations in patients with no objective physical pathology; there are no verifiable physiological or biochemical markers–such as abnormal imaging, lab, or clinical findings–to confirm the GD diagnosis.[16]

Second, the condition's *natural course* (also known as "natural history")—i.e., what happens when the condition remains untreated—appears to tend toward resolution absent medical and/or social transition interventions for a significant number of affected youths (see Chapter 4). While the condition will persist in some affected adolescents into adulthood, the Cass Review, commissioned by England's National Health Service (NHS), found that while "a diagnosis of gender dysphoria has been the basis for initiating medical treatment … this is not predictive that the individual will go on to have longstanding trans identity."[17]

Third, the treatments recommended by the medicalized approach are invasive, usually irreversible, and their purported benefits are based on poor quality evidence. In addition

[15] Cass (2024a, p. 13).
[16] Laidlaw et al. (2019). The same goes for the ICD's diagnosis of "gender incongruence": for discussion, see Section 13.4.
[17] Cass (2024a, p. 146).

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to infertility and impairment of sexual function, the anticipated harms include adverse effects on bone health, cardiovascular function, and possible negative impacts on brain development (see Chapter 7).

When taken separately, *none* of these features is unique in medicine. Nearly all mental health and some physical health diagnoses are made on the basis of self-reports and behavioral observations. Also, there are other pediatric conditions such as mild ear infections and strep throat that are self-limiting but still treated to reduce discomfort, promote faster recovery, or prevent complications. Lastly, there are instances in which patients are offered treatments even if the benefits of those treatments are profoundly uncertain and harms are expected. For example, craniotomies are performed to remove certain malignant brain tumors, even though these interventions carry a high risk of permanent adverse effects and the overall prognosis remains poor even with treatment. (In such cases, however, the alternative to intervention is a significantly shorter life expectancy.) What makes PGM exceptional is not any one of these features, but their combination.

Is the fundamental goal of treatment to manage gender dysphoria, a condition recognized in the DSM's catalogue of mental disorders? Or is it to manage common comorbidities such as depression, anxiety, and suicidal ideation? Or, alternatively, is it to help individuals realize their "embodiment goals" (i.e., cosmetic desires)? The stated rationales for these interventions have shifted over time, following decades of research that failed to provide credible evidence of benefit (see Chapter 5). This unclarity surrounding the treatments' fundamental aims is yet another way in which PGM is exceptional. In contrast, there is broad consensus about the purpose of medical intervention for conditions like appendicitis, diabetes, or severe depression.

1.2 Evidence

When assessing a medical intervention, one of the most important questions is: Is it safe and effective? Does drug X reduce all-cause mortality for cancer patients? Does talk therapy alleviate depression? Does knee surgery relieve arthritis pain with few postoperative complications? Even if the treatment is effective, it may not be safe, and there may be better alternatives.

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In the case of invasive treatments for GD, medical authorities in the United States have issued statements indicating that the matter is settled. According to the American Medical Association (AMA):

> Improving access to gender-affirming care is an important means of improving health outcomes for the transgender population. Receipt of gender-affirming care has been linked to dramatically reduced rates of suicide attempts, decreased rates of depression and anxiety, decreased substance use, improved HIV medication adherence and reduced rates of harmful self-prescribed hormone use.[18]

In 2022, the then Assistant Secretary for Health at the U.S. Department of Health and Human Services, Admiral Rachel Levine, gave an even more unqualified endorsement:

> Gender-affirming care is medical care. It is mental health care. It is suicide prevention care. It improves quality of life, and it saves lives. It is based on decades of study. It is a well-established medical practice.[19]

However, according to the U.K.'s April 2024 Cass Review, the most comprehensive assessment of PGM to date:

> This is an area of remarkably weak evidence, and yet results of studies are exaggerated or misrepresented by people on all sides of the debate to support their viewpoint. The reality is that we have no good evidence on the long-term outcomes of interventions to manage gender-related distress.[20]

Whether the approach endorsed by the AMA is based on adequate evidence is the subject of intense controversy. What is considerably less controversial is the best framework for assessing the efficacy of treatments. That framework is EBM, adopted by this Review.

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[18] American Medical Association (2022).
[19] Levine (2022).
[20] Cass (2024a, p. 13).

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1.2.1 Evidence-based medicine

The physician and researcher Gordon Guyatt—who coined the term "evidence-based medicine" in 1991—describes EBM as follows:

> Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature.[21]

EBM sees carefully controlled clinical trials as especially important, along with "systematic reviews" (SRs), methodical syntheses and evaluations of all relevant available evidence. Various "hierarchies of evidence" have been proposed, with SRs at the top and the opinions of individual clinicians, which, although usually valuable, are subject to a variety of biases, at the bottom. EBM has been widely accepted by health authorities around the world.[22]

In keeping with EBM principles, this Review is informed by a methodologically rigorous assessment of the evidence underpinning PGM. An overview of SRs was conducted, and its findings are presented in Chapter 5 and in Appendix 4. In brief, the overview independently confirms Cass's observation that "this is an area of remarkably weak evidence."

Given its emphasis on clinical trials, EBM is less sensitive to evidence about known mechanisms of drug action or relevant biology more broadly. This limits the ability of SRs to uncover potential causal pathways or to understand observed associations or their absence (Chapter 6). Accordingly, Chapter 7 supplements the overview of SRs with evidence from basic science, including physiology. As detailed in that chapter, the risk of harm from the medicalized approach to treating pediatric GD is serious.

[21] Guyatt et al. (1992, p. 2420). See also Akobeng (2005).
[22] E.g. Darzi (2008); Margolis (2018); Carande-Kulis (2022).

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It is important to recognize that evaluating the evidence for a treatment's efficacy does not, on its own, determine whether the treatment ought to be offered. SRs or other sources of high-quality evidence are not rigid formulas for making medical decisions; rather, they are essential components of the decision-making process. The principle is explicitly acknowledged in EBM. Medical evidence is not sufficient to justify clinical recommendations or decisions; other considerations—such as patient values and preferences—also play a critical role.[23] However, as emphasized below, these preferences do not override physicians' ethical and professional duties.

1.2.2 History lessons

An unreasonable skepticism toward medical expertise can lead to patient harm and even death.[24] On the other hand, while physicians are often capable of remarkable healing, they are not immune to human error or bias. However well-intentioned, doctors are not infallible. Even the consensus of professional medical associations can, at times, be mistaken.

Peanut allergies are a recent example. In 2000, the American Academy of Pediatrics (AAP) advised that infants deemed "high risk" should avoid peanuts—and that breastfeeding mothers do the same. In practice, this guidance was widely interpreted as a recommendation for all infants to avoid peanuts as a precaution. Peanut allergies increased dramatically, and in 2017 the AAP reversed course, recommending early *introduction* of peanuts for the highest-risk infants.[25]

This is just one of many examples.[26] Medical error is more prevalent than many Americans realize. Consensus does not guarantee correctness—in fact, it can sometimes entrench error. Nor should it be assumed that all treatment recommendations are motivated by altruism, as the opioid overprescription crisis has starkly demonstrated. This is not to suggest that medical consensus is inherently untrustworthy, but rather that it should be approached with critical scrutiny, not

[23] Djulbegovic & Guyatt (2017, p. 416); see also Guyatt et al. (2000).
[24] Centers for Disease Control (2025).
[25] Makary (2024, Chapter 1).
[26] Apart from Makary (cited above), see Prasad & Cifu (2019, Chapters 1, 2) and Patashnik et al. (2017, Chapter 2).

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unquestioning acceptance. The physicians and researchers Vinay Prasad and Adam Cifu succinctly make this point:

> We expect that medical therapy will change and evolve with time. Good treatments will replace bad ones, and then better ones will replace those. Antibiotics have replaced arsenic, and anesthesia has replaced a bullet held bracingly between the teeth. Recently, however, change has occurred in surprising ways. If you have followed the news about prostate cancer screening, mammography for women in their forties, hormone replacement, cholesterol-lowering medications, and stents for coronary-artery disease, you might think doctors cannot get anything straight. These common practices were not replaced by better therapies; they were found to be ineffective. In some cases, they did more harm than good. You might be worried that some medical practices are nothing more than fads. In some cases, you would be right.[27]

1.3 Ethics

Finding safe and effective treatments is only part of medicine's mission. Questions of ethics–and the complex theoretical issues they raise–emerge immediately alongside clinical decision-making. What if a treatment is effective but the patient doesn't want it? When is informed consent needed before starting treatment? Should doctors ever lie to their patients? What is the difference between cosmetic procedures and those that alleviate a medical problem? What should we do when clinicians disagree with pediatric patients or their parents about the best medical course of action? These and numerous similar questions are the topic of the academic field known as *medical ethics*.[28]

EBM is only decades old, but medical ethics is as old as medicine itself. The Hippocratic Oath, originating in the fourth century BCE, and attributed to the ancient Greek physician Hippocrates, is a pledge to uphold ethical principles in medicine. The Hippocratic writings include: "I will use treatment to help the sick according to my ability

[27] Prasad & Cifu (2019, p. 11).
[28] An alternative name is *biomedical ethics*. *Bioethics* is a broader field encompassing ethical issues in the life sciences beyond healthcare. Although medical ethics is an academic discipline, medical ethicists often work in clinics and hospitals, supporting patients and their families, and assisting clinicians in developing policies.

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and judgment, but I will never use it to injure or wrong them."[29] This commitment laid the foundation for the medical maxim *Primum non nocere*: First, do no harm.[30] Together with the duty of non-maleficence (avoiding harm), the duty of beneficence (promoting the patient's well-being) "undergirds all medical and health care professions and their institutional settings."[31] These duties have been continually affirmed by professional medical societies. For example, the World Medical Association's Declaration of Geneva, first published in 1948 and last revised in 2017, requires physicians to respect the "autonomy and dignity" of patients but recognizes the primacy of non-maleficence and beneficence: "The health and well-being of my patient will be my first consideration."[32]

Importantly, the physician's duties of non-maleficence and beneficence are not overridden by the patient's desire for a particular course of treatment. In 2002, the American Board of Internal Medicine Foundation, the American College of Physicians Foundation, and the European Federation of Internal Medicine articulated this point in a "Physician Charter." Among the three "fundamental principles" of the charter is the "Principle of patient autonomy," defined as follows:

> Physicians must have respect for patient autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients' decisions about their care must be paramount, *as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care*.[33]

One central question this Review attempts to answer is whether pediatric medical transition—and in particular the provision of hormonal or surgical interventions to children and adolescents—is consistent with widely-accepted principles of medical ethics. This is examined in Chapter 13. Another treatment approach—psychotherapy (talk therapy)—is examined in Chapter 14.

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[29] Beauchamp & Childress (2019, p. 155). Graduating medical students today recite a variety of oaths, sometimes composing them themselves (Weiner, 2018).
[30] The Latin phrase does not trace back to ancient times: it may have been devised by the seventeenth century English physician Thomas Sydenham (1624-1689), the "English Hippocrates" (Smith, 2005).
[31] Beauchamp & Childress (2019, p. 155).
[32] Parsa-Parsi (2017, p. 1971).
[33] American Board of Internal Medicine Foundation (2002, emphasis added).

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The innovation and responsiveness of the U.S. medical system has made it the envy of the world. However, errors are unavoidable in healthcare. The test of a medical system is not its ability to avoid mistakes, but rather how it responds once mistakes become apparent.

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Chapter 2 Terminology in Pediatric Gender Medicine

The choice of words can affect medical decision-making. Medical providers have a professional duty to apprise their patients of their conditions and the treatment options in language that is accurate, ethically neutral, and in no way misleading.[1] In the case of pediatric gender medicine (PGM), language has distorted the clinical picture, obscuring important distinctions. This chapter addresses that issue. Section 2.1 examines commonly used terminology, while Section 2.2 clarifies the specific terms adopted in this Review.

2.1 Terminology in pediatric gender medicine

Concerns about proper terminology and disclosure of all relevant information are common in medicine generally, particularly in the context of physician-patient interactions.[2] PGM, however, presents unique challenges. In this context, the understandable desire to avoid exclusionary or pathologizing language—combined with beliefs firmly embedded in the field—has led to a vocabulary and a mode of communicating that is scientifically ungrounded, that presupposes answers to ethical controversies, and that is in other ways misleading.[3]

Nearly all the core terms used in PGM exhibit these kinds of issues. As mentioned in Chapter 1, the preferred label for the treatment approach endorsed by the World Professional Association for Transgender Health (WPATH), the Endocrine Society (ES), the American Academy of Pediatrics (AAP) and the American Medical Association (AMA) is "gender-affirming care." The surgical removal of breasts (mastectomy) in physically healthy females is called "gender-affirming chest surgery" or "top surgery."[4] "Affirming" has a positive connotation, and someone who objects to "gender-affirming

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[1] Importantly, accuracy and neutrality are not enough. "80% of patients given drug A recovered" is ethically bland; suppose it is also true. Absent further context that statement is misleading if 80% of patients *not* given drug A also recovered. Another example: if a physician truthfully tells a patient, "You either have cancer or a harmless cyst," knowing that the patient has cancer, the patient has been misled.
[2] Shaw et al. (2022).
[3] For related examples in the field of women's health, see Gribble (2025). See also Bartick et al. (2025); the authors make the point that "transgender and gender-diverse people need clear and unambiguous health communications, including those related to sex-based needs, conditions, and symptoms, as much as any other group" (p. 5).
[4] E.g. Coleman et al. (2022, p. S130).

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surgery" sounds lacking in compassion. The euphemisms "chest surgery" and "top surgery" gloss over the relevant fact that breasts are removed.

Word choices can obscure patients' young ages. Terms such as "people" or "folks" are sometimes used by proponents of medicalized interventions instead of "children" or "adolescents." It is frequently emphasized that prepubertal children are not prescribed hormones or surgeries. That is true. However, clinical guidelines recommend initiating puberty blockers (PBs) at pubertal onset, which can occur at 8 or 9 years old—meaning that such interventions may be started during childhood. In discussions of this recommendation, "young people" or "adolescents" are sometimes substituted for "children."[5] Again, this helps camouflage the fact that sometimes serious medical interventions are performed on children's healthy bodies.[6]

Some adolescents transition and later detransition, reverting to living as their sex, changing their name back and making other necessary social adjustments. If the adolescent has undergone some degree of medical transition, the process of detransitioning can present significant challenges.[7] These difficulties are sometimes downplayed through the use of "retransitioning"[8] instead of "detransitioning," or writing

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[5] E.g., from a National Association of Social Workers fact sheet: "MYTH: Gender-affirming hormones, or hormone replacement therapy (HRT), are given to *children*," and: "During and after puberty, some medical treatments may be available [for] the *youth*" (National Association of Social Workers, n.d., emphasis added). According to the AAP, childhood spans ages 2-12 (Hardin et al., 2017).

"Adolescent" is often used for children in the early stages of puberty, when a layperson would use "child." As a member of WPATH put it in an email: "I would avoid children and hormones, and stick to medical definitions: when a young person reaches … puberty, [they are] therefore classed as adolescents (whether they are 9 or 12)," quoted in Boe v. Marshall, No. 2:22-cv-00184: 557-9/700-2 (2024, p. 16). See also Ryan (2025): "Dr. Olson-Kennedy generally avoids using the words 'child,' 'children' or 'kids'"; and Levine et al. (2022b, p. 117). The Endocrine Society made a simple factual error when it stated that "medical intervention is reserved for older adolescents and adults" (Endocrine Society, 2023).

[6] Another phrase is "wrong puberty": e.g., "pubertal blockers … block the progression of puberty so the young person doesn't go through the wrong puberty" (Jacoby, 2022). Apart from presupposing the correct treatment, it is misleading to suggest that the "right puberty" induced by estrogen in males or testosterone in females amounts to a cross-sex version of puberty, because puberty centrally and definitionally involves maturation of the capacity for reproduction. The Endocrine Society guideline adopts this language, writing of the "induction of female puberty" in males (Hembree et al., 2017, Table 8); see also Section 7.4.1.

[7] MacKinnon, Expósito-Campos et al. (2023).

[8] Olson et al. (2022). "Retransitioning" does have a legitimate use, to describe the process of transitioning again, going from detransitioning to living as the other sex (MacKinnon, Expósito-Campos et al., 2023, p. 1).

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of “dynamic desires for gender-affirming medical interventions.”[9] This conceptualizes an experience that can be profoundly distressing for the patient as simply another stop along their “gender journey.”[10]

The lead author of the AAP’s 2018 policy statement (reaffirmed in 2023), “Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents,” has even described detransition as part of the “gender affirming” approach itself, thus making treatment failure impossible to conceive.[11]

The problems go deeper. The terminology of “sex,” “male,” and “female” is indispensable if the medical and ethical issues are to be discussed responsibly. And yet proponents of medicalization go to extraordinary lengths to avoid the plain use of these words, and related words such as “boy” and “girl.” When “sex” is defined, the definition is rarely correct,[12] and in any case the preferred phrase is “sex assigned at birth.” According to the ES’s “Clinical Practice Guideline for the treatment of Gender-Dysphoric/Gender-Incongruent Persons,” “the terms biological sex and biological male or female are imprecise and should be avoided.”[13] Pediatric female patients are not “girls” or “young women,” but rather “AFAB individuals” (people “assigned female at

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[9] Turban, Brady et al. (2022).

[10] Jorgensen (2023b): “we should be cautious about adopting euphemisms that might mask iatrogenic harm” (p. 2180).

[11] “Rafferty [the lead author of the AAP 2018 policy statement] told me patients who live with harms or regrets do not signal a failure of the affirmative care model. If a child or patient doesn’t like the effects of an intervention, or begins to feel different in their identity, then the provider continues to affirm by discontinuing treatment. ‘They’re not treatment failures if that’s what’s affirming’ he said” (Block, 2023d).

[12] E.g. the entry for “sex” in Hembree et al. (2017, Table 1) conflates sex with characteristics highly correlated with sex in humans (“sex chromosomes,” “sex hormones,” etc.); the entry in Rafferty et al. (2018, Table 2) erroneously says that sex is “an assignment that is made at birth.” For the orthodox conception of sex in biology, see, e.g., Dawkins (1976, pp. 183-184); Parker (2011); Futuyama & Kirkpatrick (2017, p. 249). The orthodox conception is in an Endocrine Society “Scientific Statement” (Bhargava et al., 2021), and in a Health and Human Services document (Health and Human Services, 2025).

[13] Hembree et al. (2017, Table 1). Hembree et al. don’t take their own recommendation completely to heart, writing at one point that “in females [i.e. “biological females”] … the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain” (p. 3880). This ES guideline is an update of “Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline,” published in 2009. In that earlier guideline the conventional meaning of sex is used, and the authors use the allegedly imprecise phrase “biological females” (Hembree et al., 2009, p. 3139). The AMA also claims that “sex assigned at birth” is “more precise” than “sex” (American Medical Association, 2021, p. 14).

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birth"). Some authorities in PGM say that the patients wanting mastectomies are in fact "young men."[14]

"Assigned sex at birth" is not a harmless euphemism. It suggests an arbitrary decision—not unlike "assigned seating"—rather than the observation of a characteristic present long before birth, namely the child's sex. Moreover, if the phrase "assigned sex" were intended merely as a gentler way of referring to sex in conversations with patients and families, one would expect more direct language to be used in the specialty medical literature. In professional contexts, where clarity is paramount, euphemisms are generally avoided. Yet "assigned sex" is ubiquitous in clinical and academic publications. Not only that: use of such terminology is now *mandated* by certain medical journals.[15] The American Psychological Association (APA) style guide, for example, classifies "birth sex" and "natal sex" as "disparaging terms" which problematically "imply that sex is an immutable characteristic."[16] As law professor Jessica Clarke observes, "'Sex assigned at birth' is not a euphemism for 'biological sex' but a critique of the very concept."[17]

The term "gender identity" is an especially important example of how words can sow confusion. When first introduced in the 1960s, it meant "the sense of knowing to which sex one belongs, that is, the awareness 'I am a male' or 'I am a female'."[18] Almost

[14] "I don't advocate removal [of] breast tissue from young women. I advocate for chest reconstruction in young men" (Olson-Kennedy, 2019, p. 38); this use of language has the effect of making mastectomies for adolescent girls sound unalarming. See also Ehrensaft (2017b, p. 7): "transgender boys are boys and transgender girls are girls."

[15] *The Lancet*'s "Information for Authors" mandates the use of "sex assigned at birth," instead of "biological sex," "birth sex," or "natal sex" because "it is more accurate and inclusive." The same document also incorrectly states that sex is not "binary," that it exists "along a spectrum," and that a person's sex can change (The Lancet, 2025).

[16] American Psychological Association (2024a).

[17] Clarke (2022, p. 1828). The language of "assigned sex" was used in the 1950s for exceedingly rare cases of disorders of sex development (DSDs), where a baby with ambiguous genitalia could be raised as either a boy or a girl (Money, 1955).

[18] Stoller (1964, p. 220); see also Greenson (1964, p. 217). For discussion see Byrne (2023b, 2023a); Haig (2023); D. F. Janssen (2023).

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everyone has a gender identity in this sense, and moreover one that is congruent with their sex: males know that they are male, and females know that they are female.[19]

However, today the phrase "gender identity" is used in a significantly different way. For example, WPATH defines "gender identity" in the glossary to their current clinical practice guideline (SOC-8) as:

> A person's deeply felt, internal, intrinsic sense of their own gender.[20]

This new definition is unclear. For instance, what does "gender" mean in this context? The glossary in SOC-8 offers little clarification—though it does correctly acknowledge that the word is highly ambiguous. One meaning of "gender" given in the glossary is "gender identity." But "gender" in the definition above cannot mean "gender identity," otherwise the definition would be circular. Another meaning provided is "gender expression," but this too leads to circularity, because "gender expression" is itself defined in the same glossary in terms of "gender."[21]

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[19] Some children distressed about their sexed bodies are mistaken about whether they are male or female, but some are not. Accordingly, being mistaken about one's sex is not required for a diagnosis of Gender Dysphoria in Childhood in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM): "A strong *desire* to be of the other gender" is enough. Although the diagnostic criteria for children also mention "an insistence that one *is* the other gender," this is not a necessary criterion, and is altogether absent from the DSM criteria for Gender Dysphoria in Adolescents and Adults (American Psychiatric Association, 2022, pp. 512-513, emphasis added).

[20] Coleman et al. (2022, p. S252). Along the same lines: "On one level, gender identity is something deeply felt and can be difficult to put into words. I often refer to this as one's *transcendent* sense of gender. You simply *feel* a certain gender" (Turban, 2024, p. 38); "Gender identity is a person's inner sense of belonging to a particular gender, such as male or female" (Ehrensaft, 2017b, p. 7). This latter definition would sound strange if "particular gender" was replaced by "particular sex": the implication would then be that there are more sexes beyond male and female.

[21] Another definition of "gender" given in SOC-8 is "social gender role, including understandings and expectations culturally tied to people who were assigned male or female at birth" (Coleman et al., 2022, p. S252). Consider the suggestion that this is the intended sense of "gender" in WPATH's definition of "gender identity." That is, "gender identity" is defined as: "a person's deeply felt, internal, intrinsic sense of their own social gender role." Now it is true that a person might have a sense of their "social gender role." A woman, say, might be aware that in her culture certain expectations apply to women. However, here the language of "deeply felt/internal/intrinsic" is quite inappropriate, which is one piece of evidence that the present suggestion is wrong. More importantly, there is no room for any "mismatch" between a person's sex and their social gender role. A woman may (perhaps rightly) disapprove of the expectations that her culture imposes on females; that is, she may disapprove of her social gender role. Since she has this gender role because she was "assigned female" at birth, her "gender" in this sense will *always* match her sex. But evidently WPATH wishes to define "gender identity" in such a way as to allow for *mismatches* with a person's sex. Hence, the "gender role" sense of "gender" is of no help in defining "gender identity" either. [Note continued on next page.]

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In short, “gender identity” as it appears in SOC-8 and related literature is ill-defined.[22] It may be true that a person’s gender identity is subjective, or undetectable by blood tests or neuroimaging,[23] or otherwise beyond the reach of science, but the more critical point is that no tolerably clear definition of “gender identity” has been offered in the first place.[24] This is a serious problem, because the term figures centrally in the justification for medical intervention.

The term “transgender” is typically explained in terms of gender identity. Transgender people are those whose gender identities do not “align with” or “match” their sex (or “sex assigned at birth”).[25] Since “each of us has a gender identity, though many of us never give it much thought,”[26] the rest of humanity have gender identities that match their sex; these people are said to be “cisgender.” It is important to realize that “transgender” is not a clinical term and does not correspond to a medical diagnosis.[27] Indeed,

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Another way of explaining “gender” is to give a list of representative “genders” with the expectation or hope that the reader will see the pattern. In principle, this sort of explanation can be satisfactory. However, WPATH’s previous guideline offered the following examples: “male (a boy or a man), female (a girl or woman) … boygirl, girlboy, transgender, genderqueer, eunuch” (Coleman et al., 2012, p. 221). Notice that the list includes the category *transgender*, which is itself explained in terms of gender identity and hence gender, introducing a circularity. Another point is that if *eunuch* is a (contemporary) gender, then “gender” as it figures in WPATH’s definition of “gender identity” cannot possibly be explained in terms of “social gender role” (see the first paragraph of this note). Eunuchs had a special social role in Imperial China; they have no such role today. WPATH’s current guideline has an entire chapter on eunuchs, so clearly WPATH thinks the gender *eunuch* is not an anachronism.

[22] Here is another example. The AAP’s 2018 policy statement defines gender identity as “[a] person’s deep internal sense of being female, male, a combination of both, somewhere in between, or neither” (Rafferty et al., 2018, Table 1). The policy statement also says that a “transgender” person is someone “whose gender identity does not match their assigned sex.” Clearly “gender identity” as the AAP defines it cannot mean what it originally did, because a transgender man, for instance, might not be mistaken about being female. How to interpret “female” and “male” in the AAP’s definition is far from clear.

[23] See, e.g. Baldinger-Melich et al. (2020); Levin et al. (2023); Bakker (2024).

[24] The original 1960s explanation of gender identity (see above) was perfectly clear, but that is not the contemporary conception in gender medicine.

[25] Boe v. Marshall, No. 2:22-cv-00184: 558-16 (2024); Ehrensaft (2017b); Olson-Kennedy (2022). According to the previous WPATH guideline (SOC-7): “The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth” (Coleman et al., 2012, p. 221). Remarkably, sometimes “transgender” is defined to include commonplace gender non-conformity, *regardless* of any “mismatched” gender identity. For instance, according to SOC-8, if a person’s “gender expressions are not what is typically expected for the sex to which they were assigned at birth,” they are transgender (Coleman et al., 2022, p. S252).

[26] Forcier et al. (2020, p. 2). Similarly: “Gender identity … is a core and *universal* component of human identity” (Boe v. Marshall, No. 2:22-cv-00184: 592-12, 2024, p. 6, emphasis added).

[27] Thus a recent article on assessing “transgender and gender diverse adolescents” for puberty suppression recommends reassuring patients that the goal is not to determine whether they “are actually transgender” (Turban et al., 2025, p. 14). But see Section 13.3.

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proponents of the medicalized approach emphasize that some transgender people neither desire nor need medical or surgical interventions of any sort.

It is often claimed that gender identity is "innate or fixed at a young age," and so "cannot be changed."[28,29] Putting that idea together with the definition of "transgender," the result is that being transgender is a close-to-immutable trait. (The same goes for being cisgender.) A "transgender child," in this framework, is a child whose unalterable gender identity does not align with their sex, while cisgender children are the other kind.[30] Once this binary paradigm of "trans kids" and "cis kids" is accepted, therapeutic exploration of the underlying causes of a child's discomfort with his or her sexed body is readily dismissed as "conversion therapy," an unethical attempt to interfere with the development of the child's authentic self.[31,32]

According to many authorities in PGM, there is a test to determine whether a child is transgender or cisgender. This is because children "know who they are." Specifically, they know their "gender."[33] If a child's "gender" matches their "assigned sex," they are cisgender; if not, they are transgender. So, to determine whether a child is transgender or cisgender, one only need ask.

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[28] Adkins (2016, p. 4); Ehrensaft (2017b, p. 7); Olson-Kennedy (2022, p. 9). However, an earlier paper on the PMT approach, which has Ehrensaft and Olson-Kennedy as co-authors, states that it is a "myth" that gender identity is "immutable" (Hidalgo et al., 2013, p. 288), indicating at least some confusion about key terms.

[29] In his expert witness report for *Boe v. Marshall*, Aron Janssen, a gender clinician and vice chair of clinical affairs at Lurie's Pritzker Department of Child and Adolescent Psychiatry, wrote that gender identity, "a person's innate sense of their gender," "cannot be altered through medical or psychological interventions" (Boe v. Marshall, No. 2:22-cv-00184: 592-12, 2024, p. 6).

[30] Some PMT authorities would dispute this characterization and claim that a transgender child's gender identity *does* match their sex—what it *doesn't* match is their "birth-assigned sex" (Ehrensaft, 2017b, p. 9).

[31] "Psychotherapy may be beneficial but should not be a requirement for gender-affirming treatment, and conversion treatment should not be offered" Coleman et al. (2022, p. S10). On "conversion therapy," see Section 14.5.2.1.

[32] Two books that discuss the "transgender child" are Gill-Peterson (2018) and Meadow (2018). On Gill-Peterson, see Byrne (2024b, pp. 243-244). For an early expression of skepticism, see Brunskell-Evans & Moore (2018).

[33] [R]esearch substantiates that children who are prepubertal and assert an identity of TGD [transgender and gender-diverse] *know their gender* as clearly and as consistently as their developmentally equivalent peers who identify as cisgender and benefit from the same level of social acceptance" (Rafferty et al., 2018, emphasis added). Also: "Individuals whose sex assigned at birth is opposite to the gender they *know themselves to be* are often referred to as *transgender*" (Turban & Ehrensaft, 2018, p. 1, first emphasis added); "studies show that trans children and adolescents know themselves and their gender" (Ashley, 2022b, p. 15).

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An immediate problem is posed by the undeniable phenomenon of temporary youthful transgender identification. (See Section 4.3.1.4.) Attempting to address this difficulty, Aron Janssen, vice chair of clinical affairs at the Pritzker Department of Child and Adolescent Psychiatry at Lurie Children's Hospital in Chicago, and chair of the American Academy of Child and Adolescent Psychiatry's Sexual Orientation and Gender Identity Issues Committee, stated in a deposition that although gender identity is "static" and "fixed," "one's understanding of it can evolve over time."[34]

Dysphoric children and socially transitioned children are routinely referred to as "transgender children." In some cases, this is for convenience or as a gesture of respect.[35] However, its use may subtly influence clinical reasoning. The label "transgender" implies a mismatch between gender identity and the person's sexed body, and that mismatch can supposedly cause gender dysphoria.[36] Since an adolescent's gender identity cannot be changed, the obvious solution to relieve the distress is to change their body.[37]

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[34] Boe v. Marshall, No. 2:22-cv-00184: 558-16 (2024, pp. 104-110). Some PMT clinicians maintain that such change in understanding is not likely: "there is [a] small but non-zero possibility of one's understanding of their gender identity evolving over time" (Turban et al., 2025, p. 2). According to UCSF's Diane Ehrensaft, "My own clinical experience told me that you could discern one group of children from the other prior to adolescence, not with 100% accuracy, but not far from it" (Ehrensaft, 2014, p. 578). As Ehrensaft puts it in her book *The Gender Creative Child*, "we can tell the apples (the transgender children) from the oranges (the gender-nonconforming but not trans kids), sometimes as early as when they are three years old. So, why hold the apples back if they already know who they are?" (Ehrensaft, 2016, p. 55). Put without the framing of "trans kids," the clinical issue is whether one can discriminate between gender dysphoric children whose dysphoria will resolve without any medical intervention, and those whose dysphoria will persist into adulthood (see Section 4.3.2).

[35] E.g. Olson et al. (2022).

[36] According to WPATH, gender dysphoria is "distress that is *caused by* a discrepancy between a person's gender identity and that person's sex assigned at birth" Coleman et al. (2012, p. 221, emphasis added). The quotation continues, "(and the associated gender role and/or primary and secondary sex characteristics)"; so at least in theory, one way of relieving gender dysphoria would be to change the "associated gender role."

[37] The AAP policy statement includes more young people as candidates for medicalization that just those with mismatched or incongruent gender identities. The title of the policy statement is "Ensuring Comprehensive Care and Support for Transgender *and Gender-Diverse* Children and Adolescents" (Rafferty et al., 2018, emphasis added). Transgender youth, the policy statement says, are "a subset of gender-diverse youth." The policy statement explicitly equates "gender diverse" with "gender nonconforming" (the latter term being deprecated only because of its allegedly pejorative connotation). Thus, gender-nonconforming youth *in general* are singled out as potential recipients of sex-related hormone therapy and surgery. The same points apply to WPATH's SOC-8, *Standards of Care for the Health of Transgender and* Gender Diverse *People*, which also deprecates the use of "gender-nonconforming" (Coleman et al., 2022, p. S11, emphasis added); SOC-7 (Coleman et al., 2012) has "gender-nonconforming" in its title.

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2.2 Terminology in this Review

While communication with patients and families must always be sensitive and compassionate, describing sex as a matter of "assignment" is, at best, confusing and accordingly not truly respectful. Patients and their legal caregivers are entitled to the facts regarding their medical situation; this is essential for informed participation in the medical decision-making process. Just as importantly, evidence assessments must use accurate and precise language when referring to sex, in order to maintain scientific integrity and support sound clinical judgment.

Treatment of children and adolescents with GD presents an especially complex case of doctor-patient communication because doctors understandably do not want to alienate their patients; trust is the bedrock of shared decision-making.

There is growing international awareness of the importance of using accurate sex-based language. As the recent U.K.'s *Review of Data, Statistics and Research on Sex and Gender* (RSG) asserts:

> Analysts must be able to use clear and familiar language in reporting findings on sex. Terms such as women, men, boys and girls are synonymous with (respectively) adult human females and males and children of each sex. Similar considerations apply to terms such as mothers and fathers, sons and daughters.[38]

The RSG also recommends against using the phrase "sex assigned at birth," remarking that it is "misleading."[39]

The RSG notes that the word "gender" has "multiple distinct meanings, including: a synonym for sex; social structures and stereotypes associated with sex; and gender identity."[40] For this reason, the RSG cautions against using the word when misunderstandings could arise. A prime example is WPATH's definition of "gender identity" discussed above, which uses the word "gender" without an adequate

[38] Sullivan (2025, p. 11). The Review was commissioned by the previous Conservative government and welcomed by the present Labour Secretary of State for Health and Social Care (Scott, 2025).
[39] Sullivan (2025, p. 7).
[40] Sullivan (2025, p. 5).

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explanation. Because of its unclarity and ambiguity, “gender” will generally be avoided in this Review. “Gender identity” inherits the obscurity of “gender” and will not be used either.[41] As discussed, the term “transgender child” suggests that medical intervention is the default or primary course of action. For this reason, it will be avoided.[42]

The Review will use “social transition” for the process of changing one’s sex-associated name, presenting oneself as a member of the other sex, being referred to with third-person pronouns for the other sex,[43] and so on.

“Gender dysphoria” (GD) is in the DSM and at present has no accepted alternative; therefore, it will be used despite problems with the word “gender.” “Gender nonconformity” is a familiar and well-understood phrase, so it will also be used (although some may prefer “sex-stereotype nonconformity”). As already indicated, “pediatric gender medicine” (PGM) will be used for the clinical field that treats children and adolescents with GD, sometimes with medical interventions. Instead of the term “gender-affirming care” this Review will use “PMT” (pediatric medical transition), as in phrases such as “the PMT approach.” This is more accurate and carries no positive or negative connotation. The PMT approach does not always involve hormones or surgeries, but some of its proponents do tend to view even social transition as an initial step toward medical transition. The older term “cross-sex hormones” (CSH)[44] is more neutral and informative than “gender-affirming hormone therapy.” Surgeries to alter sex characteristics[45] for adolescents will be given medically standard, clinical, neutral descriptions—e.g. “mastectomy.” Finally, the older term “sex reassignment surgery” (SRS) will be used rather than the more recent “gender confirmation surgery.”

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[41] Also relevant from the RSG: “Questions on gender identity should recognize that the concept of gender identity as such will be unfamiliar, unclear or irrelevant to some respondents, and that many respondents may not perceive themselves as having a gender identity. Questions should not assume that respondents will agree that they have a gender identity” (Sullivan, 2025, p. 9). The RSG illustrates how “gender identity” is now firmly embedded, not just in gender medicine, but also in social statistics (and, it could be added, pedagogy). For an illuminating discussion of the history, see Brubaker (2025).

[42] Needless to say, terminology that makes other treatment pathways prominent is equally undesirable.

[43] Or *they* or neo-pronouns (*xe*/*xem* and the like).

[44] Even this terminology is not perfect: estrogens are normally present in males, although at lower levels than in females; vice versa for androgens (including testosterone).

[45] Sex characteristics are either *primary* (the external and internal reproductive organs), or *secondary* (characteristics that emerge at puberty, such as breasts in females and facial hair in males).

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Chapter 3 History and Evolution of Adult and Pediatric Gender Medicine

Medical transition for gender dysphoric youth is a comparatively recent practice and grew out of the clinical experience of transitioning mature adults. It is common in medicine to extend medical treatments to children once they have been proven safe and effective in adults. In this case, however, the opposite occurred. The rationale for transitioning adolescents emerged from the observation that medical transition in adults often failed to produce the desired positive outcomes. This chapter explains how this came about and provides additional historical context.

Sections 3.1, 3.2, and 3.3 briefly review the history of medicalized transitions, which are barely a century old. Sections 3.4 and 3.5 explain how the observed failure of medical transition to produce positive psychosocial outcomes for adults led clinicians in the Netherlands to propose an early intervention model, resulting in the "Dutch Protocol." The final section describes how the Dutch Protocol evolved into the "gender affirming care" approach to pediatric medical transition (PMT), a shift that was accompanied by significant changes in the pediatric patient population presenting with GD—both in terms of size and demographic composition.

3.1 *The Transsexual Phenomenon*

Extremely gender-nonconforming people, including those who live their lives either as members of the other sex, or as a so-called "third gender," have been documented throughout human history.[1] One famous example is the French diplomat and spy Chevalière d'Eon (1728-1810), who dressed and "passed" as a woman during the final 32 years of his life. Everyone was convinced, including the last king of France, Louis XVI.[2] In the early 20th century, the English physician and sexologist Henry Havelock Ellis coined *eonism*, after the Chevalière, for "people who took pleasure in behaving and

[1] See, e.g., Bullough et al. (1997); R. Green (1966); Herdt (1996); Peled (2016); Vasey & VanderLaan (2014). Many earlier cultures and some contemporary ones have "third genders": some people of one sex (typically feminine same-sex attracted males) occupy social roles (somewhat) similar to those of the other sex. It is a mistake to take this phenomenon to be akin to the contemporary Western "transgender moment"—see Vasey (2022).
[2] Kates (2001, p. 218).

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dressing like the opposite sex and yet were not sexually inverted; that is, their sexual feelings were not directed towards persons of their own sex."[3] "Eonism" later came to label a broader category, including individuals with strong cross-sex wishes who were same-sex attracted.[4] In 1949, an American physician, David Cauldwell, used the term "transexual" to label "individuals who are physically of one sex and apparently psychologically of the opposite sex."[5]

"Transsexualism" was popularized by Harry Benjamin, a German-American endocrinologist and the father of transgender medicine. Benjamin's 1966 book, *The Transsexual Phenomenon*, was the first comprehensive English-language discussion of medicalized treatment for people who "want to undergo corrective surgery … so that their bodies would at least resemble those of the sex to which they feel they belong and to which they ardently want to belong."[6] Cross-sex hormones (CSH) followed by surgery, Benjamin thought, could "change a miserable and maladjusted person of one sex into a happier and more adequate, although by no means neurosis-free, personality of the opposite sex."[7]

In the first half of the 20th century, there were few recorded instances of transsexuals. One of the first people to undergo sex-reassignment surgery (SRS) was Einar Wegener, a Danish artist who modeled while cross-dressed for his wife Gerda Gottlieb, a talented painter. In pursuit of the body modifications he so desperately desired, Wegener sought help from the sexologist Magnus Hirschfeld, a long-time friend of Harry Benjamin's and founder of the Institute for Sexual Science in Berlin.[8] Castration, penectomy, and ovarian implantation were performed on Wegener in Berlin and Dresden in 1930, with

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[3] Havelock Ellis (1937, p. 1, Part Two); quoted in Byrne (2024b, pp. 113-114). According to d'Eon's biographer, the historian Gary Kates, "d'Eon was neither a transvestite nor a transsexual … there is simply no indication that d'Eon hated his own body or that he wanted, or even imagined he would be better off with, the body of a woman" (Kates, 2001, p. xxii); quoted in Byrne (2024b, p. 229).
[4] See, e.g., Hamburger et al. (1953) (a report on Christine Jorgensen's case; see the following section). See also Benjamin (1967b, p. 107) and Blanchard (1989, p. 240).
[5] Quoted in Meyerowitz (2009, p. 44). This quotation is from Cauldwell's 1950 *Questions and Answers on the Sex Life and Sexual Problems of Trans-Sexuals*, which hyphenates "transsexual." Cauldwell used "psychopathic transexual" (one "s") in 1949 (Cauldwell, 2006, p. 41).
[6] Benjamin (1966, p. 14)
[7] Benjamin (1966, p. 164).
[8] Li (2023).

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additional procedures the following year. These were unsuccessful. Einar Wegener, transformed into Lili Elbe, died in September 1931, after an "abyss of suffering."[9]

3.2 From George to Christine

Transsexualism was not then a phenomenon. That changed in 1952, when the news broke that George Jorgensen, a 24-year-old American of Danish descent had undergone sex reassignment surgery (SRS) in Denmark:

> [H]er celebrity began December 1, 1952, when a banner headline screaming "EX-GI BECOMES BLONDE BEAUTY: OPERATIONS TRANSFORM BRONX YOUTH" greeted readers of the *New York Daily News*. Hearst Publications' popular Sunday newspaper supplement, *American Weekly*, subsequently paid twenty thousand dollars for an exclusive interview with Jorgensen that brought her story to millions of American homes, and whetted the appetite of the world press. When she returned to the United States in 1953, an unprecedented three hundred reporters were on hand to meet her plane at New York International Airport … Her "sex-change" was viewed by many as a miracle of God in which not Christ, but Christine—Man reborn as Woman—heralded a new dispensation of human history.[10]

Jorgensen met Harry Benjamin in New York that year, and they enjoyed a long friendship. In a 1965 letter, just before the publication of *The Transsexual Phenomenon*, Benjamin wrote: "Without you, Christine, none of this would have happened."[11]

Growing up in the Bronx, the young George was teased for his "girlish qualities," and was greatly conflicted by his homosexuality:

> One question was especially troubling for George: He had learned at church and from his school friends that homosexual relationships were considered sinful and immoral. In the Jorgensen household, the word was never spoken. Among his

[9] Elbe et al. (2020, p. 203); quoted in Joyce (2021, p. 17). Lili apparently had no regrets, writing in June 1931, "The price which I have paid seems to me very small" (Elbe et al., 2020, p. 198). On regret, see Section 13.4. The 2015 movie *The Danish Girl*, starring Eddie Redmayne, is loosely based on Einar/Lili's story.
[10] Stryker (2000, pp. v-vi).
[11] Jorgensen (1967, p. xi).

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> neighbors, “homos” or “queers” were thought to be unacceptable, even dangerous people. Hence, a series of romantic attractions to other young men became his greatest teenage conflict. Try as he might to avoid these crushes, George persistently fell in love with other male youths of his age. This conflict would contribute to episodes of depression, low self-esteem, low aspiration for success, and much personal unhappiness.[12]

George himself fixated on a hormonal explanation for his femininity and same-sex attraction—a “glandular imbalance”[13]—and was also (wrongly) convinced that his genitals were “underdeveloped.”[14] It is a plausible conjecture that George found an English translation of Lili Elbe’s autobiography while hunting in New York City libraries, “hoping to find other keys to my dilemma.”[15] In any event, in search of the hormonal and surgical treatment he felt he needed, George went to Denmark on a one-way ticket in 1950. There the “Bronx youth” became a patient of Christian Hamburger, a Copenhagen endocrinologist:[16]

> Perhaps Hamburger felt a special compassion for homosexuals because his sister was a lesbian. Despite Denmark’s comparatively liberal national policies, Hamburger surely knew from his sister’s experience how discrimination against gays and lesbians could be profoundly troubling for a homosexual. He could offer no medical intervention to help his sister, but he believed there might be some steps he could take to help George Jorgensen, and he was willing to try.[17]

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[12] Docter (2013, pp. 25-26).
[13] Docter (2013, p. 63).
[14] Docter (2013, p. 46).
[15] Jorgensen (1967, p. 80); for the conjecture, see Docter (2013, p. 38).
[16] Hamburger had a distinguished career (Pedersen-Bjergaar, 1964). Contrasting with Hamburger’s academic record, before Benjamin became interested in transsexuality he was a prominent proponent of endocrine “rejuvenation therapy,” a medical fad. In 1931 he sued the editor of the *Journal of the American Medical Association* (*JAMA*) “for calling his treatment quackery,” and lost (Pettit, 2013, p. 1070).
[17] According to Hertoft & Sørensen (1979), a “sex change” was not the original plan: “the Danish team regarded Chris Jorgensen as a homosexual man suffering from his homosexuality and since he himself asked for castration, they would not deny him this operation. Not until afterwards, when the press published the case, did the team behind the procedure accept it as a sex change. The rest of the story is well known” (p. 168). Hamburger is said to have denied that Jorgensen was a homosexual in Christine’s autobiography (Jorgensen, 1967, p. 101). See also Docter (2013, p. 81).

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In a case report he later wrote for the *Journal of the American Medical Association* (*JAMA*) Hamburger described George's desire "with medical assistance to be able to obtain permission to live on 'as nearly a woman as possible.'"[18] Hamburger prescribed estrogen, and George's application for castration to the Danish Ministry of Justice was approved in 1951.[19] Castration was followed by penectomy and a later unsatisfactory attempt at creating an artificial vagina. "As a nationally recognized personality, Christine Jorgensen's flame burned with exceptional brilliance for about thirty years,"[20] dimming in the 1980s. A heavy drinker and smoker, Christine died of cancer in 1989, at the age of 62.

3.3 "Dear Dr. Hamburger"

After the "sensational publicity" over George Jorgensen's metamorphosis into Christine, Hamburger received "a unique collection of letters from a considerable number of men and women who desire to change their sex."[21] He analyzed all 756 of them, from 465 people, and published the results in a European endocrinology journal, *Acta Endocrinologica*. His correspondents wrote from all over the world. Over three quarters were men, and some of the letter writers were young teenagers. Not everyone mentioned their sexual orientation, but the women were the most forthcoming, with 71% offering at least some information. Fewer than half the men gave "any information about their sexual impulses."[22] Homosexuality predominated[23] among the men and was universal among the women:

> It is remarkable that not one single woman admits to heterosexuality, which is the case in 22 per cent of all male letter writers … Not a single woman mentions attraction to men; on the contrary. Women who have experienced shorter or longer periods of married life, felt the physical part of matrimony to be intolerable. Completely different are the transvestic men: they do not appear to have felt any

[18] Hamburger et al. (1953, p. 393).
[19] Jorgensen (1967, pp. 114-116).
[20] Docter (2013, p. 255).
[21] Hamburger (1953, p. 361).
[22] Hamburger (1953, p. 368).
[23] Of the 45% of men who disclosed information about their sexual orientation, Hamburger classified 65% as homosexual (Hamburger, 1953, Table 3).

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> aversion to the female body, although the erotic attraction, if any, is stated to have declined with passing years, or to have led to impotence.[24]

A 16-year-old American girl wrote:

> I've always acted like a boy and did the things they did. When I was smaller I used to wear my brothers [sic] clothes and I even do now sometimes when no one is home. This isn't the worst of it though, ever since I've been in High School I've been in love with a girl! and as much as I try to forget this love the more I realize I don't want to forget it. - - - I've also read about transvestites who only wanted to dress like the opposite sex but that's not how I feel. I want to dress like a boy yes, but it's not so bad that I can't control it.[25]

Childhood gender-nonconformity is strongly associated with later homosexuality.[26] Because childhood- or early-onset gender dysphoria (GD)[27] involves extreme gender-nonconformity, young children distressed by their sexed bodies will likely grow up to be same-sex attracted. As the current *Diagnostic and Statistical Manual* (DSM-V-TR) puts it, "Studies have shown a high incidence of sexual attraction to those of the individual's birth-assigned gender, regardless of the trajectory of the prepubescent child's gender dysphoria."[28] Harry Benjamin put his own spin on George Jorgensen's homosexuality: "since the psychological status of a transsexual male is that of a female, it is natural that sex attraction centers on a male."[29]

Despite the sensational publicity, in the 1960s the "transsexual phenomenon" was still in its infancy. By 1965, Benjamin had seen 307 cases of which he deemed 220 "true transsexuals," the remainder being classed as "transvestites." Almost 90% of the transsexuals were male. Only 62 males and 11 females had had surgery.[30] Reflecting

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[24] Hamburger (1953, p. 369).
[25] Hamburger (1953, p. 370).
[26] Bailey & Zucker (1995); R. Green et al. (1987); Steensma et al. (2013).
[27] Ristori & Steensma (2016); Singh et al. (2021). For other forms of GD, see Bailey & Blanchard (2017); Zucker et al. (2016). See also Section 4.3.1.
[28] American Psychiatric Association (2022, p. 516).
[29] Benjamin (1967a, p. ix).
[30] Benjamin (1966, p. 163).

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this imbalance, *The Transsexual Phenomenon* had only one slim chapter on "the female transsexual."

By 1979, the demand for "sex change" became significant enough for clinicians caring for this patient population to form a professional association, the Harry Benjamin International Gender Dysphoria Association (HBIGDA), which published the first *Standards of Care* in 1979. In that short typewritten document, "Principle 2" of 32 was: "Hormonal and surgical sex reassignment are procedures requiring medical justification and are not of such minor consequence as to be performed on an elective basis."[31]

In the third edition of the DSM in 1980, the disorder of "transsexualism" was said to be "apparently rare."[32] In 1994 DSM-IV reported: "Data from smaller countries in Europe with access to total population statistics and referrals suggest that roughly 1 per 30,000 adult males and 1 per 100,000 adult females seek sex-reassignment surgery."[33] The "transgender tipping point"[34] had not yet arrived.

3.4 Outcomes of adult transitions

Pediatric medical transition began in the Netherlands, which had offered adult treatment in an academic hospital starting in the 1970s, with the costs of a medical transition reimbursed through the Dutch national health insurance system.[35] The availability of comprehensive and reliable medical records gave clinicians the opportunity to study how patients fared, and a paper detailing the results was published in 1988: "Sex reassignment surgery: A study of 141 Dutch transsexuals." The research was led by the psychologist Peggy Cohen-Kettenis, who had worked earlier with adult transsexuals at the Department of Sexology at Utrecht University. In 1987 she moved to the Department

[31] Harry Benjamin International Gender Dysphoria Association (1979).
[32] For the diagnostic criteria, see Appendix 2. The first two versions of the DSM fleetingly included "transvestism" (American Psychiatric Association (1952, p. 39) and "transvestitism" (American Psychiatric Association (1968, p. 44). See also Drescher & Yarbrough (2024).
[33] American Psychiatric Association (1994, p. 535). See also Dhejne et al. (2014). According to the first *Standards of Care*, "As of the beginning of 1979, an undocumentable estimate of the number of adult Americans hormonally and surgically sex-reassigned ranges from 3,000 to 6,000" (Harry Benjamin International Gender Dysphoria Association, 1979).
[34] The title of a *Time* cover story in 2014 (Steinmetz, 2014).
[35] Bakker (2021, p. 29).

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of Child and Youth Psychiatry at the Academic Hospital Utrecht (now UMC Utrecht), where she began to see children and adolescents with GD.[36]

Cohen-Kettenis and her co-author and student Bram Kuiper sent recruitment letters to all 229 patients diagnosed by the Netherlands Gender Care Foundation (NGCF) as "transsexuals and who … had at least started hormone therapy." The 141 who agreed to participate were "36 FMs (female-to-male transsexuals) and 105 MFs (male-to-female transsexuals)."[37] They were at varying stages of medical transition. Some had completed surgery, while others had just started on CSH; follow-up time from the start of treatment ranged from one month to more than 10 years. The patients' average ages were late-20s (the FMs) and mid-30s (the MFs). They were assessed by interview, and all but three were interviewed in their homes.

On the positive side, 65% reported feeling happy or very happy, while 11% said they were unhappy or very unhappy. Almost all the FMs and nearly 80% of the MFs described their ability to "pass as a member of the newly assumed gender" as good or very good. None of those who had had surgery "felt any significant doubts about the decision to get rid of their own primary and secondary sex characteristics and to have the body surgically adjusted to the characteristics of the opposite sex," except for one FM who nonetheless had no regrets about living as a man.[38]

On the other hand, while the self-reported subjective outcomes were good, objective measures told a different story. One in seven MFs and one in 36 FMs had attempted suicide after treatment began. (Of the total number of patients seen at the NGCF in the previous 10 years, three had committed suicide after treatment.) 60% of the MFs and 37% of the FMs were unemployed and 59% of the MFs and 33% of the FMs had no romantic partners.[39] Commenting on previous studies of SRS, the researchers noted: "it is possible to discern a trend in these reports that the subjective well-being of the

[36] Bakker (2021, p. 113).
[37] Kuiper & Cohen-Kettenis (1988, p. 442).
[38] Kuiper & Cohen-Kettenis (1988, p. 450).
[39] Kuiper & Cohen-Kettenis (1988, p. 447).

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transsexuals has increased, whereas an 'improvement' in their actual life situation is not always observed."[40]

Did medical transition at least alleviate gender dysphoria? Interestingly, there was no relationship between reported happiness and stage of transition:

> Although a fair number of persons attribute their feelings of happiness to SRS, there appears to be no direct relation between the subjective well-being and the phase of therapy. Those who have completed SRS are not happier or less happy than those who are still in the initial phase of therapy. In other words, a person's positive evaluation of his/her life-in-its-totality is not directly related to his/her progress in physical adjustment to the opposite sex.[41]

The researchers speculated that this might be due to an expectation effect:

> However, it does not seem justifiable to conclude that it is irrelevant to a person's happiness whether physical adjustment has or has not taken place and that the operations could therefore just as well have been omitted. One has to bear in mind that in general the [FMs and MFs who had not completed treatment] are happy in the knowledge that the operations will be performed within a reasonable time. They are taking a loan on the future.[42]

Although the researchers claimed that "there is no reason to doubt the therapeutic effect of sex reassignment surgery," they were clear that there were significant costs:

> SRS is no panacea. Alleviation of the gender problems does not automatically lead to a happy and lighthearted life. On the contrary, SRS can lead to new problems.[43]

Why were the MFs, in particular, doing so poorly? Three possible explanations were floated. One was that "passing" is easier for FMs, because of the power of

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[40] Kuiper & Cohen-Kettenis (1988, p. 440). Dhejne et al. (2011) examined the long-term outcomes of 324 people in Sweden receiving sex-reassignment surgery (SRS) over the period 1973-2003 (191 MFs, 133 FMs). Dhejne et al. concluded: "Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population."
[41] Kuiper & Cohen-Kettenis (1988, p. 454).
[42] Kuiper & Cohen-Kettenis (1988, p. 454).
[43] Kuiper & Cohen-Kettenis (1988, p. 455).

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testosterone.[44] Second, "society in general is inclined to take a milder view of women who dress and/or behave like men."[45] Finally, the MFs had transitioned later and were more likely to have married and to have children, with a consequent "heavier burden of a past life as a person of the original gender."[46,47]

One possibility that the Dutch researchers did not consider was that the FMs were doing better because their romantic relationships were easier to preserve after transition. As Hamburger reported from his correspondence in 1953, "No less than 10 women say, in so many words, that they want their sex changed in order to be able to marry their female friend or to have the relationship legalized."[48] Also apparently ignored was the related possibility that transition may appeal to young gay men and lesbians suffering from social disapproval of their homosexuality.[49]

3.5 The rationale for youth gender transition

Medically transitioning earlier gave patients a better chance to "pass" and reduced the "burden of a past life," so perhaps intervening at younger ages would improve transsexuals' quality of life. Cohen-Kettenis thought so. As sociologist Michael Biggs explains,

> Cohen-Kettenis believed that transsexuals would experience better outcomes if they started treatment before adulthood. By the mid-1990s, she was referring some patients aged 16 and 17 to the Amsterdam clinic for endocrinological intervention prior to cross-sex hormones … Johanna, for example, "fulfilled all necessary requirements for early treatment": she did not favor girly things (though neither did her sisters), she was fond of soccer, she never dated in school (perhaps not surprising given that she was homosexual), and her parents discovered her wearing a tight t-shirt to conceal her breasts … Brought to the clinic at 17, she was prescribed progestin for four months and then testosterone.

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[44] This works both ways. First, testosterone can dramatically transform the female body; second, the effects of pubertal testosterone on the male body are hard or impossible to undo. See Section 7.4.
[45] Kuiper & Cohen-Kettenis (1988, p. 455).
[46] Kuiper & Cohen-Kettenis (1988, p. 456).
[47] See also Smith et al. (2005, p. 97).
[48] Hamburger (1953, p. 370).
[49] See Barnes (2023, pp. 159-164).

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> Within two years Jaap (as Johanna had become) underwent mastectomy, hysterectomy, and oophorectomy, and obtained a new birth certificate.[50]

In 1991 Cohen-Kettenis and her colleague Louis Gooren lowered the eligible age for CSH to 16, but Cohen-Kettenis was not yet recommending puberty blockers (PBs).[51] The Dutch pediatric endocrinologist Henriette Delemarre-van de Waal had treated the first patient with blockers some years earlier, in 1987. "FG" was a girl with early-onset gender dysphoria:

> From the age of 5, FG "had made it very clear that I was supposed to be a boy." It later transpired that FG was sexually attracted to women. FG's father, an Italian with traditional views on gender, disapproved of his daughter's masculinity, and serious conflict ensued. Extensive psychotherapy did not improve matters; FG wrote a suicide note at the age of 12.[52]

At age 13, FG was prescribed puberty blockers and remained on them until age 18, after which many surgeries followed, including mastectomy and hysterectomy.

FG had come to the Utrecht gender clinic three years after starting PBs; as Cohen-Kettenis recounts:

> I'll never forget that first boy treated with Decapeptyl[53] by Henriette Delemarre. He made an impression with his boyish appearance at 16—naturally, because he hadn't entered puberty. Henriette and I embarked upon the adventure. No one knew what the long-term effects of administering puberty blockers would be. Yes, I was nervous: suppose you've got it wrong with an adolescent like that and you have to reverse it![54]

With the collaboration of Cohen-Kettenis and Delemarre-van de Waal, the "Dutch Protocol" for youth medical transition was born.[55] As of 1997, for carefully selected

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[50] Biggs (2023b, p. 350).
[51] Bakker (2021, p. 118).
[52] Biggs (2023b, p. 350).
[53] The brand name of triporelin, a gonadotropin releasing hormone agonist (GnRHa); triptorelin acts on the pituitary gland, blocking puberty in adolescents. See Section 7.3.
[54] Bakker (2021, p. 115).
[55] Delemarre-van de Waal & Cohen-Kettenis (2006).

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"juvenile transsexuals," with early-onset GD worsening at puberty, PBs could be given as early as 12.[56] Cross-sex hormones could be administered at 16, with surgeries at 18.[57] Patients were required to be otherwise mentally healthy and have family support.

FG was followed up 22 years later at age 35:[58]

> FG did not regret transition, but scored high on the measure for depression. Owing to "shame about his genital appearance and his feelings of inadequacy in sexual matters," he could not sustain a romantic relationship with a girlfriend. Ironically, a "strong dislike of one's sexual anatomy" is one of the diagnostic criteria for gender dysphoria in children (according to DSM-5), and so in this respect it is not clear how the dysphoria had been resolved … Now aged 48, FG has given two recent interviews. FG's situation seems to have improved, and he now has a serious girlfriend. He describes puberty suppression as "life-saving" in his case … but also recommends that it should require a significant assessment process.[59]

3.6 The spread of the Dutch Protocol and the rise of "gender-affirming care"

In the United States, HBIGDA endorsed puberty blockers in their sixth version of their clinical guideline, the *Standards of Care* (SOC-6, 2001):

> Two goals justify this intervention: a) to gain time to further explore the gender identity and other developmental issues in psychotherapy; and b) to make passing easier if the adolescent continues to pursue sex and gender change. In order to provide puberty delaying hormones to an adolescent, the following criteria must be met:

[56] Bakker (2021, p. 121).
[57] In fact, surgery was mandatory until 2014 (Gregory, 2021).
[58] Cohen-Kettenis et al. (2011).
[59] Biggs (2023b, p. 355).

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1. throughout childhood the adolescent has demonstrated an intense pattern of cross-sex and cross-gender identity and aversion to expected gender role behaviors;

2. sex and gender discomfort has significantly increased with the onset of puberty;

3. the family consents and participates in the therapy.[60]

SOC-6 also erroneously characterized PBs as "fully reversible" (see Chapter 7). As Biggs points out, "the published evidence for the benefits of puberty suppression then comprised a single case study of one patient—FG—awaiting final surgery."[61]

In the U.S., PBs were first prescribed for GD at Boston Children's Gender Management Service (GeMS, now Gender Multispeciality Service) around 2007, with the U.K.'s Gender Identity Development Service (GIDS) following four years later.[62] GeMs did not set a minimum age limit, and in 2015 neither did the U.K.'s National Health Service.[63] The relatively strict gatekeeping of the Dutch Protocol soon gave way to a more patient-led approach (see Section 4.1. and Chapter 11). This occurred not just in the U.S. but other countries, including the U.K.:

> From 2014, puberty blockers moved from a research-only protocol to being available through routine clinical practice … In addition, the strict inclusion criteria of the Dutch protocol were no longer followed, and puberty blockers were given to a wider range of adolescents … These included patients with no history of gender incongruence prior to puberty, as well as those with neurodiversity and complex mental health presentations.[64]

HBIGDA became the World Professional Association of Transgender Health (WPATH) in 2007. Reflecting in 2009 on the "new paradigms [that] have emerged about the nature

[60] Harry Benjamin International Gender Dysphoria Association (2001, p. 10).
[61] Biggs (2023b, p. 353).
[62] GIDS was closed in March 2024; see also Barnes (2023).
[63] Biggs (2023b, p. 354).
[64] Cass (2024a, p. 73).

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of transgender identity and experience," Lin Fraser, then President-elect of WPATH, wrote:

> The new model views gender as a continuum rather than a male/female dichotomy and calls for individualized gender trajectories, which may or may not include hormonal therapy and sex reassignment surgery.[65]

The seventh version of the *Standards of Care* (SOC-7) was published in 2012 and was a significant departure from SOC-6, moving away from medical gatekeeping and towards the "gender-affirming" model. For example, SOC-6 recommended that CSH be given only to patients aged 18 or older, who either had "real-life experience" ("living in the desired gender") or had been in psychotherapy for at least three months. SOC-7 had no age limit for CSH, only requiring that the adolescent give "informed consent" and that the parents or guardians have also "consented to the treatment and are involved in supporting the adolescent." Recommendations for psychotherapy or real-life experience were absent. SOC-7 effectively relegated the role of mental health professionals to provide assessments needed by insurance companies for reimbursement.

Another change was apparent from SOC-7's title. SOC-6 was the standards of care "for Gender Identity Disorders," but SOC-7 was "for the Health of Transsexual, Transgender, and Gender Nonconforming People." "Non-binary" would have to wait its turn, appearing for the first time in the current guideline, SOC-8 (2022), with a chapter dedicated to it.[66] The first version of the *Standards of Care* was authored by just six people and comprised slightly over 3,000 words; SOC-8 has more than 100 contributors and more than 100,000 words.

In 2011, Cohen-Kettenis and colleagues published a follow-up study of 70 adolescent patients who received PBs in the Netherlands between 2000 and 2008. The results

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[65] Fraser (2009, pp. 113-114, citations omitted). One of the citations omitted from the quotation is *The Apartheid of Sex: A Manifesto on the Freedom of Gender*, by Martine Rothblatt. Chapter 1 of that book is called "Five Billion Sexes," and begins: "There are two sexes, male and female, right? Wrong! In fact, there is a continuum of sex types, ranging from very male to very female, with countless variations in between" (Rothblatt, 1995, p. 1).

[66] A 2020 survey of U.S. youth aged 13-24 who identified as LGBTQ found that, of the 11,914 who identified as transgender or non-binary, more than 60% identified as the latter (A. E. Green et al., 2022, p. 645).

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were interpreted as encouraging: “Behavioral and emotional problems and depressive symptoms decreased, while general functioning improved significantly during puberty suppression.”[67] A 2014 study of the same patient cohort after sex reassignment surgery—but with just 55 of the original 70 subjects—contained a similarly positive conclusion: “After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved.”[68] These two studies form the foundational evidence base of the Dutch Protocol, and are widely cited to support it. (As subsequent analysis revealed, they do not: see Section 4.3.6.)

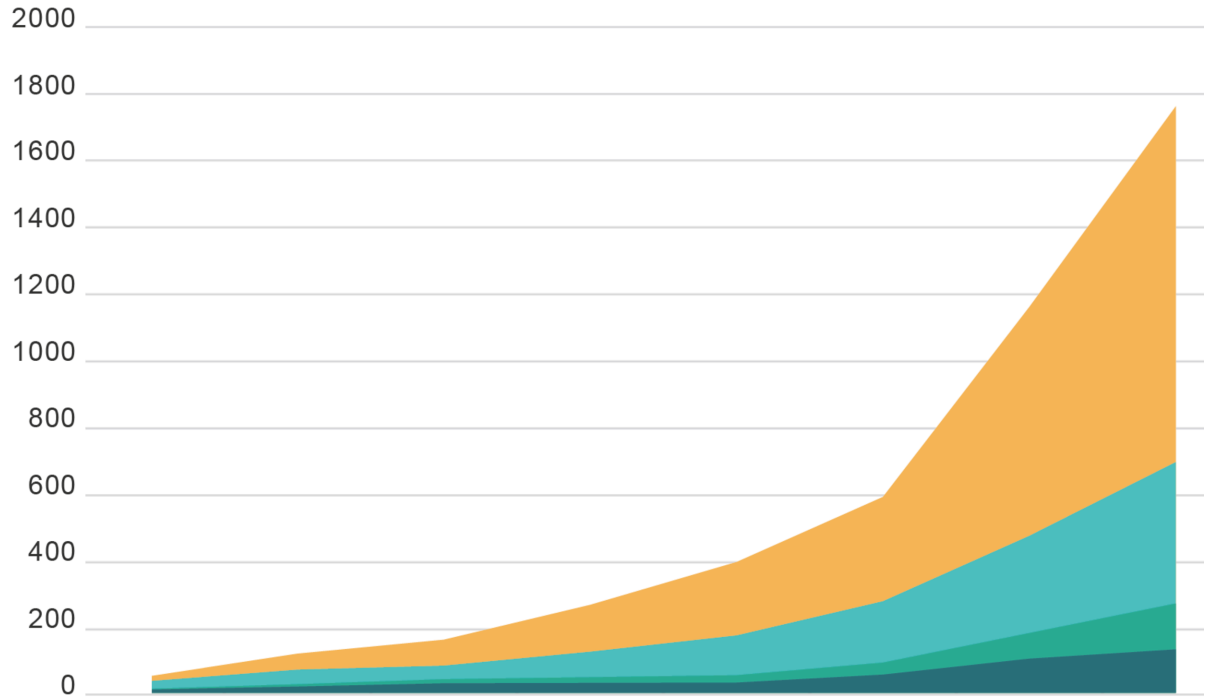
The previously observed tendency for early-onset GD patients to be gay continued with the Dutch cohort. Of the initial group of 70, only one reported heterosexuality; the other 69 reported either homosexuality (62), bisexuality (six), or “don’t know yet” (one).[69] (See also Section 13.3.1.)

Around the time Cohen-Kettenis and colleagues published their first study, clinicians started to observe a rapid increase in the pediatric patient population. More notably, the demographic profile of these patients was shifting, with adolescent females emerging as the predominant group. This trend is illustrated in Figure 3.1, which charts referrals to GIDS from 2009 to 2016.

[67] de Vries et al. (2011, p. 2276).
[68] de Vries et al. (2014, p. 696).
[69] de Vries et al. (2011, Table 1).

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Figure 3.1: Sex ratio in children and adolescents referred to GIDS in the U.K. (2009-16)[70]



	2009	2010	2011	2012	2013	2014	2015	2016
Adolescent F	15	48	78	141	221	314	689	1071
Adolescent M	24	44	41	77	120	185	293	426
Children F	2	7	12	17	22	36	77	138
Children M	10	19	29	30	31	55	103	131

In a related trend, Western countries began reporting a growing number of adolescents who, often unexpectedly, disclosed a transgender identity—frequently to the surprise of their parents.[71] The number of pediatric patients seeking medical transition can only be roughly estimated,[72] but the demand in European countries has outstripped supply, with waitlists approaching 2 years or longer. In response to the growing demand, the U.S.—characterized by its decentralized and privatized healthcare system—saw the

[70] Reproduced from Cass (2024a, p. 70); original in de Graaf et al. (2018, Figure 1).
[71] See Section 4.3.1.4.
[72] According to the Human Rights Campaign (HRC), "there are more than 300,000 high school-aged (ages 13-17) transgender youth in the United States today, *many of whom need gender-affirming care*" (Human Rights Campaign, n.d.), emphasis added). See also Williams Institute (2024).

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emergence of many new specialty gender clinics, along with a proliferation of independently practicing clinicians.[73] According to a recent conservative estimate, as of March 2023 there were 271 clinics offering PMT in the U.S., though 70 were inactive due to legislative restrictions.[74]

As clinical experience with treating youth with GD across the world has grown, concerns about the PMT model have become increasingly apparent. In response, public health authorities in several European countries have launched formal investigations into the practice. The most comprehensive is the U.K.'s 2024 Cass Review, mentioned in Chapter 1. As a result of such inquiries, some European health authorities are now restricting eligibility for medical transition and implementing new research requirements and safeguards. In the U.S., where government health authorities play a more limited role, and medical practice is primarily regulated at the state level, many states have turned to legislative measures to restrict or prohibit pediatric medical transition.[75]

As Hilary Cass observed in 2022, "it is not helpful to exceptionalise gender identity issues."[76] The consensus in pediatric gender medicine (PGM) of 10 years ago was driven by that exceptionalization, which has now begun to change. The following chapter explains why this change is underway.

[73] Levine et al. (2022a, p. 708).
[74] Borah et al. (2023, pp. 375-376).
[75] Harmon (2024).
[76] Cass (2022b).

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Chapter 4 International Retreat from the "Gender-Affirming" Model

Since the publication of the Dutch Protocol in 2006, the practice of "gender-affirming" (or "affirmative" care) has rapidly expanded. Now, a global reversal is underway. Several national health authorities have restricted hormonal and surgical interventions for minors. Section 4.1 provides a brief overview of the rise of pediatric medical transition (PMT) as the primary response to childhood and adolescent gender dysphoria (GD). Section 4.2 summarizes the ongoing practice reversal that is now taking place in an increasing number of countries. Section 4.3 explores the reasons behind these reversals.

4.1 The rise of the affirmative care model

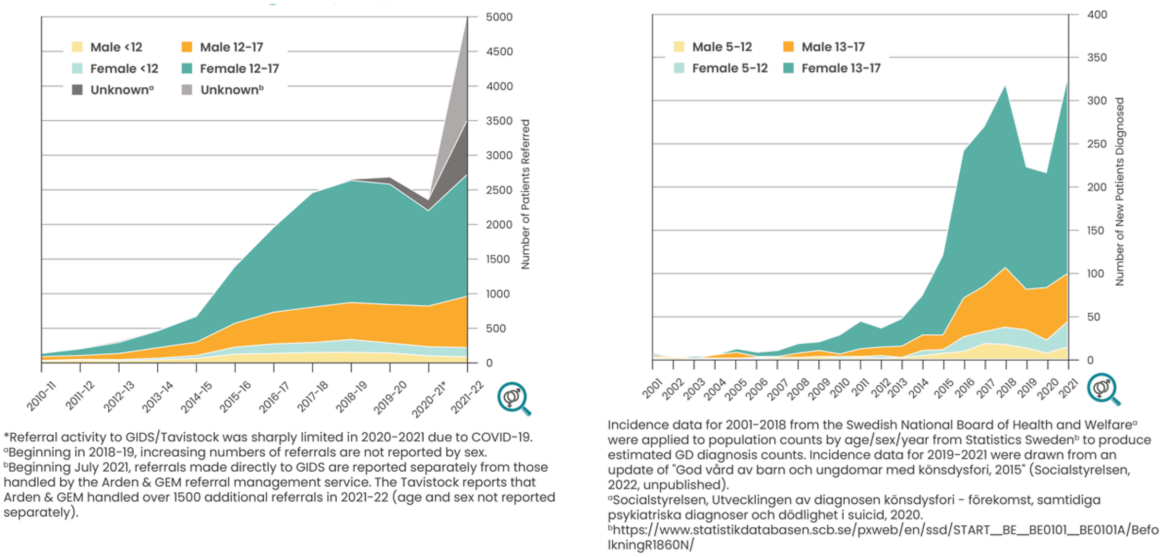
Following the publication of the Dutch Protocol in 2006,[1] puberty blockers (PBs) and cross-sex hormones (CSH) were incorporated into the Endocrine Society's 2009 clinical practice guideline (CPG),[2] which recommended that hormonal interventions should be used for certain pediatric patients with GD. This approach was also recommended by the World Professional Association for Transgender Health's (WPATH) guidelines in 2012.[3] Notably, these endorsements occurred before the final analysis of psychological outcomes from the original Dutch cohort was published in 2014[4]—and several years before the first systematic reviews of evidence (SRs) commissioned by public health authorities began to appear in 2019 and 2020.[5] During this same period, the number of children and adolescents reporting symptoms of GD and seeking medical intervention surged—a trend that has since become widespread across Western countries. At the same time, the epidemiological profile of patients changed markedly: while earlier

[1] Delemarre-van de Waal & Cohen-Kettenis (2006). Outcomes from the first patient cohort treated according to the protocol were published in 2011 and 2014 (de Vries et al., 2011, 2014).
[2] Hembree et al. (2009).
[3] The 2012 guidelines were the organization's seventh CPG (Coleman et al., 2012). The fifth and sixth CPGs, published in 1998 and 2001, briefly mentioned the potential use of "LHRH agonists" (Levine et al., 1998; Harry Benjamin International Gender Dysphoria Association, 2001), but the use of PBs as the central part of the treatment for adolescents did not emerge until the seventh version.
[4] de Vries et al. (2014).
[5] National Institute for Health and Care Excellence (2020b, 2020a); Pasternack et al. (2019).

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cohorts consisted mainly of prepubertal boys, more recent referrals have been dominated by teenage girls (see Figure 4.1 below).

Figure 4.1: Child and adolescent referrals for GD (U.K., left; Sweden, right)[6]



*Referral activity to GIDS/Tavistock was sharply limited in 2020-2021 due to COVID-19.
[a]Beginning in 2018-19, increasing numbers of referrals are not reported by sex.
[b]Beginning July 2021, referrals made directly to GIDS are reported separately from those handled by the Arden & GEM referral management service. The Tavistock reports that Arden & GEM handled over 1500 additional referrals in 2021-22 (age and sex not reported separately).

Incidence data for 2001-2018 from the Swedish National Board of Health and Welfare[a] were applied to population counts by age/sex/year from Statistics Sweden[b] to produce estimated GD diagnosis counts. Incidence data for 2019-2021 were drawn from an update of "God vård av barn och ungdomar med könsdysfori, 2015" (Socialstyrelsen, 2022, unpublished).
[a]Socialstyrelsen, Utvecklingen av diagnosen könsdysfori - förekomst, samtidiga psykiatriska diagnoser och dödlighet i suicid, 2020.
[b]https://www.statistikdatabasen.scb.se/pxweb/en/ssd/START__BE__BE0101__BE0101A/BefolkningR1860N/

The scientific foundation for the rapid expansion of PMT was largely underpinned by two Dutch studies, published in 2011 and 2014,[7] which followed the same patient cohort. The first study, which focused on the use of PBs,[8] reported psychological outcomes in 70 adolescents who had completed the PB phase and were beginning CSH. The findings suggested modest "pre-post" improvements in some mental health measures following PB treatment—but notably, no improvement in GD itself, as assessed by the newly developed Utrecht Gender Dysphoria Scale (UGDS).

For more than a decade, many of the study's methodological flaws remained largely overlooked. One of the study's limitations was its retrospective selection of 70 subjects from a larger "intent-to-treat" group of 111 using non-randomized methods. This selection process inadvertently biased the sample toward cases with the most favorable prognoses, thereby limiting the generalizability of the study's findings.[9]

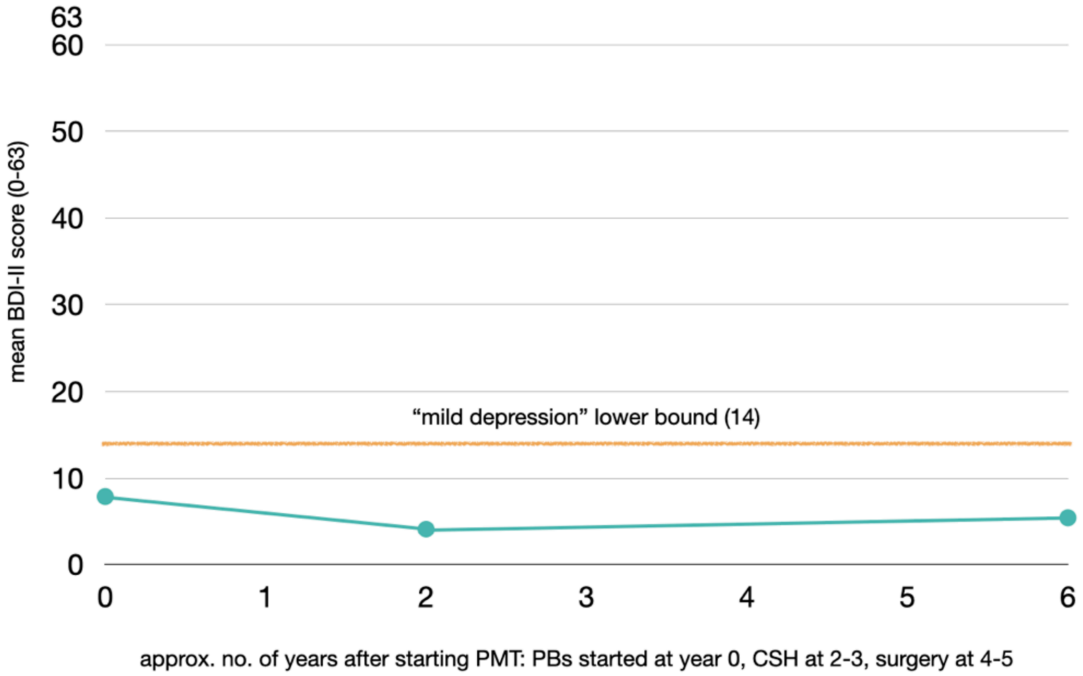
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[6] Source: Society for Evidence-Based Gender Medicine (SEGM).
[7] de Vries et al. (2011, 2014).
[8] de Vries et al. (2011).
[9] The study's inclusion criteria defined eligibility for analyzing the effects of puberty blockers (PBs) based on the start date of the subsequent phase—CSH. This approach introduced significant bias by excluding,

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In 2014, a follow-up study was published assessing the participants' functioning after CSH and surgery.[10] The sample size was further reduced to just 55 participants, and critical measures of psychological health—such as depression, anxiety, and overall functioning—were assessed in as few as 32 participants. Moreover, although the reported improvements reached statistical significance, their clinical relevance was limited (see the depression scores plotted in Figure 4.2: the orange line indicates the *threshold* for "mild depression," with 63 being the maximum score; mean scores remained below the mild depression threshold at baseline and throughout treatment).

Figure 4.2: Depression scores in Dutch cohort[11]



Noting the high-functioning status of the adolescent/young adult cohort at the end of the study, the authors concluded that the Dutch Protocol provided patients with "the

from the outset, any subjects who discontinued treatment, underrepresenting psychologically complex cases who remained in the "diagnostic" PB phase for longer periods, and skewing the sample toward older subjects. Because eligibility hinged on starting CSH at 16, only those who reached this threshold were included—potentially explaining why the average age for initiating PBs in the study was 15, despite the protocol recommending initiation around age 12 (Abbruzzese et al., 2023).

[10] de Vries et al. (2014).

[11] Graph of data contained in de Vries et al. (2011) and de Vries et al. (2014).

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opportunity to develop into well-functioning adults."[12] The study failed to consider that the subjects were already high-functioning at baseline—comparable to Dutch peers without GD.[13] This was likely attributable, at least in part, to the original Dutch Protocol's stringent selection criteria.

Moreover, the study failed to account for or appropriately consider potential signals of harm. One participant died due to post-surgical treatment complications associated with early pubertal suppression,[14] at least three were diagnosed with uncontrolled diabetes or morbid obesity while on hormones, and at least one subject discontinued treatment.

These and other serious limitations—including subject selection bias and methodological flaws (such as the post-treatment reversal of the UGDS[15])—remained largely unacknowledged, even as the study became the foundational pillar[16] of PMT protocols worldwide. Attempts to replicate the Dutch findings regarding PBs in the U.K. were unsuccessful[17]—and the publication of those unfavorable results was delayed for several years.[18] It has also been reported that the attempts to replicate the benefits of PBs in a National Institutes of Health (NIH)-funded study in the U.S. yielded less-than-favorable results.[19]

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[12] de Vries et al. (2014, p. 696).
[13] As explained in Abbruzzese et al. (2023), the requirement of psychological stability was built into the protocol, and earlier research from the same clinic had stated that "when both pre- and posttest group means were compared with Dutch normative data, all scores turned out to be within the average range" (Smith et al., 2001, p. 277).
[14] de Vries et al. (2014) noted that "1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis" (p. 697). A 2023 analysis of the original Dutch papers found that the researchers "did not mention the fact that this death was a consequence of puberty suppression: the patient's penis, prevented from developing normally, was too small for the regular vaginoplasty and so surgery was attempted with a portion of the intestine, which became infected" (Biggs, 2023b, p. 8). See also Negenborn et al. (2017).
[15] The reversal of the GD scale post-surgery may have entirely invalidated the study's key finding of the resolution of GD post-treatment (Abbruzzese et al., 2023). Of note, another clinical research study in this field (López de Lara et al., 2020) also switched GD and body image scales.
[16] One of the authors of the original Dutch research noted, in 2022, that those papers are "still used as main evidence for provision of early medical intervention including puberty blockers in transgender youth" (de Vries, 2022, p. 109). The Cass Review's final report described that instead of the usual, slow evolution of clinical practice over "many years before strongly positive research findings are incorporated … the reverse happened in the field of gender care for children. Based on a single Dutch study … the practice spread at pace to other countries …" (Cass, 2024a, p. 13).
[17] Carmichael et al. (2021).
[18] See Chapter 6.
[19] Ghorayshi (2024c).

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Spurred on by the belief in the success of the Dutch Protocol and its central premise—reliance on PBs —the expanding availability of PMT services was met by a surge in demand: "first gradually, then suddenly."[20] By 2015, nearly every European country was reporting a dramatic increase in the number of gender-dysphoric youth seeking hormonal interventions at pediatric gender medicine (PGM) clinics—a trend whose underlying cause remains the subject of ongoing debate. The endorsement of PMT was further solidified by the publication of the 2017 Endocrine Society (ES) guidelines,[21] co-authored by psychologist Peggy Cohen-Kettenis—the pioneer of the original Dutch Protocol—who had first introduced the recommendations for PMT into the 2009 ES guidelines, and later reinforced them in the 2012 WPATH *Standards of Care 7* guidelines (SOC-7).[22]

One striking characteristic of the surge of adolescents presenting with a wish to undergo medical transition is the disproportionate number of female adolescents without prior childhood history of GD who present with high rates of comorbid mental health conditions. This pattern drew the attention of Finnish researchers, who were the first to publish on these changing demographics and to raise concerns that the Dutch Protocol might not be helping—and might even be harming—patients.[23] Finland subsequently became the first country to revise its national guidelines,[24] sharply limiting medical interventions based on the findings of an SR.[25] In the years that followed, other countries began conducting their own evaluations of the evidence and arrived at similar conclusions. A global trend has since emerged, away from use of PBs, CSH, and surgeries in youth with GD. This ongoing reversal is explored in greater detail in the following section.

4.2 The international practice reversals

Starting in 2020, PMT began to face growing scrutiny from public health authorities worldwide, resulting in substantial reversals of clinical protocols in an increasing number

[20] Abbruzzese et al. (2023, p. 12).
[21] Hembree et al. (2017).
[22] Coleman et al. (2012); Hembree et al. (2009).
[23] Kaltiala et al. (2020); Kaltiala-Heino et al. (2015).
[24] Council for Choices in Health Care Finland (2020a, 2020b, 2020c).
[25] Pasternack et al. (2019).

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of countries. The most influential effort to date has been the Cass Review—a four-year independent evaluation of PGM that was published in April 2024.[26] The findings of the Cass Review led to the closure of the U.K.'s PGM clinic, the Gender Identity Development Service (GIDS), which had been given a rating of "inadequate" by the Care Quality Commission in 2021.[27] The Cass Review recommended a restructuring of the care delivery model—away from the centralized "gender clinic" model of care toward a more holistic framework centering psychosocial support, to be delivered through regional hubs. The Cass Review's findings also led the U.K. to ban the use of PBs outside clinical trials,[28] and to significantly restrict CSH.[29] While CSH are still officially an available treatment, the National Health Service (NHS) recently revealed that since the Cass Review was published, no minor has been found eligible to receive CSH according to the updated policy.[30] In the U.K., minors have never received GD-related surgery through the NHS.

Finland was the first country to curtail PMT, issuing revised national guidelines in 2020.[31] In 2022, Sweden's National Board of Health and Welfare concluded that, for most young people, the potential harms of hormonal interventions outweigh the benefits, and subsequently restricted both to research settings or exceptional cases.[32] Denmark followed Sweden's lead in 2023, restricting the use of endocrine intervention in minors,[33] and Norway's public health agency (the Norwegian Healthcare Investigation Board) advised that PBs and CSH should be considered experimental treatments.[34] Most recently, hormonal interventions have been restricted in Brazil,[35] Chile,[36] the province of Alberta in Canada,[37] and the state of Queensland in Australia.[38]

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[26] Cass (2024a).
[27] Care Quality Commission (2021).
[28] Department of Health and Social Care (2024).
[29] National Health Service England (2024c).
[30] Spencer (2025).
[31] Council for Choices in Health Care Finland (2020a, 2020b, 2020c).
[32] Socialstyrelsen (2022a, 2022b, 2022c).
[33] Hansen et al. (2023). See also Society for Evidence-Based Gender Medicine (2023b).
[34] Block (2023b).
[35] AFP (2025).
[36] Lane (2024).
[37] Government of Alberta (2024).
[38] Australian Associated Press (2025).

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At the same time, several other countries are in the process of determining how best to care for youth with GD. In Australia, following Queensland's statewide pause in January 2025 on initiating PBs and CSH for new patients under 18, the Australian Government commissioned the National Health and Medical Research Council with developing new clinical practice guidelines for youth with GD. The guidelines are expected to be completed within three years, with interim recommendations on PBs available in 2026.[39] In Italy, the Italian Bioethics Committee updated its position on the use of PBs for GD,[40] and a formal guideline development process is underway.[41] France is expected to release new national guidelines in 2025, which are expected to spark considerable debate due to anticipated endorsement of PMT[42]—a position previously criticized by the French National Academy of Medicine.[43]

Germany recently published guidelines[44] that continue to generate considerable debate in German-speaking countries, including Austria and Switzerland. The controversy stems from concerns about the non-evidence-based nature of the recommendations, their *a priori* reliance on WPATH positions, and deep divisions in the professional community[45] regarding the appropriate approach to caring for youth with GD. Even the Netherlands—the birthplace of the Dutch Protocol—has not been immune to debate.[46] In May 2024, the Dutch Minister for Medical Care formally requested that the Health Council of the Netherlands produce an independent scientific advisory report on healthcare for minors with GD. This ongoing review will include an evaluation of the Dutch Protocol and a comparison with other countries' guidelines.[47]

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[39] Australian Government National Health and Medical Research Council (2025).
[40] Italian National Bioethics Committee (2024). See also Society for Evidence-Based Gender Medicine (2024d).
[41] Curridori (2024).
[42] Sugy (2024).
[43] Society for Evidence-Based Gender Medicine (2022a).
[44] German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP) (2025).
[45] Zepf, Buchmann, et al. (2024).
[46] Society for Evidence-Based Gender Medicine (2023c).
[47] Health Council of the Netherlands (2024).

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4.2.1 The Cass Review and its reception

The Cass Review has had a profound influence on international debates. Commissioned by NHS England, the Cass Review assessed the safety, efficacy, and delivery of PGM services for children and adolescents. Conducted over four years under the leadership of Hilary Cass, pediatrician and a past president of the Royal College of Paediatrics and Child Health, the review engaged a broad range of stakeholders and relied on SRs from the National Institute for Health and Care Excellence (NICE)[48] and the University of York,[49] as well as additional research. The Cass Review identified significant limitations in the evidence base for PBs and CSH. It recommended that PBs be offered only as part of a clinical trial until further data are available, and that all potential interventions should be tested within a research context.[50] The review emphasized a multidisciplinary, developmentally-informed model of care for youth with GD that prioritizes psychological support and the development of "an explicit clinical pathway … for non-medical interventions."[51]

Recent criticisms of the Cass Review—particularly claims that it fails to meet CPG standards—reflect a misunderstanding of the Cass Review's purpose and scope. The Cass Review was not a CPG; it was an "independent review." This is a U.K.-specific process of conducting a service-level evaluation intended to inform policy, not prescriptive clinical decisions. Such processes are invoked when an area of clinical care begins to operate in ways that compromise care quality and threaten patient safety.[52]

Criticism of the Cass Review appears to stem largely from a U.S.-based group of motivated advocates for the continued legality of PMT.[53] The critiques are ridden with

[48] National Institute for Health and Care Excellence (2020a, 2020b).
[49] Hall et al. (2024); Heathcote et al. (2024); Taylor, Hall, Heathcote et al. (2024a, 2024b); Taylor, Hall, Langton et al. (2024a, 2024b); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024).
[50] "The overarching conclusion from the evidence presented in this Review is that the puberty blocker trial, which is already in development, needs to be one part of a much broader research programme that seeks to build the evidence on all potential interventions, and to determine the most effective way of supporting these children and young people" (Cass, 2024a, p. 197). See "Recommendation 6" (Cass, 2024a, p. 35).
[51] Cass (2024a, p. 157).
[52] Cheung et al. (2025).
[53] Of these, the white paper McNamara et al. (2024), produced by the Yale Integrity Project, has been most influential.

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misrepresentations of the Cass Review and contain multiple factual errors.[54] In the U.K., the Cass Review has been widely accepted as a foundational document for realigning pediatric gender medicine (PGM) with the principles of evidence-based medicine (EBM) and child safeguarding.[55] It has been welcomed by both major political parties in the U.K., and was fully accepted by the NHS for implementation, which is well underway.[56]

4.3 Rationale for international reversals

A defining feature of these global reversals has been the rejection of the "gender clinic" model, which typically promotes PMT. Internationally, this model is increasingly being supplanted by more traditional, holistic approaches to adolescent distress. Rather than referring youth with GD to specialty clinics oriented toward transition, emerging models emphasize standard mental health services, where young people receive comprehensive psychosocial and psychotherapeutic support—and, when indicated, psychiatric care.

The global reversals away from PMT can be attributed to six main factors: a significant shift in the patient population; uncertainty surrounding the natural history and prognosis of GD; increasing recognition of the risks associated with medical interventions; a more accurate understanding of the suicide risk; the collapse of the original treatment rationale; and a weak underlying evidence base. The following subsections (1-6) examine each of these factors in turn.

4.3.1 Changes in the patient population

The population of young people for whom the Dutch Protocol was originally developed differs significantly from those presenting for care today.

4.3.1.1 Epidemiological shifts

Over the past decade, the population presenting to PGM clinics has changed in two key ways: a rapid increase in numbers and a significant shift in demographic composition. Before hormonal interventions became widely available, pediatric referrals for GD were

[54] Cheung et al. (2025); McDeavitt et al. (2025).
[55] Abbasi (2024).
[56] National Health Service England (2024a).

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relatively rare,[57] and the majority were prepubertal boys with early-onset GD.[58] Over the past decade, the increase in patients has been described as exponential,[59] a trend driven primarily by adolescent females who typically have no childhood history of GD.[60]

4.3.1.2 Mental illness and neurodevelopmental diagnoses

The current patient population has a high rate (relative to the general population) of comorbid mental health problems, including depression, anxiety, suicidality, self-harm, and eating disorders; as well as neurodevelopmental conditions like autism spectrum disorder (ASD).[61] Importantly, register-based research conducted in Finland, which has national databases, found that 75% of patients presenting to PGM clinics in the mid-2010s had severe mental health problems that appeared to have *predated* the emergence of GD.[62] High rates of comorbid mental illness have been documented in the U.S. and other countries.[63]

The high prevalence of ASD among youth presenting with GD has been recognized for some time.[64] At the U.K.'s clinic, ~35% of patients had comorbid moderate-to-severe autistic traits (compared to <2% of the general population).[65] Although some researchers have postulated that the social difficulties in youth with these co-occurring conditions may not result from ASD but instead from GD and may be ameliorated by targeting this distress,[66] limited research thus far has not supported this hypothesis.[67] In

[57] For example, the U.K.'s clinic saw 12 total patients in 1994 and 24 in 1996; it saw 150 total patients between its opening in 1989 and the year 2000 (Barnes, 2023, pp. 15-16).
[58] Steensma et al. (2018).
[59] E.g. Coleman et al. (2022, p. S9, S43); Baker & Restar (2022); de Vries et al. (2021); Olson-Kennedy, Okonta et al. (2018). The figure in McDeavitt et al. (2025) shows that the rate of increase in referrals to the U.K.'s clinic (for example) is well-approximated by an exponential. A Reuters investigation did not describe exponential growth but did find that referrals to PGM clinics have sharply increased in the U.S. (Respaut & Terhune, 2022).
[60] See Kaltiala-Heino et al. (2015, 2018); Taylor, Hall, Langton et al. (2024b); Thompson et al. (2022a); Wagner et al. (2021); Wood et al. (2013); Zhang et al. (2021). One study in this field claimed that there was no disproportionate increase in female adolescents (Turban, Dolotina et al., 2022). However, this finding was based on a survey in which there was "uncertainty as to whether transgender students responded to the sex question with their sex or gender identity" (Johns et al., 2019).
[61] See Becerra-Culqui et al. (2018); Kaltiala-Heino et al. (2015), (2018); Kozlowska et al. (2021); Taylor, Hall, Langton, Fraser, et al. (2024b); Thompson et al. (2022b).
[62] Kaltiala-Heino et al. (2015).
[63] E.g., Becerra-Culqui et al. (2018); Kozlowska et al. (2021).
[64] E.g. de Vries et al. (2010); Strang et al. (2018).
[65] Barnes (2023, p. 156).
[66] E.g., Ehrensaft (2016); Edwards-Leeper & Spack (2012); J. L. Turban (2018).
[67] Russell et al. (2021).

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2018, recognizing the clinical entity of co-occurring GD and ASD traits, researchers published preliminary guidelines for this specific population of children and adolescents,[68] recommending that "due to differences in social communication, insight and flexible thinking … extended diagnostic periods should be considered in cases where [ASD] is suspected or diagnosed."[69]

4.3.1.3 Nonbinary identities

The original Dutch research did not study patients with nonbinary identities; such patients were not deemed to be appropriate candidates for medical transition.[70] However, nonbinary identities now feature prominently in contemporary clinical settings and research populations. In a 2020 research project funded by the Trevor Project, for example, 63% of the 11,914 survey respondents identified as nonbinary.[71] In a study of youth who received mastectomies, 11% identified as nonbinary or "other."[72] This creates a new set of ethical challenges, as patients seek interventions that have never before been contemplated, including keeping patients in puberty-suppressed states for extended periods of time to allow them to maintain a sex-ambiguous appearance. The risks of such interventions may be considerable.[73]

4.3.1.4 Social influence

The role of social influence is a likely factor in these epidemiological changes. In 2018, physician and researcher Lisa Littman popularized the phrase "rapid onset gender dysphoria," or ROGD, in the peer-reviewed literature, describing the clinical picture of

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[68] Strang et al. (2018).
[69] See description in Russell et al. (2021, p. 2074). In contrast to the 2018 Dutch guidelines that recommended more caution for patients with co-occurring ASD, leading specialists in the United States have criticized parents who are reluctant to consent to PMT for their autistic children. They have proposed clinicians "depend on drawings" for severely autistic, nonverbal adolescents who cannot speak but are able to draw pictures (Transparency Podcast, n.d.). See also: whistleblower account of therapist Tamara Pietzke (Section 11.4.3).
[70] de Vries et al. (2006, p. 88): "Adolescents whose wish for sex reassignment seems to originate from factors other than a genuine and complete cross-gender identity are served best by psychological interventions."
[71] A. E. Green et al. (2022).
[72] Ascha et al. (2022).
[73] In 2020, researchers published a case report in which clinicians considered the possibility of keeping an "agender" patient with low bone density on PBs for at least seven years in order to provide affirmation for this identity (Pang, Notini, et al., 2020). Contemporary WPATH guidelines have eliminated barriers to hormonal interventions and surgeries for minors with nonbinary and other identities.

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"adolescent-onset or late-onset gender dysphoria where the development of gender dysphoria is observed to begin suddenly during or after puberty in an adolescent or young adult who would not have met criteria for gender dysphoria in childhood."[74] This phenomenon has also been described in research from the U.K.,[75] the Netherlands,[76] Finland,[77] and Canada.[78] Other terms have been used—e.g. "adolescent onset gender dysphoria," "postpuberty adolescent-onset transgender histories"[79]—for pubertal-onset gender dysphoria disproportionately affecting female adolescents.

Research into experiences of detransition and regret (detransition refers to stopping or reversing transition after having received medical and/or surgical interventions; it can overlap with but is not synonymous with regret) have suggested social influence or pressure have played a role in the transient transgender identifications of some patients.[80] Concerns about the possible role of social influence underlying epidemiological shifts in presentations have been articulated elsewhere in the literature,[81] including by some proponents of PMT.[82] WPATH's guidelines note that "susceptibility to social influence impacting gender may be an important differential to consider" for some adolescents; the guidelines also acknowledge "situations in which a young person experiences very recent or sudden self-awareness of gender diversity and a corresponding gender treatment request, or when there is concern for possible excessive peer and social media influence on a young person's current self-gender concept."[83]

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[74] Littman (2018, p. 2). This research surveyed 256 parents of children with adolescent-onset GD, finding that in roughly half the cases, the rapid onset of GD appeared to have coincided with the onset of similar distress within the children's friend groups, and with an increase in social media/Internet use. "Rapid onset gender dysphoria" appeared in scholarly work a year earlier, in a poster abstract by Littman in the *Journal of Adolescent Health* and (following Littman's research) also in Marchiano (2017).
[75] de Graaf et al. (2018); Hutchinson et al. (2020).
[76] de Vries (2020).
[77] Kaltiala-Heino et al. (2018); Kaltiala-Heino & Lindberg (2019).
[78] Zucker (2019).
[79] Kaltiala-Heino & Lindberg (2019); de Vries (2020).
[80] Littman (2021); Littman et al. (2024).
[81] Bailey & Diaz (2023); Wood et al. (2013).
[82] Edwards-Leeper & Anderson (2021); Shrier (2021b).
[83] Coleman et al. (2022, p. S45, S58).

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4.3.2 Unclear natural history and prognostic uncertainty

Prior to the widespread availability of hormonal interventions, most cases of childhood GD resolved naturally by the end of puberty, with the majority of patients having a homosexual sexual orientation in adulthood.[84] The Dutch Protocol was developed on the assumption that only GD that persisted into adolescence would likely be permanent.[85] As referrals shifted toward patients with adolescent-onset distress, this assumption of permanence was generalized to all adolescent GD regardless of whether it *intensified* in adolescence or *appeared for the first time* in adolescence. The belief that any GD in adolescence is likely permanent and warrants medical treatment remains "central to the rationale for medical intervention" in adolescents.[86]

4.3.2.1 New evidence about the natural history of gender dysphoria

Recent close examination of the literature has called into question the assumptions regarding the permanence of adolescent GD.[87] Although the natural history of GD—i.e., its course absent medical interventions—is currently impossible to measure given the wide availability of interventions, new evidence suggests that GD has a low diagnostic stability. For example, a German longitudinal analysis of an insurance claims database showed that over 70% of adolescent females aged 15-19 no longer had the diagnosis

[84] The largest such study was Singh et al. (2021), which included a comprehensive overview of prior research on persistence of childhood GD (pp. 2-4). Some have argued that changes to diagnostic criteria—from the older "Gender Identity Disorder" (for which dysphoria, described as "discomfort," was a criterion) to the contemporary "Gender Dysphoria" diagnosis—render findings of older studies irrelevant (Temple Newhook et al., 2018). These arguments have been effectively countered (Zucker, 2018). (For the diagnostic criteria, see Appendix 2.) Low persistence rate of childhood GD has been recognized in the literature: e.g. "gender variant children, even those who meet the criteria for GID prior to puberty, for the most part are not gender dysphoric at a later age" (de Vries & Cohen-Kettenis, 2012, p. 306); also see Ristori & Steensma (2016, p. 6); Cohen-Kettenis & Gooren (1999).

[85] E.g. Cohen-Kettenis & Pfäfflin (2003); de Vries et al. (2006); de Vries & Cohen-Kettenis (2012); de Vries et al. (2014).

[86] Rosenthal (2021a, p. 585): "Longitudinal studies have indicated that the emergence or worsening of gender dysphoria with pubertal onset is associated with a very high likelihood of being a transgender adult. This observation is central to the rationale for medical intervention in eligible transgender adolescents."

[87] Byrne (2024a).

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five years later.[88] Another recent study from the Netherlands found that "gender non-contentedness" continues to decline steadily into the early twenties.[89]

4.3.2.2 Concerns about identity development

There is considerable concern that "pubertal suppression may alter the course of gender identity development, essentially 'locking in' a gender identity that may have reconciled with biological sex during the natural course of puberty."[90] This concern is not new. Some early critics of the Dutch approach pointed out that initiation of hormonal interventions in early to mid-puberty "might affect the further development of gender identity, or … even iatrogenically induce persistence [of GD]."[91] In 2024, the European Academy of Pediatrics cautioned that puberty suppression may undermine long-term autonomy by creating a path dependency that leads to cross-sex hormones and surgery.[92] Several studies have suggested continuation rates from PBs to CSH exceed 90%.[93] The perception of PBs has shifted—from being seen as a reversible "pause button" to more like a "gas pedal" that accelerates medical transition.

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[88] Bachmann et al. (2024) was an insurance claims study looking at the International Classification of Diseases, tenth version (ICD-10) code F64 ("Gender Identity Disorder"), which was the billing code used in Germany over the course of the study period (Society for Evidence-Based Gender Medicine, 2024c). A recent *BMJ* analysis of claims data and medical records concluded that for some groups, including young people, "GD is not a permanent diagnosis" (Sun et al., 2023).

[89] Rawee et al. (2024, p. 1813). "Gender non-contentedness" was defined based on endorsement of item 110 in the Youth Self Report/Adult Self Report (YSR/ASR), "Wishes to be the opposite sex." Although item 110 is not synonymous with the diagnosis of GD, it is frequently used as a rough proxy for the clinical diagnosis as it captures the primary criterion of the desire to be the opposite sex. See Zucker (2005).

[90] Jorgensen et al. (2022, p. 1005). See also the Cass Review's final report: "Blocking [puberty] means that young people have to understand their identity and sexuality based only on their discomfort about puberty and a sense of their gender identity developed at an early stage of the pubertal process. Therefore, there is no way of knowing whether the normal trajectory of the sexual and gender identity may be permanently altered" (Cass, 2024a, p. 178).

[91] Korte et al. (2008, p. 839).

[92] Brierley et al. (2024).

[93] E.g., Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018). Some have claimed that "the most likely explanation for why most youth who receive early, supportive interventions [i.e., puberty blockers] continue onto gender-affirming hormone therapy [is] that they are indeed transgender. It is not ... puberty-pausing medications that drive a persistent transgender identity" (McNamara et al., 2024, pp. 20-21). However, the very research studies that comprise the evidence base in this area recognized the possibility that the intervention may induce persistence; e.g., "Due to the observational character of the study, it is not possible to say if [puberty blocker] treatment itself influenced the outcome" (Brik et al., 2020, p. 2611); "[there is] the potential that treatment could influence the continuation of their GD" (Carmichael et al., 2021).

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Social transition in childhood may have similar effects, with some low-quality studies suggesting the majority of children who socially transition[94] before puberty progress to medical interventions.[95] These patients "are likely [to] seek blockers or hormones."[96] Prepubertal transition was not recommended in the original Dutch approach (the researchers actually recommended *against* the practice),[97] but was originally championed by American clinicians.[98]

Prepubertal social transition is now recommended for certain patients, including in the Netherlands.[99] However, there are no reliable methods to distinguish which patients will experience long-term GD.[100] There is growing concern about administering irreversible treatments that may lead to lifelong medical dependency for a condition that, in many cases, may naturally resolve.

4.3.3 Concerns about treatment-associated risks and harms

Awareness of the risks and potential harms of PMT is growing.[101] Concern has been raised about the unknown or potentially harmful effects of suppressing normally timed puberty on adolescent physical and mental health, especially with regard to bone mineralization and brain development.[102] Hormonal interventions can lead to infertility and impaired sexual function, and in some cases, if the patient proceeds to genital

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[94] In this context, social transition refers to "a 'complete' binary social transition ... including changing their pronouns to the binary gender pronouns that differed from those used at their births" (Olson et al., 2022, p. 2), not to changes in hairstyle, clothing, etc.
[95] Olson et al. (2022, 2024). See also Society for Evidence-Based Gender Medicine (2022b).
[96] Olson et al. (2022, p. 4).
[97] E.g., "In a qualitative follow-up study, several youths indicated how difficult it was for them to realize that they no longer wanted to live in the role of the other gender and to make this clear to the people around them… Another reason we recommend against early transitions is that some children who have done so (sometimes as preschoolers) barely realize that they are of the other natal sex. They develop a sense of reality so different from their physical reality that acceptance of the multiple and protracted treatments they will later need is made unnecessarily difficult. Parents, too, who go along with this, often do not realize that they contribute to their child's lack of awareness of these consequences" (de Vries and Cohen-Kettenis, 2012, p. 308).
[98] E.g. Ehrensaft (2016); Olson et al. (2016).
[99] Bazelon (2022a).
[100] Cass (2024a, pp. 22, 134, emphasis added). "… clinicians have told us *they are unable to determine with any certainty* which children and young people will go on to have an enduring trans identity … Many clinicians, both nationally and internationally, have [acknowledged] that there is *no reliable way to accurately predict* which young people might benefit from a medical transition and which might benefit from alterative pathway(s) or interventions(s)."
[101] See Chapter 7 for detailed discussion.
[102] E.g., Baxendale (2024); Biggs (2021).

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procedures, riskier operations.[103] Surgical procedures themselves carry the risk of complications.

The emergence of detransitioners has brought renewed attention to a risk acknowledged in the original Dutch Protocol, which is that initiating medical transition while a young person's identity is still developing carries the risk of "false positives"—patients who undergo irreversible hormonal and/or surgical interventions but ultimately do not continue to identify as transgender.[104] In the past five years, a growing body of research and peer-reviewed literature has examined the phenomena of detransition and regret.[105] Personal accounts from detransitioned patients who report having been harmed by PMT have played a significant role in drawing public and regulatory attention to these issues.[106]

4.3.4 More appropriate understanding of suicide

Proponents of PMT often describe it as lifesaving.[107] Some physicians recommending PMT have urged anxious parents to consent to irreversible interventions for their distressed children, warning that not doing so may increase the risk of suicide.[108] Such claims are not supported by the evidence and have been criticized as unethical.[109]

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[103] See Lee et al. (2023), for example.
[104] Delemarre-van de Waal & Cohen-Kettenis (2006, p. S132). "It is conceivable that lowering the age limit increases the incidence of 'false positives.'"
[105] E.g. Entwistle (2020); Littman (2021); MacKinnon, Expósito-Campos et al. (2023); Roberts et al. (2022).
[106] According to a Reuters investigation, a patient told her gender clinic at age 16 that she was "sure of my identity … I thought nothing would change my mind." After starting CSH she experienced worsening mental health and had several suicide attempts and psychiatric hospitalizations. She detransitioned at age 20 and identifies as a lesbian: "I do wish my doctors had said to me, 'It's OK to feel disconnected from your body. It's OK to like girls. It's OK to be gender non-conforming'" (Respaut et al., 2022). For an overview of the role of detransitioner Keira Bell in drawing regulatory attention to pediatric gender medicine in the U.K., see Cass (2024a, pp. 78-80).
[107] E.g., ACLU (2021); Boerner (2022, 3/31/2025 update); Georges et al. (2024); Lee & Rosenthal (2023); Sandhu et al. (2025); Szilagyi (2022b); The Lancet Child & Adolescent Health (2021). See also Section 1.2.
[108] In 2011, Johanna Olson-Kennedy, pediatrician and leader in the field of pediatric gender medicine, told ABC News that "We often ask parents, would you rather have a dead son than a live daughter?" (ABC News, 2011). See also Singal (2018).
[109] E.g., Clayton (2023); Levine et al. (2022a).

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Adolescents and adults with GD do exhibit higher rates of suicidality—including suicidal thoughts, self-harm, and suicide attempts—compared to the general public.[110] However, completed suicide among adolescents with GD remains rare.[111] Moreover, there is no evidence that elevated suicidality can be attributed solely to GD, as it frequently co-occurs with other mental health conditions. A 2020 report by the Swedish National Board of Health and Welfare (Socialstyrelsen) concluded that "people with gender dysphoria who commit suicide have a very high rate of co-occurring serious psychiatric diagnoses, which in themselves sharply increase risks of suicide … it is not possible to ascertain to what extent GD alone contributes to suicide."[112]

Further, the evidence for whether PMT reduces *suicidality*-related outcomes in adolescents—such as self-reported frequency of suicidal thoughts, or healthcare utilization for self-harm or suicide attempts—is inconsistent.[113] When the focus turns to preventing *suicide mortality*, there is no evidence that hormonal interventions are effective. A large, register-based study from Finland found that overall suicide mortality in patients with GD was rare and that when mental health comorbidities were controlled for, the rate did not differ from that of the general population. The study authors concluded that hormonal interventions did not appear to have impacted suicide risk.[114] An SR of suicide prevention for youth with GD rated the evidence as low quality,[115] and WPATH's own SR of mental health outcomes, which focused on adult populations, acknowledged that "It was impossible to draw conclusions about the effects of hormone

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[110] E.g., Biggs (2022); Erlangsen et al. (2023); Heino et al. (2023); Marconi et al. (2023); Van Cauwenberg et al. (2021); Wiepjes et al. (2020).
[111] Biggs (2022); Ruuska et al. (2024); Society for Evidence-Based Gender Medicine (2023a).
[112] Socialstyrelsen (2020); see also Ruuska et al. (2024). Additionally, de Graaf et al. (2022) found that adolescents with GD or transgender identification had similar self-reported suicidality measures to comparator adolescents without GD who were receiving specialized mental healthcare for other psychiatric diagnoses.
[113] Small to medium-size studies have reported improvement over time in self-report scores related to suicidality (Achille et al., 2020; Allen et al., 2019) or decrease in healthcare utilization for suicidal or self-harm behavior (Kaltiala et al., 2020; Khatchadourian et al., 2014); other larger studies found the percent of patients with suicidal thoughts/behaviors increased after initiating PBs/CSH (Kuper et al., 2020) and increases in healthcare utilization related to suicidality (Hisle-Gorman et al., 2021). Kuper et al.'s before-after comparison is compromised by the unequal time periods over which suicidality was measured.
[114] Ruuska et al. (2024).
[115] Christensen et al. (2025). Similar findings were also reported in a recent narrative review focused on adults (Jackson, 2023). With respect to surgeries, evidence is limited. A recent systematic review of mastectomies in young females found very low certainty evidence with respect to effect on death by suicide (Miroshnychenko et al., 2024).

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therapy on death by suicide."[116] As summarized in the Cass Review's final report, "it has been suggested that hormone treatment reduces the elevated risk of death by suicide in this population, but the evidence found [does] not support this conclusion."[117] Consequently, claims that PMT is "lifesaving" appear to be unsupported by the evidence.

These findings also have been confirmed by the Appleby Report, commissioned by the U.K. government, which reviewed suicides among young people with GD. The report strongly criticized the way suicide and GD have been discussed on social media, characterizing it as insensitive, distressing, dangerous, and in violation of established guidance on the safe reporting of suicide. Appleby emphasized that many of the public claims made about suicide do not meet basic standards for statistical evidence. The report also urged a shift away from viewing PBs as the primary marker of supportive care, warning that such a narrow focus oversimplifies complex clinical needs.[118]

4.3.5 Collapse of clinical rationale

An original rationale for prescribing PBs, as outlined in the Dutch Protocol, was to provide adolescents with "time to think" by pausing puberty, thereby allowing for the exploration of identity without the added distress of physical development.[119] However,

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[116] Baker et al. (2021, p. 12). Another more recent systematic review also found very low certainty evidence for the effect of CSH on death by suicide (Miroshnychenko, Ibrahim et al., 2025).
[117] Cass (2024a, p. 33). An example of commonly cited evidence—e.g., American Psychological Association (2024b); The Lancet Child & Adolescent Health (2021), via reference to Rew et al., (2021); Turban (2020)—in support of this suggestion is Turban, King et al. (2020), a cross-sectional analysis of Internet-based survey data that found that respondents who had accessed PBs had lower lifetime suicidal ideation when compared to those who had wanted PBs but not accessed them. The online survey, the 2015 U.S. Transgender Survey (USTS) (James et al., 2015), had multiple methodological weaknesses. For example, it was a convenience sample, likely not representative of transgender adults in the U.S, and respondents may have confused PBs for CSH (Biggs, 2020; Clayton et al., 2021). Additionally, the survey relied on adult respondents' retrospective recall of childhood and adolescence, and such memories "are subject to confabulation, modification, bias, and simply forgetting;" for example, "31% of respondents recalled realizing they were transgender by age 5, including some who recalled they were transgender at the age of 1 and 2—long before autobiographical memories begin" (Kulatunga Moruzi & Lawler, 2024, pp. 11, 4). The Turban et al. study has also been criticized for its inaccurate assumption that PBs for GD were available in the U.S. starting in 1998, and it has been pointed out that on multivariate analysis, there were no statistically significant between-group differences on five other measures of suicidality, including history of suicide attempts (Biggs, 2020; Clayton et al., 2021).
[118] Appleby (2024).
[119] Delemarre-van de Waal & Cohen-Kettenis (2006).

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data suggest that adolescents who start PBs go on to take CSH.[120] This means that PBs may not function as a neutral pause, but rather the first step on the path to medical transition. This has prompted many experts to abandon the "time to think" rationale, a reversal reflected in more recent WPATH guidelines and professional statements.[121] PBs and CSH are now understood to be a continuous treatment pathway.[122]

Given the risk profile of PBs as outlined in Chapter 7, and the possibility that their use may lead to lifelong medical dependency carrying additional long-term risks, their role in the current treatment paradigm is unclear. In male patients, testosterone suppression can be achieved with anti-androgens alongside estrogen for feminization. In female patients, testosterone alone effectively suppresses estrogen, while also inducing masculinization. Therefore, if PBs are not being used to provide time to think, their rationale in this context remains uncertain.[123]

4.3.6 Lack of reliable evidence of benefit

The original intent behind the use of hormonal interventions in pediatrics was to improve mental health outcomes[124] by preventing sexual development and causing the development of physical characteristics typical of the other sex. This approach was

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[120] Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).

[121] Although WPATH's 2012 guidelines stated (consistent with the original Dutch research) that PBs would "[give] adolescents more time to explore their gender nonconformity and other developmental issues," (see Coleman et al., 2012, p. 177), this clinical rationale is absent in the latest version of the organization's guidelines, Coleman et al. (2022). A recent article by leaders in the field about eligibility and screening evaluations for patients interested in PBs made no mention of the "time to think" rationale (Turban et al., 2025). See also amicus brief acknowledging that PBs and CSH should not be considered separate treatment pathways because they constitute a "care continuum" and "the vast majority of adolescents with gender dysphoria who receive puberty blockers progress to cross-sex hormone therapy" (U.S. v. Skrmetti (No. 23-477), Expert Researchers and Physicians, Amicus curiae brief, 2024).

[122] There are exceptions to this understanding; some research papers and organizations still claim PBs provide time to think (e.g. Fisher et al., 2024; U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief, 2024, p. 13).

[123] The Cass Review found that although there may be "a very narrow indication for the use of puberty blockers in birth-registered males as the start of a medical transition pathway in order to stop irreversible pubertal changes," there were no other reasonable, proven rationales for use of PBs, and, notably, no indication for use of PBs in females (Cass, 2024a, p. 180). Experts have questioned "the rationale for depriving an adolescent of sex hormones for years during puberty and risking the effects on bones and brains" (Ryan, 2024b).

[124] Researchers were originally motivated to initiate hormonal interventions in children and adolescents because they were concerned about poor mental health in adult patients and hoped to mitigate this by preventing development of sex characteristics that were distressing for these adults (discussed in more detail in Chapter 3).

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based on the hypothesis that avoiding "an unfavorable physical appearance"[125] would "improve the ability to 'pass' as the desired gender."[126] While these interventions do alter physical appearance, SRs have not found credible evidence that they lead to meaningful improvement in mental health.[127] Multiple SRs have concluded that the evidence supporting the benefits of pediatric transition interventions—from PBs to CSH and surgery—is of "very low certainty." (See Chapter 5.) This means that findings from studies reporting mental health improvements[128] are not considered reliable. In contrast, all medical interventions carry the potential for harm.

Ultimately, medical interventions should be used when the balance of benefits clearly outweighs the risks. Every public health authority that has conducted a systematic review of the evidence has concluded that the benefit/risk profile of PMT is either unknown or unfavorable.

[125] Delemarre-van de Waal & Cohen-Kettenis (2006).
[126] Costa et al. (2015).
[127] The other original clinical rationale was decreasing need for future surgeries. One study has reported that female patients who started PBs early in puberty were less likely to receive mastectomies than patients who started PBs later, suggesting relative lack of breast tissue precluded need for mastectomy. However, this study also found greatly increased odds of intestinal vaginoplasty in male patients who received PBs in early puberty (van de Grift et al., 2020). One adolescent mastectomy study suggested chest-related dysphoria increased after testosterone use (Olson-Kennedy, Warus, et al., 2018). Theoretically, increasing chest dysphoria could lead to pursual of mastectomy. In the adult literature there have been reports of females undergoing hysterectomy due to pelvic pain caused by reproductive organ atrophy (e.g., Zwickl et al., 2023).
[128] Across the studies looking at mental health outcomes, statistically significant improvements have been inconsistently reported. Of longitudinal mental health outcome studies in this field, some reported improvements in one or more mental health outcomes (Achille et al., 2020; Allen et al., 2019; Chelliah et al., 2024; Chen et al., 2023; de Vries et al., 2011, de Vries et al., 2014; Fisher et al., 2024; Kaltiala et al., 2020; Kuper et al., 2020; Lavender et al., 2023; López de Lara et al., 2020; Olson-Kennedy et al., 2025); the largest study found worsening in mental health outcomes (Hisle-Gorman et al., 2021), while others reported no change (Becker-Hebly et al., 2020; Cantu et al.. 2020; Carmichael et al., 2021; Eisenberg et al., 2024; Khatchadourian et al., 2014; Russell et al., 2021; Tordoff et al., 2022). One study reported similar improvement in a group treated with PBs and a group treated with psychotherapy only (Costa et al., 2015).

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PART 2

EVIDENCE REVIEW

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Chapter 5 Overview of Systematic Reviews

This chapter reviews the best available information regarding the risks, benefits, and uncertainties of interventions commonly used to address gender dysphoria (GD) in youth. It summarizes the findings of the overview of systematic reviews (SRs) (also known as an "umbrella review") conducted for this Review. Section 5.1 defines some terminology and describes the methodology used to produce the overview of SRs. Sections 5.2-5.6 summarize the overview's findings for the following interventions: social transition; puberty blockers (PBs); cross-sex hormones (CSH); surgery; and psychotherapy. The chapter concludes with a discussion section (5.7).

Chapter 6 explains the limitations of SRs and the need—especially in the context of pediatric gender medicine (PGM)—to consider other types of scientific evidence. Chapter 7 is an overview of those other types of evidence, including evidence from basic science, from known mechanisms of drug action, and from endocrinological disorders that approximate the effects of medical transition. This broader base of evidence allows for a more comprehensive assessment of potential harms. Chapter 8 briefly summarizes the implications of these findings for decision-makers.

5.1 Methodology

A fundamental principle of evidence-based medicine (EBM) is that optimal decision-making "requires awareness of the best available evidence, which ideally will come from systematic summaries of that evidence."[1] The cornerstone of EBM is the *systematic review*,

> [which] attempts to collate all empirical evidence that meet prespecified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.[2]

[1] Guyatt et al. (2015, p. 10).
[2] Higgins et al. (2019, p. xxiii).

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The conclusions of any individual study will be limited by study design and other factors. Collating, synthesizing, and assessing all relevant studies on the topic of interest, using systematic and reproducible methods to minimize biases and mistakes, makes possible more reliable conclusions.

SRs sit atop of the "hierarchy of evidence."[3] However, not all literature reviews are SRs, even when titled as such, so it is important to evaluate the process used in the production and reporting of any evidence review that claims to be an SR. For example, the "Cornell Review" has been extensively cited in the field of PGM to support a claim of low regret, but that review's findings do not support that conclusion.[4]

An overview of SRs essentially applies the methodology of SRs to SRs themselves, making the SRs the unit of analysis, rather than individual primary studies. In the present case, an overview of SRs was prepared because the field is already saturated with SRs, many of which evaluate the same studies. By assessing the quality of these SRs, an overview allows for a clearer understanding of the overall strength, consistency, and gaps in the evidence base.

The methodology of the overview followed the recommendations for overviews of SRs in the *Cochrane Handbook for Systematic Reviews of Interventions*.[5,6] Medline, Embase, and the psychological database PsycINFO were searched for SRs on the effects of social transition, PBs, CSH, surgeries, and psychotherapy for youth with GD up to age 26 years.[7] A complementary literature search was also conducted for "grey

[3] See Appendix 3.
[4] Cornell University & What We Know Project (2017). The Cornell Review claimed that "regrets are most likely to result from a lack of social support after transition or poor surgical outcomes using older techniques." But this review did not properly synthesize evidence from included studies, nor assess the quality of the evidence. The review findings should therefore be interpreted with caution. The Cornell Review was not included in the present overview because the target population was mature adults, and thus is not clearly applicable to children and adolescents with GD (see Section 4.3.1.1).
[5] Higgins et al. (2019).
[6] See Appendix 4 for the detailed methodology and results of this overview.
[7] SRs in this area have usually involved patients under 18 or under 26. To encompass the inclusion of those aged 18, the Review made the decision to search for SRs for patient populations below the age of 26. This balances the comprehensiveness and the directness (applicability) of evidence review. Though there is concern regarding the directness of evidence, the evidence for <18 and patients who are older than 18 years did not identify any significant differences in outcomes.

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literature"[8] and reference lists of eligible SRs. Two reviewers independently screened titles and abstracts, and then full texts, to determine study eligibility. Reviewers resolved disagreement by discussion. The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) was used to assess the included SRs.[9] Data extraction and risk of bias assessment were completed by one reviewer and checked by a second. ROBIS assesses the quality of the SR in four domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis of findings. Additionally, ROBIS assesses the overall risk of bias in an SR's process. SRs with concerns identified in the four domains can still be assessed at low risk of bias if the SRs have properly addressed those concerns in the evidence interpretation.

The following five sections of this chapter summarize the outcome data across SRs published in English and classified at low risk of bias. The evidence synthesis was organized by the outcomes of interest for each treatment strategy. These outcomes included GD, mental health and well-being, physiologic effects (e.g., suppression of sex hormones for PBs), need for or progression to further treatment, safety outcomes including side effects and adverse outcomes, and regret. For each outcome, this overview summarized the effect estimates and the quality of evidence (the confidence in the effect estimates), following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

In GRADE, quality of evidence is equivalent to certainty of evidence.[10] Quality of evidence can be downgraded for various reasons: risk of bias (study limitations), inconsistency (unexplained variation in results), indirectness (evidence not directly applicable), imprecision (wide confidence intervals or small samples), and publication bias (selective reporting).[11] Conversely, quality may be upgraded if there is a large

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[8] "Gray literature" refers to research and information produced outside of traditional academic publishing channels and therefore may not be formally peer-reviewed or indexed in major databases.
[9] Whiting et al. (2016).
[10] "The quality of evidence is very low" is equivalent to "the certainty of evidence is very low" (Balshem et al., 2011; Guyatt et al., 2008).
[11] Balshem et al. (2011); Guyatt et al. (2008); Guyatt, Oxman, Kunz, Brozek et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter et al. (2011); Guyatt, Oxman, Kunz,

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effect size, a clear dose-response relationship, or if confounding factors would likely reduce the observed effect but the effect was nonetheless observed.[12]

Evidence is then classified into four categories by level of quality: high, moderate, low, or very low.[13] High quality evidence means that "we are very confident that the true effect lies close to that of the estimate of the effect." Very low quality evidence indicates that "we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect." This overview summarizes the GRADE ratings from the original SRs for the respective outcome wherever it is available. Nevertheless, two modifications were made:

1. Where a formal GRADE appraisal had not been performed by the SR, but expressions such as "we are very uncertain" or "no conclusions could be drawn" were used in the SR's conclusions, these were considered equivalent to a "very low quality" GRADE assessment.[14]
2. Where SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale.

After screening, 17 SRs met the inclusion criteria. These examined the effects of social transition (n = 2),[15] PBs (n = 9),[16] CSH (n = 8),[17] surgery (n = 3),[18] and psychotherapy (n = 5)[19] among children or adolescents with GD. Of the 17 included SRs, ten were rated

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Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou et al. (2011); Guyatt, Oxman, Montori, et al. (2011); Guyatt, Oxman, Vist et al. (2011).
[12] Guyatt, Oxman, Sultan et al. (2011).
[13] Balshem et al. (2011). See also Appendix 3.
[14] Balshem et al. (2011); Santesso et al. (2020).
[15] Dopp et al. (2024); Hall et al. (2024).
[16] Chew et al. (2018); Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan et al. (2025); Ramos et al. (2021); Rew et al. (2021); Taylor, Mitchell, Hall, Heathcote et al. (2024); Thompson et al. (2023); Zepf, König et al. (2024).
[17] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024); Thompson et al. (2023); Zepf, König et al. (2024).
[18] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[19] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).

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as having a low risk of bias overall.[20] SRs rated as a "low risk of bias" nevertheless may still have limitations in one or more domains. Seven SRs were rated as having a high risk of bias overall,[21] often due to limited or poorly defined research questions and eligibility criteria, lack assessment for risk of bias, and inadequate synthesis of findings. The variation in methodological rigor highlights the need for cautious interpretation of findings, especially from reviews rated at high risk of bias.

Of note, this overview excluded two SRs performed by the National Institute for Health and Care Excellence (NICE) in October 2020 to inform the Cass Review.[22] These were excluded because several subsequent SRs commissioned from the University of York to inform the Cass Review were published. The latter SRs are more comprehensive and updated the findings of the two NICE SRs.

This overview also excluded the 2021 SR by Baker et al.,[23] because participants in most of the included studies for that SR were mature adults. Notably, the Baker et al. review was cited to support Statement 2.1 in the World Professional Association for Transgender Health's *Standards of Care for the Health of Transgender and Gender Diverse People*, Version 8 (WPATH SOC-8).[24] That statement—"We recommend health care systems should provide medically necessary gender-affirming health care for transgender and gender diverse people"—was then cited in support of the recommendations in SOC-8's Adolescent chapter. Because of the way this SR has been relied on in the field of PMT, Baker et al. was subjected to a separate ROBIS analysis which found it to be at high risk of bias due to limitations in ROBIS domains of "data collection and study appraisal" and "synthesis and findings." The ROBIS assessment of Baker et al. is included in Section 2.3 of Appendix 4, while Appendix 3 provides an

[20] Dopp et al. (2024); Hall et al. (2024); Heathcote et al. (2024); Ludvigsson et al. (2023); Miroshnychenko et al. (2024); Miroshnychenko, Ibrahim et al. (2025); Miroshnychenko, Roldan et al. (2025); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024); Zepf, König et al. (2024). SRs conducted by the same research group generally followed the same methodology approach.
[21] Chew et al. (2018); Expósito-Campos et al. (2023); Karalexi et al. (2020); Malpas et al. (2022); Ramos et al. (2021); Rew et al. (2021); Thompson et al. (2023).
[22] National Institute for Health and Care Excellence (2020b, 2020a).
[23] Baker et al. (2021).
[24] Coleman et al. (2022).

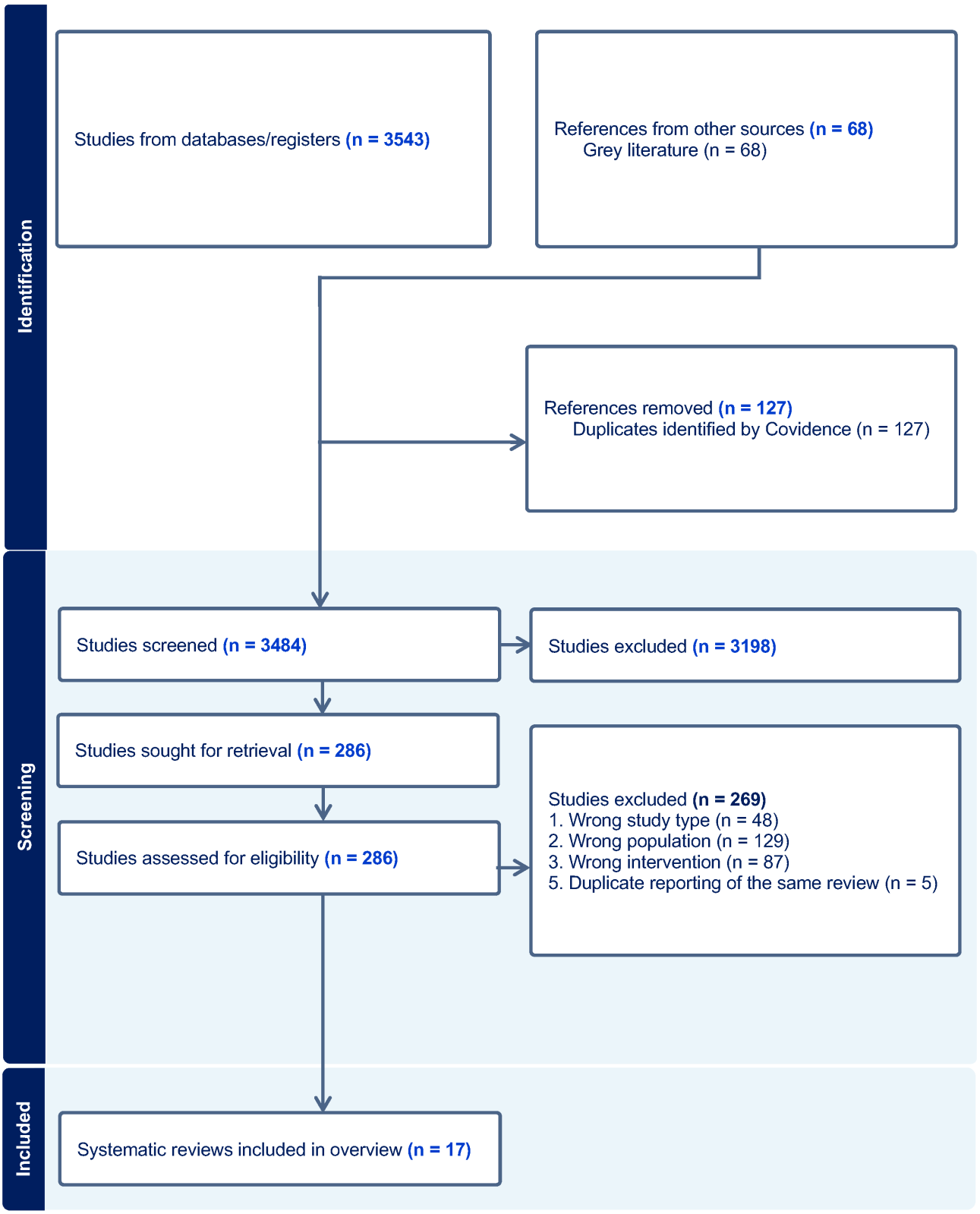
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introduction to SRs and EBM. Figure 5.1 below provides a flow diagram for the searching, screening, and inclusion process.

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Figure 5.1 Searching, screening, and inclusion process



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5.2 Outcomes of social transition

Social transition involves changing one or more aspects of one's presentation or expression, such as name, appearance, or behavior, with the goal of being perceived and treated as a member of the other sex, or to avoid being perceived and treated as a member of one's own sex. As noted in the Cass Review, even though social transition is undertaken outside healthcare settings, "it is important to view [social transition] as an active intervention because it may have significant effects on the child or young person in terms of their psychological functioning and longer-term outcomes."[25]

This overview identified two SRs evaluating the impact of social transition. Both are assessed at low risk of bias.[26] The results suggest that the impact of social transition on long-term GD, psychological outcomes and well-being, and future treatment decisions such as hormones or surgeries remains poorly understood. Evidence on regret associated with social transition is extremely limited. The certainty of evidence for these outcomes is very low.

Significant evidence gaps remain in the evaluation of social transition as an intervention for children and adolescents with GD. Most available studies are cross-sectional and there are no prospective longitudinal studies with appropriate comparison groups, making it unclear whether observed associations reflect the effects of social transition or other underlying factors. Additionally, published studies often do not disentangle the effects of social transition from concurrent interventions such as psychotherapy or medical treatments, further complicating interpretation.

5.3 Outcomes of puberty blockers

Gonadotropin-releasing hormone agonists (GnRHa), known as "puberty blockers" (PBs), are used to prevent or arrest the development of sex characteristics in peripubertal and pubertal children and adolescents with GD. This overview identified nine SRs that assessed the treatment effects of PBs. Among these four were English-

[25] Cass (2024, p. 158).
[26] Dopp et al. (2024); Hall et al. (2024).

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language SRs[27] assessed at low risk of bias. The eligibility criteria and number of included studies varied in these four SRs, and the certainty of evidence is very low regarding the effect of PBs on GD (or gender incongruence), improvement in mental health, and safety. There is high certainty evidence that PBs exert physiological effects (such as sex hormone suppression) and often cause infertility when followed by CSH, depending on the patient's pubertal stage and sex.[28] Low certainty evidence suggests that PBs may compromise bone health.[29] A high proportion of youth proceed to CSH after PBs, though the certainty of evidence regarding any causal role PBs play in this progression is very low.

Important gaps remain in both the range and quality of outcomes assessed across the existing literature. Many primary studies were not adequately designed for measuring or reporting on the outcomes related to PBs. For example, few primary studies included in the SRs assessed the impact of PBs on outcomes such as GD or mental health. Although PBs are frequently described as a "pause button,"[30] no studies have systematically examined their role in the decision-making process or the outcomes of those who discontinue treatment.

When outcomes were assessed, the focus was largely on short-term psychological or physiological changes, or surrogate outcomes—such as suicidal ideation or bone mineral density, rather than on endpoints like suicides or fractures. The evidence is particularly limited regarding long-term outcomes related to fertility, growth, and neurocognitive development.

While studies suggest a high proportion of youth proceed to CSH after puberty suppression,[31] there is minimal evidence on the impact of this combined pathway

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[27] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan et al. (2025); Taylor, Mitchell, Hall, Heathcote et al. (2024).
[28] See subsequent discussion of fertility in Chapter 7.
[29] See subsequent discussion of physiologic mechanisms whereby induced hypogonadotropic hypogonadism negatively impacts bone development.
[30] See, for example, a puberty blocker fact sheet from Cambridge Health Alliance/Harvard Medical School Teaching Hospital (Cambridge Health Alliance, n.d.).
[31] In the systematic reviews that were assessed at low risk of bias, only two studies (Carmichael et al., 2021; Karakılıç Özturan et al., 2023a) reported data on this outcome, each reporting progression rates from PBs to CSH of >95%. Other studies not captured by this overview, cited elsewhere in this Review,

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compared to CSH alone, or on how this pathway affects longer-term outcomes such as undergoing surgery. Furthermore, no studies have clearly examined the physical or psychosocial trajectories of the small minority of those who undergo PBs but do not proceed to CSH. As a result, there is little data on what happens after treatment ends, and the assumption that the effects of PBs are reversible remains largely untested. Another important limitation is that most of the primary studies have not distinguished the effects of PBs on females versus males. Overall, the absence of long-term, high-certainty evidence on these critical outcomes (including suicides, fractures, fertility, growth, and neurocognitive development) leaves substantial uncertainty about the effects of PBs.

5.4 Outcomes of cross-sex hormones

Estrogen for males and testosterone for females are used off-label to induce physical changes in the sex characteristics of youth with GD. This overview identified eight SRs on the treatment effects of CSH, among which four were in English language and assessed at low risk of bias.[32] The certainty of evidence is very low regarding the effect on GD or incongruence, improvement in mental health, and safety metrics including fertility and bone health. There is high certainty evidence that CSH exert physiological effects.

As with PBs, important evidence gaps exist for CSH. Many studies were not specifically designed to capture the full range of long-term outcomes and have primarily concentrated on short-term psychological or physiological changes. Key outcomes such as effects on GD, other mental health outcomes, and quality of life have been inconsistently measured and, when reported, often are derived from small, observational studies with limited follow-up. Critically important long-term outcomes remain poorly understood. Sexual dysfunction, despite being highly relevant to long-

also reported >90% progression rate from PBs to CSH: Brik et al. (2020); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).

[32] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024).

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term well-being, has been infrequently assessed. Although a few studies have reported cardiovascular event rates, long-term follow-up is needed to evaluate cumulative risk.[33]

Evidence on fertility is sparse, with little data on whether reproductive effects vary by age at treatment initiation or whether these effects are reversible. Furthermore, the compounded effects of sequential (and sometimes concurrent, especially among males) treatment with PBs followed by CSH—such as their impact on bone health recovery, final adult height, or the likelihood of requiring surgical interventions—have not been adequately investigated. As with PBs, the lack of methodologically rigorous, long-term studies significantly limits researchers' understanding of the broader health implications of CSH use during adolescence. A lack of primary studies that separately evaluate the effects of estrogen in males and testosterone in females is a significant limitation, as hormone-sex interactions may meaningfully influence outcomes.

5.5 Outcomes of surgery

Masculinizing mastectomy for adolescent females is the most frequently performed surgery in the context of youth with GD. This overview identified three SRs on surgeries for children or adolescents with GD, with most primary studies considering mastectomy only.[34] Two SRs were assessed at low risk of bias.[35] There is high certainty evidence that mastectomy is associated with predictable surgical complications such as necrosis and scarring. The certainty of evidence is very low regarding the effect of surgery on GD or incongruence, improvement in mental health including suicidality and depression, and long-term outcomes such as sexual function, quality of life, and regret.

There are substantial gaps in the evidence on surgeries for adolescents with GD. Most studies are case series or small observational designs, with limited or no comparator groups, and thus are unable to isolate the effects of surgery from prior medical or psychosocial interventions. Outcomes such as effects on GD, mental health, and quality

[33] This is particularly true for pediatric medical transition (due to starting CSH in adolescence, the duration of treatment will be longer than for previously studied populations of adults).
[34] Dopp et al. (2024) included 18 studies; more than half of the included studies were on mastectomy. Miroshnychenko et al. (2024) included 39 studies and only assessed the effects of mastectomy. The other SR included 25 participants receiving surgeries, of which 24 received mastectomy. See Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[35] Dopp et al. (2024); Miroshnychenko et al. (2024).

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of life are inconsistently reported and often lack validated measures. Long-term outcomes, including the durability of psychological benefits, sexual function, need for revision surgeries, as well as satisfaction and well-being into adulthood, remain poorly characterized. Furthermore, while regret is a frequent topic of public discussion, existing studies do not provide robust data on the factors influencing regret. There are also knowledge gaps for other types of surgeries, including genital surgeries.

5.6 Outcomes of psychotherapy

Discussions about the role of psychotherapy in the treatment of youth with GD suffer from internal inconsistencies in the field of gender medicine, whereby psychotherapy is both recognized as an important tool but is also stigmatized if its aim is the resolution of GD (Chapter 14). The overview identified a total of five SRs assessing psychotherapy among children or adolescents with GD. Only two were assessed at low risk of bias.[36]

The evidence on the effects of psychotherapy is limited. A 2024 review conducted by Dopp et al. included one randomized controlled trial (RCT) evaluating the effects of "coping-oriented brief videos" on suicidality, which did not provide direct evidence about the effect of psychotherapy in youth with GD. There are no other RCTs. Both SRs found that psychotherapy interventions were delivered through a range of formats, highlighting considerable heterogeneity in delivery. Formats for both face-to-face and online interventions varied widely, including individual, group, family-based, and combined approaches. Face-to-face interventions took place in diverse settings, such as specialist gender services, community programs, community mental health clinics, a weekend retreat, and an acute residential treatment program. These heterogeneities limit the generalizability of evidence. For mental health outcomes, the certainty of evidence was very low. However, no harms were reported.

The overview found no evidence on the effect of psychotherapy on GD itself. This evidence gap may be due to a conflation of psychotherapy with "conversion therapy." As noted by the Cass Review, "[the] role of psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an

[36] Dopp et al. (2024); Heathcote et al. (2024).

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unhelpfully polarised debate around conversion practices."[37] There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with childhood or adolescent GD,[38] including depression, anxiety, eating disorders, self-harm, and suicidality. Early reports often did not isolate the effects of psychotherapy from those of other concurrent interventions such as social transition, PBs, or CSH, making it difficult to attribute observed outcomes to psychotherapy alone. There is little understanding of which therapeutic approaches may be more or less effective for specific subgroups. The lack of robust research was acknowledged by the Cass Review, which noted that "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[39]

Of note, although the direct evidence for psychotherapy in children and adolescents with GD is limited, there is available evidence to support the role of psychotherapy in treating children and adolescents with other mental health problems, including depression, anxiety, eating disorders, self-harm, and suicidality (See Section 14.5.1).

5.7 Discussion

5.7.1 Findings of this overview

This overview of SRs includes 17 SRs evaluating the effects of interventions for children or adolescents with GD. For social transition, the certainty of benefits and harms is very low due to problems in the study designs. While studies suggest that early social transition is associated with a high rate of persistence of GD and a >90% rate of continuation to PBs and CSH,[40] from a methodological perspective there is uncertainty due to very low-quality evidence about causal explanations/pathways. Specific to medical transition, this overview highlights a consistent pattern across interventions for children or adolescents with GD: while PBs, CSH, and surgeries reliably produce expected physiological changes, there remains substantial uncertainty about their psychological and long-term health impacts. High-quality evidence confirms that PBs suppress pubertal development and CSH induce changes to sex characteristics. There

[37] Cass (2024a, p. 150).
[38] See Chapter 14.
[39] Cass (2024a, p. 155).
[40] Hall et al. (2024).

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is low quality evidence suggesting that PBs compromise bone health.[41] However, the quality of evidence for outcomes such as GD, mental health, quality of life, and regret remains very low across all intervention types. The interpretation of many of the SRs' findings should be approached with caution, particularly given the sources of uncertainty, the robustness of this overview's conclusion, and the methodological limitations inherent in the evidence reviews.

5.7.2 Sources of uncertainty in evidence

Across the included SRs, the quality (certainty) of evidence is predominantly limited by lack of methodologically rigorous studies. For instance, across all primary studies included in the nine SRs on PBs, there were no eligible randomized controlled trials.

The lack of proper controls is another common methodological limitation in the studies. This overview found that across all primary studies in the nine SRs on PBs, only six were observational studies with parallel control groups that compared PBs with no PBs among children or adolescents with GD.[42] However, the overall certainty of evidence was influenced not only by methodological shortcomings, but also by factors such as small sample size and small or no effects, which signify imprecision in GRADE terminology. For instance, the sample sizes of the six comparative observational studies addressing PBs were small, with three studies which each included fewer than 100 participants. One SR downgraded the quality of evidence on the effect of PBs on global function for imprecision, noting that the evidence "suggests both a possibility of a benefit or a harm in the outcome."[43]

Inconsistent study findings are another frequently cited concern that lowers the quality of evidence. For instance, one SR of CSH found "limited or inconsistent evidence regarding GD, body satisfaction, psychosocial and neurocognitive outcomes, fertility, height/growth, bone health and cardiometabolic effects."[44] Similar limitations were

[41] Physiological mechanism for PBs' effect on bone mineralization is discussed in Chapter 7.
[42] Becker-Hebly et al. (2021); Costa et al. (2015); Grimstad et al. (2021); Jensen et al. (2019); McGregor et al. (2024); Tordoff et al. (2022).
[43] Miroshnychenko, Roldan et al. (2025).
[44] Taylor, Mitchell, Hall, Langton et al. (2024).

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observed across studies evaluating other medical and surgical interventions for youth with GD.

Thus, it is important to clarify that the absence of high- or even moderate-quality evidence is not only due to a lack of randomized controlled trials (RCTs). The quality of evidence could have been improved through well-conducted observational studies,[45] which can provide moderate and even high-quality evidence when effects are large, consistent, and clearly attributable to the intervention.

5.7.3 Robustness of this overview's conclusion

Although this overview focused on English-language SRs assessed at low risk of bias, another low risk of bias SR, published in German, reached similar conclusions, reinforcing the overall patterns identified here.[46] As stated earlier, this overview did not include the NHS-commissioned SRs on PBs and CSH in 2020, as they were superseded by the SRs published in 2024 to inform the Cass Review. However, these two earlier SRs also concluded that the evidence was of very low quality,[47] and their inclusion would not have altered the conclusions of this overview.

Furthermore, it is also important to note that while this overview focused on SRs assessed at low risk of bias, this designation does not imply that these SRs were without methodological limitations. The "low risk of bias in the systematic review" in ROBIS allows for some flexibility. The included SRs still had shortcomings, such as limited search strategies, outdated literature searches,[48] or lack of precision in evidence assessments. In contrast, SRs assessed at high risk of bias consistently exhibited serious methodological flaws, including poorly defined eligibility criteria, absence of risk of bias assessments for included studies, and unsystematic synthesis approaches. These SRs were judged to be too biased to inform reliable conclusions. The findings

[45] See the checklist for ways to improve observational research in this field in Ludvigsson et al. (2023).
[46] Zepf, König et al. (2024).
[47] National Institute for Health and Care Excellence (2020b, 2020a).
[48] According to the Cochrane Handbook, reviews should be as up-to-date as possible. However, as recency is not the sole consideration, SRs with outdated search strategies can still be considered at low risk of bias overall (Higgins et al., 2019).

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presented in this overview, therefore, reflect a deliberately cautious approach, drawing only from the most trustworthy sources currently available.

Finally, rather than extending beyond what the evidence can support, this overview is confined to summarizing the conclusions of SRs. As a result, it may not include some of the most recently published studies (due to the timing of the SRs' literature searches). However, a targeted search[49] of recently published studies did not reveal any published or ongoing studies that would significantly change the conclusions, especially those pertaining to benefits. This is due to ongoing problems such as an absence of comparison groups, inadequate sample sizes, and limited follow-up. Should the contemplated U.K. RCT trial of PBs[50] receive ethics approval, it might improve the evidence base for short-term (24 month) effects of PBs on certain outcome measures. However, based on the elements of the study design publicly disclosed to date, it might not provide information about the effect of treatment when PBs are followed by CSH—a clinical trajectory which appears to occur more than 90% of the time.[51] Such combination use would have a different risk/benefit profile than the use of PBs alone, both in terms of possible benefits and possible harms. Finally, the anticipated short-term follow-up will not adequately address the key question of long-term outcomes.

Without a meaningful shift toward more robust research designs—such as RCTs that test each intervention as it is currently provided (i.e., sequential treatment of PBs followed by CSH), prospective cohorts with suitable comparators, or natural experiments—the quality of evidence likely will remain low.[52] Conducting new SRs to answer the same research questions in the near future is unlikely to yield novel insights. This dearth of robust research and evidence has direct implications for clinical guidance

[49] A targeted search in this field identified recent publications based on observational studies from the U.S. (Hidalgo et al., 2024; Olson-Kennedy et al., 2025; Wittlin et al., 2025), Canada (Lawson et al., 2024), the Netherlands (van der Meulen et al. 2025), and the U.K. (Morandini et al., 2023). These studies have similar limitations (including study design, small sample size, short-term follow up, etc.) to the primary studies included in the SRs.
[50] National Institute for Health and Care Research (2024).
[51] Brik et al. (2020); Carmichael et al. (2021); van der Loos, Klink, et al. (2023); Wiepjes et al. (2018).
[52] There is debate about whether high-quality research on effects of PBs/CSH in minors should be pursued. Ethical deliberations factor into this debate. Some have argued that research should focus on patients who already received PBs, CSH or surgery (Ryan, 2024b). The Cass Review called for more robust research into psychotherapeutic approaches to GD, which is a promising treatment approach so-far neglected by research (Cass, 2024a).

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and policy development, where expectations of benefit must be weighed against the persistent uncertainty of the evidence documented in the literature.

5.7.4 Limitations and strengths of this overview

All SRs and overviews of SRs have limitations. SRs aim to capture all relevant research that meets predefined eligibility criteria. However, this objective may be undermined by reporting (or non-reporting) bias — a form of bias that arises when the decision to publish, delay, or selectively report study results is influenced by the statistical significance, size, or direction of the findings.[53]

As discussed in Chapter 6 of this Review, research in the field of PGM suffers from significant publication and reporting bias. The extent of the problem is difficult to quantify due to widespread poor methodology and a lack of consistency in reporting effect sizes.[54] Notably, publication bias has not been considered as a reason for downgrading the certainty of evidence in the included SRs.

Another limitation is that SRs serve to answer well-defined research questions which have prespecified outcomes, but cannot detect signals or generate hypotheses. Many studies in PGM focus on psychological outcomes but only inconsistently track other outcomes that may be signals of the intervention's adverse effects. When outcomes are not reported using rigorous methodological standards—such as being clearly listed in a dedicated outcomes table—but instead are only mentioned in the discussion section, SR methodologies are unlikely to flag the study as relevant to that outcome during the screening process. As a result, important adverse effects may go unnoticed. This issue is discussed at some length in the next chapter.

A key characteristic of SRs and overviews of SRs is their emphasis on population-level epidemiological data,[55] often with limited integration of mechanistic evidence or considerations of biological plausibility. This narrow scope limits the ability of this

[53] Guyatt, Oxman, Montori, Vist et al. (2011).
[54] Publication bias is notoriously hard to measure, and the existing statistical tools have significant limitations (Afonso et al., 2024).
[55] Guyatt et al. (1992, 2015).

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overview to elucidate potential causal pathways or to fully interpret observed associations—or their absence.

This overview of SRs has other limitations. Like all overviews, it is constrained to synthesizing published SRs and does not reanalyze primary studies. The scope of this overview was intentionally narrow, focusing on young patients and excluding indirect evidence from adult populations that may provide insight into long-term effects.

Strengths included systematic evaluation of the risk of bias across SRs using the ROBIS tool. Thus, this overview offers a transparent assessment of the reliability of each SR's conclusions. It also allows for comparison across SRs with overlapping but differently scoped studies, helping to identify consistent findings, methodological gaps, and areas of agreement or divergence.

5.7.5 Conclusion

This overview synthesizes the best available clinical evidence from population-level data, highlighting a consistent pattern across interventions for children and adolescents with GD. The benefits and harms of social transition remain unknown; PBs, CSH, and surgeries consistently produce certain physical and physiological effects; and there is considerable uncertainty regarding their psychological and long-term health outcomes.

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Chapter 6 Limitations of Systematic Reviews

As reported in the overview of systematic reviews (SRs), the quality of evidence for benefits of the interventions used in pediatric medical transition (PMT) is very low. Nevertheless, the practice has continued to expand rapidly. The “very low” quality of evidence for benefits demands additional scrutiny of the potential harms in order to arrive at a proper understanding of the risk/benefit ratio.

It is well-established that SRs are better at detecting benefits than harms.[1] Consequently, the absence of evidence of harms in published studies is not equivalent to evidence of absence of harms. In pediatric gender medicine (PGM), inadequate harm detection is amplified by the following factors:

- Insufficient time has elapsed since the widespread adoption of PMT;
- Short-term before-and-after observational studies that comprise the bulk of the evidence often have high ‘loss to follow up’ rates and do not systematically look for, track, or completely report harms;
- Publication bias impedes the recognition of harms.

The first three sections of this chapter (6.1-6.3) consider how these factors affect the ability of SRs to detect harms, with a summary in Section 6.4.

A comprehensive examination of harms associated with PMT is necessary to inform clinical practice. Harms associated with surgeries that remove healthy body parts are easy to recognize, as are some of the adverse effects of hormonal interventions. The latter are noted both in the Food and Drug Administration (FDA) drug labels[2] and on informed consent or assent forms parents and children sign prior to initiating treatment.[3] Use of these drugs off-label in PGM may add additional risk. It is well-established in adults that for the same drug, off-label uses are associated with considerably higher

[1] Loke et al. (2007); Mayo-Wilson et al. (2023); Qureshi et al. (2022).
[2] Testosterone is one of the most widely used drugs in the field and is classified as a Schedule III controlled substance due to the risk of psychological dependence and abuse.
[3] E.g. Cornell Health (n.d); Fenway Health (2024a, 2024b, 2025).

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rates of adverse effects, especially when strong scientific evidence is lacking.[4] Clinical trials have never been conducted for using puberty blockers (PBs) to stop normally-timed puberty; such use will have a different risk profile than the use of PBs to temporarily stop abnormally early (precocious) puberty.

Additional uncertainty arises from the fact that, in studies, PBs are followed by cross-sex hormones (CSH) over 90% of the time;[5] this de facto combination therapy introduces new and potentially serious risks (e.g., concerning fertility) and has never been subjected to any FDA-regulated clinical trial for any population. Further, research shows that when the evidence supporting a particular off-label use is of very low certainty—as is the case for PMT—the already elevated risk of adverse effects associated with off-label use is increased even further.[6]

6.1 Insufficient elapsed time

Although the Dutch Protocol was first published 20 years ago,[7] it was not until the late 2010s to early 2020s that there were sufficient numbers of patients to allow for studies that can estimate rates of harms and benefits.[8] In addition, because the emergence of harms may be delayed by a decade or longer, SRs conducted relatively early in the field's tenure are more likely to understate these outcomes.[9] The average patient is still quite young—typically in their teens or early twenties—at the time of follow-up. This compounds problems with risk detection, since the effect of hormones on health may be cumulative (e.g., effects of hormones on cardiometabolic disease or malignancies) and may not fully manifest until later in life.

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[4] Eguale et al. (2016).
[5] E.g., Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[6] Eguale et al. (2016).
[7] de Vries et al. (2006); Delemarre-van de Waal & Cohen-Kettenis (2006). See Chapter 3.
[8] Respaut & Terhune (2022).
[9] A study in gender medicine with longer-term follow up found "poorer outcome[s] … [which] might also be explained by longer follow-up period (median 10 years) compared to previous studies. In support of this notion, the survival curve (Figure 1) suggests increased mortality from ten years after sex reassignment and onwards" (Dhejne et al., 2011).

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6.2 Short-term observational studies

The Cass Review recognized continued reliance on poorly-designed observational studies as a "key limitation to identifying … safety of gender-affirming hormones for children and adolescents."[10] A key problem that disadvantages SRs in their detection of harms is the fact that the entire body of evidence in PGM is largely composed of short-term "before and after" observational studies that are particularly prone to bias. Such studies focus on demonstrating benefits while inconsistently reporting harms.[11] Unlike the intended benefits of an intervention, which are hypothesized before the study begins and investigated as primary outcomes,[12] harms are not always expected, surveilled, or reported. Therefore, SRs are limited by being able to identify only those outcomes reported by primary studies.[13]

An example of the difficulty in identifying harms pertains to whether PBs represent a harmless "pause button" providing "time to think"[14] or a powerful intervention that promotes iatrogenic persistence of GD and promotes continuation to CSH. At least five studies indicate >90% rate of progression from PBs to CSH.[15] As the Cass Review noted, "These data suggest that puberty blockers are not buying time to think, given that the vast majority of those who start puberty suppression continue to masculinizing/feminising hormones, particularly if they start earlier in puberty."[16] Because the high rate of persistence from PBs to CSH is often mentioned only in the text of a study (and not delineated in outcome tables or abstracts), SRs may overlook this information at the screening stage. Only one low risk of bias SR assessed the proportion of CSH use after PBs, identifying only two studies.[17]

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[10] Cass (2024a, p. 76).
[11] Loke et al. (2007); Mayo-Wilson et al. (2023); Qureshi et al. (2022).
[12] In the case of prospective studies.
[13] Researchers may want their intervention to lead to beneficial outcomes, and may be reluctant to look for or focus on harms.
[14] See Chapter 4 for discussion of the "time to think" rationale.
[15] Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[16] Cass (2024a, p. 176).
[17] Miroshnychenko, Roldan et al. (2025) was the SR that identified Carmichael et al. (2021) and Karakılıç Özturan et al. (2023a).

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There are other examples of inappropriate reporting of adverse effects.[18] Three notable ones are profiled below.

6.2.1 de Vries et al., 2011, 2014[19]

The pair of seminal Dutch studies that launched PMT worldwide can serve as an example of how harms can go unreported. The 2014 study's conclusion that treatment with PBs, CSH and surgery "leads to improved psychological functioning"[20] did not comment on the finding that at least four of the original 70 young patients experienced adverse effects during treatment. Three adolescents were diagnosed with obesity and diabetes, which disqualified them from continuing to surgery, and one patient died from complications following surgery after early pubertal suppression.[21] These serious adverse events were not reported as formal outcomes,[22] precluding any discussion of whether they were caused by the experimental intervention or occurred incidentally. More recently published evidence suggests that the postsurgical death was likely directly related to the practice of early pubertal suppression.[23] Further, because these adverse effects were noted only in the context of accounting for the reduced postsurgical sample size, the study may not have attempted to detect and report less severe adverse effects that were not disqualifying for further participation.

Inadequate reporting of harms in the Dutch study was compounded when SRs excluded this study due to its unreliable design (e.g. the study comingled the CSH and surgery phases, making it impossible to determine which outcomes were associated with which

[18] This is not atypical in medicine. Researchers who invent innovative treatments are likely to focus on the apparent benefits.
[19] de Vries et al. (2011); de Vries et al. (2014).
[20] de Vries et al. (2014, p. 703).
[21] See Chapter 4 for discussion of the weaknesses in the original Dutch Protocol research.
[22] These outcomes were only discussed in the "methods" section (de Vries et al., 2014).
[23] de Vries et al. (2014) had 15 missing cases from the original cohort of 70 participants. Of these 15 participants, three were disqualified from the study because they developed obesity and/or diabetes. One dropped out of treatment, and one died from a surgical complication that was a likely consequence of pubertal suppression (Biggs, 2023b; Negenborn et al., 2017). Several others failed to return postsurgical questionnaires for unknown reasons.

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intervention).[24] Thus, the serious harms reported incidentally by the study authors were entirely omitted from the SRs due to the study's poor design.

6.2.2 Tordoff et al., 2022[25]

Inadequate reporting of harm is also evident in more recent research. A highly influential 2022 study from Seattle Children's Gender Clinic by Tordoff et al. focused exclusively on psychological outcomes, where benefits had been hypothesized. It did not study or report physical health outcomes, where harms would have been more likely to occur.

The study by Tordoff et al. reported mental health outcome data for adolescents and young adults aged 13-20 years who were treated with PBs or CSH for up to one year. The study claimed to provide "quantitative evidence" of mental health improvements; however, the rates of depression in youth who started PBs or CSH remained unchanged—about 6 in 10 youth were moderately-to-severely depressed both pre- and post-intervention.[26] These data were reported in a supplement which was available only online. The study finding of improved mental health was derived from the odds ratios: 60% lower odds of depression and 73% lower odds of suicidality in patients treated with PBs or CSH as compared to those who were not. However, major methodological issues, including potential selection bias and confounding,[27] inappropriate statistical

[24] de Vries et al. (2014) was excluded from the systematic review of CSH by the SR conducted by the U.K.'s National Institute for Health and Care Excellence (NICE). The stated reason for exclusion was: "Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported" (National Institute for Health and Care Excellence, 2020a, p. 72). This study was also excluded from the SR by Miroshnychenko, Ibrahim et al. (2025) on CSH. Though it was included in the SR by Taylor, Mitchell, Hall, Langton et al. (2024) on CSH, it was classified as a low-quality study and not included in the evidence synthesis.

[25] Tordoff et al. (2022). This research was conducted in the U.S. at Seattle Children's Hospital/Washington State University.

[26] Raw Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) data was not reported, even in the online-only supplement.

[27] Of 104 youth aged 13-20, 62 initiated treatment with PBs or CSH during the 12-month study, and 7 were already on treatment at baseline. Participants who initiated treatment during the study contributed to both "treated" and "untreated" groups at different times, complicating interpretation.

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modeling,[28] missing participant data,[29] and selective reporting[30]—raise serious concerns about the reliability of the reported findings.

The impressive-sounding odds ratios were thus calculated by relying on progressively smaller denominators in the untreated "comparator" group. The supplementary online-only data revealed that only seven cases from the "comparator group" of patients not treated with PBs or CSH remained enrolled in the study by its end.[31] It was also unclear if or to what extent this "comparator" group could be considered representative of all untreated patients. It appears that the "untreated" group comprised youth whose mental health problems and GD issues resolved who dropped out from the gender clinic and the study (representing 80% of the total "untreated group"); the patients who were about to cross-over to the treated group after a short assessment; and the 8 patients (7 of whom provided follow-up data) who continued to attend the gender clinic 12 months later, but for an unknown reason were not starting hormonal interventions.[32]

Two recent systematic reviews have assessed Tordoff et al. for risk of bias, using two different tools (the Newcastle Ottawa Scale and ROBINS-I).[33] While both analyses identified some methodological weaknesses (e.g., short follow-up, high attrition rate), the study's inclusion of untreated youth as a comparison group somewhat boosted its

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[28] Rather than analyzing individual mental health trajectories before and after treatment, the study performed cross-sectional comparisons at various time points, leading to potential bias.
[29] At 12 months, data are missing for 17% of medicalized youth (12 of 69) and an astounding 80% of non-medicalized youth (28 of 35). It is likely that non-medicalized participants without mental health distress, including those whose gender distress resolved, would be least likely to return to the clinic
[30] The authors performed analyses following multiple strategies, reporting in the abstract only the version of the analysis that produced the most dramatic results (strongest aOR [adjusted odds ratio] and smallest p-values), raising concerns about data-dredging.
[31] Based on eTable 3 in the supplementary material, the estimated prevalence of depression in the control group was 59% at baseline, 76% at month 3, 58% at month 6, and 86% at month 12. The substantial fluctuation across time points indicates that the estimates for the control group were unstable and likely influenced by random error.
[32] There was incomplete data for 80% of patients in the untreated group. It is possible that patients whose GD resolved stopped attending appointments. Additionally, the 7 untreated patients with follow-up data at one year may not have been approved for medical transition because they did not have sufficient capacity for consent—the only scenario under which this pediatric gender clinic would not recommend medical transition if desired by the patient, according to the study's lead author ("In practice, the only instances when it would have been appropriate to delay initiation of PB/GAH is if there was a concern that a patient did not have the capacity to provide informed consent … which is exceedingly rare in adolescence" (Tordoff, 2022). Barriers to provision of informed consent can include active psychosis or mania and profound intellectual disability.
[33] Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024b). ROBIS: Risk of bias in non-randomized studies - of interventions.

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quality ratings. Systematic reviews are not always able to capture serious problems with comparison groups of this type.

This study's misrepresentation of its own results, serious confounding, and the exceptionally loss-follow-up for untreated youth have been highlighted by science journalists and discussed in peer-reviewed articles.[34] Despite these well-demonstrated problems, this study, published in the *Journal of the American Medical Association* (JAMA) Open Network, continues to be uncritically described, by authoritative sources, as evidence that PBs and CSH are beneficial to mental health, medically necessary, and lifesaving.[35]

6.2.3 Chen et al., 2023[36]

Similarly, while a National Institutes of Health (NIH)-funded initiative, "The Impact of Early Medical Treatment in Transgender Youth,"[37] registered a study protocol in 2016 that included plans to evaluate the safety of PBs and CSH, researchers committed to a short follow-up of only 24 months.[38] Upon reviewing the protocol of this study, its design appears inadequate to comprehensively assess the safety of PMT. The lack of a parallel control group impairs the ability to attribute observed safety outcomes specifically to the intervention, as it becomes difficult to differentiate treatment effects from normal developmental changes. Moreover, the exclusive reliance on biochemical markers fails to capture other critical safety outcomes such as growth and fertility. Additionally, the small sample size undermines the study's capacity to evaluate rare but clinically significant harms, such as thromboembolic events. The absence of long-term follow-up

[34] E.g., Abbruzzese et al. (2023); Biggs (2023b); Singal (2022a). The university that conducted the research was made aware of the study's problems, but chose not to disrupt the very positive medical narrative that misrepresented the authors' findings Singal (2022b).
[35] E.g., American Psychiatric Association (2023); Boerner (2022); Stringer (2023); U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024). To date, this study has been cited over 300 times in other peer-reviewed publications, and viewed nearly half a million times.
[36] Chen et al. (2023). This was an NIH-funded multi-site study performed in the U.S. at Children's Hospital of Chicago, Boston Children's Hospital, and the Los Angeles Children's Hospital.
[37] The research protocol can be found in the supplementary material in Chen et al. (2023).
[38] The study recruited patients from four pediatric gender clinics: Benioff Children's Hospital, Boston Children's Hospital, Children's Hospital Los Angeles, and Lurie's Children's Hospital of Chicago. Two young patients died by suicide while taking CSH, and "suicidal ideation" was registered as the most common adverse event (Chen et al., 2023). The protocol can be found in supplementary material.

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further limits the detection of delayed or cumulative adverse effects. These methodological limitations weaken the strength of any conclusions that can be drawn regarding the overall safety of the intervention.

The study reported mental health outcome data for 315 adolescents and young adults aged 12-20 who were treated with CSH for a period of 24 months. This study, published in the *New England Journal of Medicine* (NEJM), framed its findings in a positive light: "our findings showed improvements in psychosocial functioning ... which supports the use of [CSH] as effective treatment for transgender and nonbinary youth."[39]

However, two of the study subjects died by suicide within one year of initiating hormones, representing a rate that is 30-50 times higher than expected in adolescents of similar age.[40] The only statistically significant finding was a small improvement on the "transgender congruence scale," which has not been validated in minors.[41] Critically, only four out of 19 mental health outcomes described in the study's pre-registered protocol were reported; in particular, outcomes of GD, self-harm, and suicidality outcomes were not reported, and no explanation was provided for omitting these critical data.[42] The authors claimed that depression symptoms decreased during the study period.[43] However, further subgroup analysis by sex showed that the reported outcomes in females were of questionable clinical significance, while males experienced no statistically significant improvement in the reported measures at all.

According to the study's pre-registered protocol, the authors originally hypothesized that patients would exhibit "decreased symptoms of … gender dysphoria, self-injury, trauma symptoms, and suicidality" (among other changes) over time.[44] Instead, as mentioned,

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[39] Chen et al. (2023, p. 249).
[40] For comparison of the suicide rate in Chen et al. to that of other populations (e.g., other cohorts referred to pediatric gender clinics; patients taking antidepressants) see McDeavitt (2025).
[41] Strauss et al. (2024).
[42] In Chen et al. (2023), life satisfaction/positive affect were measured with the NIH Toolbox Emotion Battery. A recent paper describing this same patient cohort published more information on these life satisfaction/positive affect results along with information on additional measures from the NIH Toolbox Emotion Battery (Olson-Kennedy et al., 2025), but it did not report the gender dysphoria, self-harm, or suicidality outcomes, nor did it reference the two patient suicides.
[43] The mean Beck Depression Inventory score improved from 15.46 to 12.92 on a 63-point scale (Chen et al. 2023).
[44] See pp. 25-26 of the study's pre-registered protocol, which is linked to the article Chen et al. (2023) on the New England Journal of Medicine's website.

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two young patients died by suicide within one year of initiating treatment, and the most frequently occurring adverse event during hormonal treatment was "suicidal ideation."[45] Thus, the findings do not support the original hypothesis.

Although a recent systematic review was able to capture issues like study attrition in its risk of bias assessment for Chen et al., methodological analyses are not able to capture serious concerns that may be more related to research ethics than to methodology (e.g., study hypotheses changing between the protocol and the published article). Peer-reviewed critiques addressing the issues with Chen et al. were eventually published by the journal, but not until nearly a year after the article first appeared.[46]

The study continues to be widely cited and uncritically described as providing evidence of benefit for hormonal transition of minors.[47]

6.3 Publication bias

It is a well-documented problem in biomedical research that positive findings confirming an original hypothesis are much more likely to be published or published expeditiously, as compared to studies with inconclusive or negative results. "Publication bias" is not unique to this field. The U.K.'s national PGM clinic, the Gender Identity Development Service (GIDS), tried to replicate the seminal 2011 Dutch study, launching its own "early intervention" study of PBs in 2011. Although the results were available in 2016-2017, they were only released in 2021 following a complaint to the U.K. Health Research Authority.[48] Once published, the study acknowledged that the outcomes reported by the Dutch were not replicated.[49] The study also found that puberty blockade was associated with impaired bone density accumulation. Subsequent reanalysis of the same data showed that up to one-third of participants experienced a deterioration in mental health while on PBs.[50]

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[45] Chen et al. (2023, p. 241).
[46] E.g., Biggs (2023a); Hare (2023); Jorgensen (2023c); Dutch PMT researchers also published a commentary on Chen et al., which acknowledged the study's many problems (de Vries & Hannema, 2023).
[47] E.g., U.S. v. Skrmetti (No. 23-477*),* Expert Researchers and Physicians*,* Amicus curiae brief (2024).
[48] Biggs (2023b).
[49] Carmichael et al. (2021).
[50] McPherson & Freedman (2023).

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A similar pattern may be unfolding in the United States. The lead investigator of a NIH-funded PB study acknowledged delaying the publication of results—apparently due to fear that the unimpressive findings would undermine the field.[51]

A similar reluctance to report on disappointing findings is evident in other places, too. According to court disclosures, the World Professional Association for Transgender Health (WPATH) suppressed publication of SRs on at least ten of thirteen topics relating to endocrine treatment of adolescents with GD.[52] The unpublished SRs evaluated harms, including the effects of PBs on "clinical outcomes and harms"; the effects of estrogen on the risk of pulmonary embolism, deep-vein thrombosis, stroke, and myocardial infarction; the effects of testosterone on uterine, ovarian, cervical, vaginal, and breast pathology; and the effects of hormone therapy on fertility and metabolic syndrome.[53]

There also are instances of SRs arriving at conclusions that contradict the underlying evidence. One SR commissioned by WPATH found only "low" and "insufficient"[54] strength of evidence regarding the effects of hormonal interventions on mental health. Nevertheless, the SR's authors came to the unsupported conclusion that this treatment pathway "is likely associated with improvements" in quality of life, depression, and anxiety. The authors also asserted that "[t]hese benefits make hormone therapy an essential component of care that promotes ... health and well-being." Notably, there was no attempt to evaluate hormone effects on physical health.[55] The content of this SR was influenced by WPATH leadership, including approving the conclusion as a condition for eventual publication. This may explain the discrepancy between the SR's optimistic conclusion and its more problematic findings. Section 10.3.2 discusses evidence suppression by WPATH in detail.

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[51] As reported in the New York Times (Ghorayshi, 2024c). Of note, the investigator, Johanna Olson-Kennedy, denied having said this in a later deposition (Deposition of J. Olson-Kennedy in LB v Premera Blue Cross NO. 2:23:Cv-00953-TSZ, 2024).
[52] See Chapter 10.
[53] Sharma et al. (2018). See also Society for Evidence-Based Gender Medicine (2024b).
[54] Baker et al. (2021, p. 13).
[55] Appendix 4 includes a ROBIS assessment of Baker et al. (2021).

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Another 2021 SR, conducted by Bustos et al., examined postsurgical regret rates.[56] This SR is often cited as evidence that the regret rate after transition-related surgery is very low, about 1%.[57] But of the 27 studies included in Bustos et al., 23 were rated as "poor" or "fair" in quality. The few higher-rated studies suffered from substantial loss to follow-up and the reported results included deaths from suicide and complications. One included study contributed nearly half the total participants but reported a 36% loss to follow-up. The study authors acknowledged that the short follow-up period was a key limitation. However, the authors failed to address the most serious criticism, namely that their central conclusion of "extremely low regret" was unsupported.[58]

6.4 Summary

The quality of SRs in the field of gender medicine varies widely, but even the highest quality SRs typically find only "low certainty" evidence for most harms. However, there are familiar and plausible explanations for why evidence of harms may not have been sought, detected or reported. Reflecting on the state of evidence in PGM, the Cass Review noted, "it has been evident that there has been a failure to reliably collect even the most basic data and information in a consistent and comprehensive manner; data have often not been shared or have been unavailable."[59]

Unless SRs specifically search for harms (and with the provisos above), they are not well-suited to detect complications or adverse effects. This is due to the relatively recent debut and rapid growth of the field of PGM, the tendency of the predominantly short-term observational studies to focus on benefits and underreport harms, and publication bias. EBM emphasizes the role of best available evidence. To address SRs' limited ability to detect harms, decision-makers must consider other sources of scientific information. That is the topic of the following chapter.

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[56] Bustos et al. (2021) reported regret rates of around 1%. This SR was not included in this Review's overview of SRs as most of the included studies did not focus on the adolescent population.
[57] See examples of such statements in Cohn (2023).
[58] For the criticism, see Expósito-Campos & D'Angelo (2021). The authors provided a reply to the critique (Escandón et al., 2021), which addressed some but not all of the key concerns.
[59] Cass (2024a, p. 39).

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Chapter 7 Evidence from Basic Science and Physiology

When clinical studies provide insufficient information about harms, and therefore systematic reviews (SRs) are unable to reliably collate information about harms, other types of evidence should be integrated. Trustworthy evidence from other sources, including basic sciences, should be considered to arrive at a more informed understanding of the plausible effects of interventions.[1] In the case of pediatric medical transition (PMT), this involves consideration of human physiology, development, and the well-established mechanisms of action of the drugs used. The consideration of such evidence aligns with the core requirement of evidence-based medicine (EBM): the judicious use of the "best available" evidence.

The following sections explain: normal pubertal development and the mechanisms of action of PMT interventions (Section 7.1); treatment of central precocious puberty with puberty blockers (PBs) (Section 7.2); biologically plausible implications of using PBs to arrest normally timed puberty and cross-sex hormones (CSH) (Sections 7.3 and 7.4); surgical implications, particularly when pubertal development has been arrested (Section 7.5); and psychological risks of undergoing PMT interventions given what is known about child and adolescent development (Section 7.6). Mortality is discussed in Section 7.7.

7.1 Puberty

This section overviews physiology and the implications of disrupting normally-timed puberty. Of note, there are three distinct waves of hypothalamic-pituitary-gonadal (HPG) axis activity over an individual's lifespan: in utero, during the first month after birth, and in late childhood-early adolescence.[2] Only the latter is referred to as "puberty."[3] Medications can be given to suppress the HPG axis.

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[1] Sackett et al. (1996).
[2] Rohayem et al. (2024).
[3] The discussion in this section focuses on normal pubertal development. Individuals with disorders (differences) of sex development (DSDs) are not a focus of this chapter because the vast majority of adolescents with gender dysphoria do not have a DSD. Among those with DSDs, approximately 5% experience identity changes (Kreukels et al., 2018). As noted in the Cass Review, "Studies of children with DSD suggest that a complex interplay between testosterone levels, external genitalia, sex of rearing and socio-cultural environment all play a part in eventual gender identity" (Cass, 2024a, p. 102).

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7.1.1 Overview of normal pubertal development

In mammals, puberty is defined as the period of time during which immature juveniles reach adult sexual maturity and become capable of reproduction. It is a transitional phase between childhood and adulthood. In humans, pubertal onset typically occurs between ages eight and 13 in females and nine and 14 in males. It is driven by increasing levels of sex steroid hormones—primarily estrogen and progesterone in females, and testosterone in males.[4]

During puberty, sex steroid hormones promote skeletal growth, muscular development, and neurologic development. In females, estrogen initiates breast development, menarche, ovulation, and changes in body composition and skeletal morphology.[5] In males, the androgenic surge results in testicular enlargement, penile growth, spermatogenesis, deepening of the voice, and the emergence of secondary sexual characteristics such as facial and body hair. Spermatogenesis in males and ovulatory cycles in females mark the attainment of fertility.

7.1.2 Tanner Stages of puberty

Physicians use a system known as Tanner Staging to document the physical progression of puberty based on a physical examination.[6] This framework delineates five stages of maturation, from a prepubertal baseline (Stage 1) to full adult development (Stage 5). Intermediate stages capture transitional morphological and physiological characteristics.

In females, Tanner Stage 2 commences with the growth of breast tissue (thelarche), followed by hair growth (pubarche), and then the first period (menarche), typically by Tanner Stage 3 or 4. Menarche typically occurs one to two years after thelarche, at an average age of 12-13 years. The first egg release (ovulation) generally occurs within the first year following menarche, typically at Tanner Stage 4. Ovulatory function stabilizes approximately one year after menarche. Female pubertal development is accompanied by bone growth, body hair growth, widening of the hips, redistribution of fat to the hips

[4] Breehl & Caban (2025).
[5] Kuohung & Hornstein (2024).
[6] Tanner (1962).

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and breasts, and enlargement of both internal reproductive organs (i.e., uterus, ovaries) and external genitalia (i.e., labia, clitoris).[7]

In males, the initiation of Tanner Stage 2 is typically identified by increased testicular volume, followed by growth of the penis, emergence of pubic and later facial hair, and a rapid increase in lean body mass and skeletal size driven by androgens. There are significant increases in bone and muscle mass and thickening and elongation of the vocal cords results in voice deepening. First ejaculations (spermarche) generally occur about one year after the onset of puberty, with full gamete maturation following approximately one year later.[8] Spermatogenesis generally occurs during Tanner Stage 4.[9]

7.1.3 Neuroendocrine regulation of puberty

Puberty is initiated and sustained by complex endocrine signaling. In the brain, the anterior pituitary, in response to pulsatile gonadotropin-releasing hormone (GnRH) release from the hypothalamus, secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Collectively termed gonadotropins, LH and FSH act on the gonads (ovaries and testes) to stimulate the synthesis of sex steroids and promote gametogenesis.[10]

7.2 Puberty blockers and central precocious puberty

In central precocious puberty (CPP) — a condition occurring in one out of 5,000 to one out of 10,000 children, more often in girls[11]—the pituitary gland is activated prematurely, sometimes even during infancy or early childhood.[12] This leads to early-onset, or precocious, pubertal development. CPP is associated with several potential negative

[7] Breehl & Caban (2025).
[8] Breehl & Caban (2025); Kota & Ejaz (2023).
[9] Emmanuel & Bokor (2022).
[10] In males, LH stimulates Leydig cells to produce testosterone while FSH targets Sertoli cells to facilitate spermatogenesis. In females, LH and FSH coordinate estrogen production and follicular development in the ovaries.
[11] Eugster (2019). Although there are some genetic causes of CPP, it is usually idiopathic, meaning the cause is unclear. Females are generally treated for CPP with PBs if puberty occurs at age six or younger, males are generally treated if puberty occurs at age eight or younger (Ergun-Longmire et al., 2023).
[12] E.g., Nienaber & Van Der Walt (1991); Yoon & Kim (2016).

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health outcomes, including decreased adult height due to early presence of sex hormones causing premature epiphyseal fusion.

GnRHa (puberty blockers or PBs) have been approved by the Food and Drug Administration (FDA) for use in the treatment of CPP. The evidence to date comparing large populations of untreated patients to treated patients suggests that, at least for appropriately chosen female patients, treatment of CPP with PBs is associated with increased height attainment and lower body mass index (BMI).[13]

When PBs are used for CPP, the medication is discontinued when the child reaches a more typical age for pubertal onset, allowing normal puberty to resume. The goals include facilitating normal timing of puberty, so that the patient goes through puberty alongside peers (as opposed to significantly before). Although FDA-approved for this indication, PBs—like all medications—are associated with risks and side effects, even when used for CPP.

7.3 Puberty blockers and gender dysphoria

The use of PBs to arrest normally timed puberty is the central element and original contribution of the Dutch Protocol. PBs act directly on the pituitary gland to significantly reduce the release of LH and FSH. Continuous administration of these agents desensitizes GnRH receptors, suppressing LH and FSH secretion, and consequently arresting the production of endogenous sex steroid hormones. In females, this causes the cessation of normal menstrual function, if it has begun. In males, sperm production is halted or forestalled. PBs have not been approved by the FDA for the indication of gender dysphoria (GD); they are used “off-label” in pediatric gender medicine (PGM).[14] Unlike in CPP, use of PBs for PMT is not FDA-approved and safety data are lacking.

Using PBs to stop normally timed puberty effectively induces hypogonadotropic hypogonadism (HH), a condition characterized by the failure of the pituitary to

[13] Luo et al. (2021).
[14] GnRHas have been approved by the U.S. Food and Drug Administration (FDA) for various indications, with effects that can differ significantly depending on their application. For instance, the GnRHa leuprolide (commonly marketed as Lupron) is FDA-approved for androgen deprivation therapy in adult males with prostate cancer and for estrogen deprivation in adult females with endometriosis. It has also been FDA-approved to treat central precocious puberty (CPP).

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appropriately release gonadotropins. As a result, the gonads are unable to produce the sex-specific hormones testosterone or estrogen. Pubertal development is disrupted, halting the progression of physical and reproductive maturity. Left untreated, clinical research shows HH is associated with a range of risks including infertility and decreased bone mineral density, elevating the risk of osteoporosis and fractures.[15]

Although PBs for GD are typically indicated for short-term use (about two years), this time range may be considerably longer for some patients.[16] The reasons for the apparent deviation from the original Dutch Protocol in regard to the length of PB use remain unstudied, but may include increasingly younger social transition ages which 'necessitate' pubertal blockade at increasingly younger ages to allow young patients to continue living in "stealth,"[17] as well as the medical treatment of youth who identify as nonbinary and wish to maintain a sex-ambiguous appearance for an extended period of time.[18]

7.3.1 Developmental risks of blocking normal puberty

One of the key rationales for using PBs in CPP is to allow the child to experience normative psychosocial development alongside same-age peers. By contrast, in PMT, patients are maintained in a prepubertal or early pubertal stage while their peers developmentally progress. This has potential sequelae for the adolescent's psychosocial development.[19]

7.3.2 Bone mineral density and skeletal development

Puberty is recognized as providing a critical window for the accrual of peak bone mass. Sex steroid hormones play an essential role in the mineralization of the skeleton.[20] Failure to reach peak bone density may lead to increased risk of osteopenia,

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[15] Zhu & Chan (2015).
[16] A Cambridge Health Alliance fact sheet, for example, discusses using puberty blockers for up to four years (Cambridge Health Alliance, n.d.).
[17] The Cass Review's qualitative research program found that for prepubertal children who underwent full social transition "living in stealth appears to increase a child's level of stress and anxiety with resultant behaviour and mental health problems. These included social withdrawal, with children becoming increasingly isolated, including resorting to home-schooling or tutoring and even rarely leaving their house" (Cass, 2024a, p.159).
[18] Notini et al. (2020).
[19] This is noted in Vrouenraets et al. (2022), for example.
[20] Elhakeem et al. (2019).

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osteoporosis, and fractures later in life, including debilitating fractures of the spine and hip. In older adults, hip fractures are particularly concerning, as they significantly elevate the risks of morbidity and mortality.[21]

Because of the known physiological role of sex steroid hormones in skeletal development, the original Dutch research acknowledged the possibility of negative effect on bone mineralization. Researchers measured 'Z-scores,' a measure comparing individual bone density to age- and sex-matched population norms, and these scores decreased after PBs in the original Dutch cohort.[22] Since then, multiple longitudinal, observational studies on pediatric patients undergoing medical transition have consistently demonstrated decreases in Z-scores with PB use.[23] In addition to decreases in the *average* scores, a re-analysis of the United Kingdom (U.K.) data found that one third of the puberty-blocked patients had a Z-score of below -2 (indicating osteoporosis) for hip, and more than one quarter of patients had low Z-scores for spine.[24] Fracture rates have not been reported alongside Z-scores in this literature.[25]

When PBs are followed by CSH, as has occurred in studies over 90% of the time, bone mineralization will increase, but a critical developmental window for bone density accrual during adolescence may have been missed or foreshortened, as bone density accrual slows during the 20s and then begins to decline. These patients may never reach the peak bone density they otherwise would have achieved. Research on medium and long-term outcomes is limited.[26] Due to the novel nature of PMT no studies have yet followed patients into middle age or late adulthood.

7.3.3 Neurocognitive and psychosocial development

The human brain undergoes substantial reorganization during adolescence, including synaptic pruning and myelination, processes that are influenced by sex steroid

[21] Bentler et al. (2009).
[22] Delemarre-van de Waal & Cohen-Kettenis (2006).
[23] E.g., Boogers et al. (2023); Carmichael et al. (2021); Ciancia et al. (2024); Delemarre-van de Waal & Cohen-Kettenis (2006); Joseph et al. (2019); Klink et al. (2015); Navabi et al. (2021); Schagen et al. (2020); Stoffers et al. (2019); Van der Loos, Vlot et al. (2023); Vlot et al. (2017).
[24] Biggs (2021).
[25] E.g., Roy et al. (2024).
[26] Two longer-term studies (Schagen et al., 2020; van der Loos et al., 2023) found Z-scores returned to pre-treatment baseline after 3-11 years of subsequent CSH treatment in females, but not in males.

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hormones. Research suggests that sex steroid hormones impact brain regions associated with executive function, emotion regulation, and social cognition.[27] The precise neurocognitive effects of puberty suppression remain understudied,[28] and researchers in this field have recognized the limitations of the evidence in this area.[29] A recent literature review concluded that the effect of PBs on neurocognitive development is unknown, but that "there is some evidence of a detrimental impact of pubertal suppression on IQ [intelligence quotient] in children."[30] However, a 2022 Dutch study found that in patients treated with PBs the associations between pretreatment IQ and eventual education achievement were similar to population norms (the study did not longitudinally measure IQ).[31] The Cass Review has raised concern over the potential harm and unknown effects of pubertal suppression on the developing brain,[32] noting that "[t]here is increasing evidence that the changes in brain maturation described above are driven by a combination of chronological age and sex hormones released through puberty."[33]

7.3.4 Reproductive maturation

By halting the development of sex characteristics, PBs interrupt the maturation of reproductive anatomy and function. Suppression of the HPG axis can impair gametogenesis, potentially resulting in permanent infertility if CSH are started thereafter, particularly when gonadal maturation is not completed prior to the interruption of normally-timed puberty.

In adult males initiating estrogen for medical transition, testicular atrophy results, leading to impaired fertility or infertility that may be irreversible (even if estrogen were to

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[27] Cservenka et al. (2015); Gonnabathula & Yakubu (2023); Macoveanu et al. (2016); Pillerová et al. (2022).
[28] One cross-sectional study (which cannot methodologically suggest causation) found poor executive functioning in patients taking PBs >1 year, but their baseline functioning before PBs was unknown (Strang et al., 2022). Another cross-sectional study reported similar executive functioning between patients on PBs and patients not on PBs (Staphorsius et al., 2015). Arnoldussen et al. (2022), another study, is discussed in the text.
[29] Chen et al. (2020).
[30] Baxendale (2024).
[31] Arnoldussen et al. (2022).
[32] Cass (2024a, p. 115).
[33] Cass (2024b, p. 104).

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be discontinued).[34] However, adult males may choose to cryopreserve sperm prior to initiation of estrogen. This is not the case with children or early adolescents.[35] Spermatogenesis generally occurs in Tanner Stage 4 of puberty.[36] In PMT, if PBs are started in Tanner Stage 2, prior to gamete maturation, and estrogen is started thereafter (as is likely), cryopreservation of sperm cannot be completed beforehand.[37] Additionally, fertility may be affected in females initiated on PBs who proceed to take testosterone.[38] Effect of testosterone on the reproductive tract makes the likelihood of conception, pregnancy, and birth uncertain.[39] Maternal and fetal outcomes under these circumstances are also poorly studied.

It is possible that CSH use after pubertal arrest could permanently damage the immature gonadal tissues, leading to sterilization.[40] If the gonads are arrested in an immature state due to prolonged use of PBs, and this is followed by administration of CSH, there is no proven physiological mechanism by which fertility can reliably be re-established. The likelihood of permanent infertility will be substantially increased.[41,42]

With respect to fertility preservation (FP), techniques can range from relatively simple to technically challenging to not currently viable, depending on the patient's sex and Tanner Stage of development. For example, males who have undergone spermarche can produce a semen sample for long-term storage. However, males who have puberty

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[34] Cheng et al. (2019); Deutsch (2020a).
[35] Fertility preservation for natal males in early puberty remains a theoretical and experimental undertaking, with no clinically validated protocol currently available (Laidlaw et al., 2025).
[36] See above, Section 7.1.2.
[37] The original Dutch research acknowledged that infertility would result for males initiated on PBs in Tanner Stage 2 and on estrogen thereafter: "In early pubertal boys, the hypogonadotrophic state will block the development of fertility" (Delemarre van de Waal & Cohen-Kettenis, 2006, p. S134).
[38] Cheng et al. (2019). Although pregnancies can occur in adult females taking testosterone, less is known about pregnancy in females who underwent PMT in childhood/adolescence.
[39] Laidlaw et al. (2025).
[40] See the subsequent section for specific effects of CSH.
[41] It should be noted that PBs for CPP does not negatively impact fertility. In pediatric medical transition, because PBs are generally the first part of a continuum including CSH, infertility is a likely result of treatment (depending on sex and Tanner Stage of patient).
[42] There is controversy regarding minors' capacity to provide informed consent to potential loss of fertility with respect to PMT. E.g., "Can these minors make adequately autonomous decisions in the present that may impact their opportunities in the future? This is less a question of decision-making capacity…than a matter of sufficient life experience to know their future desires … How to maintain an "open future" for transgender youth is a common concern of parents and healthcare professionals" (Harris et al., 2020, p. 2459). See also Jorgensen & Masson (2024). In a study of patients in their early 30's who had begun hormonal interventions at age 15, 23% expressed regret about infertility (de Nie et al., 2024).

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blocked at Tanner Stage 2 will have immature testicles; FP necessitates testicular tissue cryopreservation, which currently remains entirely experimental.[43] For the mature female patient, oocyte preservation involves an invasive procedure (and is costly). For females in early Tanner Stages, techniques such as ovarian tissue cryopreservation, although technically possible,[44] have yet to be shown to result in viable pregnancies in patients who have undergone PMT.

Most studies on FP in adolescents with GD undergoing PMT have shown very low rates, between 0% and 4.7% of patients who underwent FP.[45] One study in which male patients were able to access fertility preservation via testicular biopsy reported that 10 out of 23 patients (43%) were able to have gametes cryopreserved prior to PB initiation (Tanner Stages were not reported).[46]

7.3.5 Risks of sexual dysfunction

Concerns have been raised about the potential consequences of PMT on sexual function, particularly with regard to the ability to experience sexual pleasure and orgasm. In 2021, Marci Bowers—a leading vaginoplasty surgeon and then-president-elect of the World Professional Association for Transgender Health (WPATH)—voiced concerns that male patients who commenced PBs at Tanner Stage 2 and subsequently received CSH were physiologically anorgasmic, prior to and following vaginoplasty surgery.

Many of these patients reported no history of genital sexual sensation before undergoing vaginoplasty. After vaginoplasty, the constructed clitoris provided no meaningful tactile or erogenous response. Bowers suggested that this issue had not been adequately addressed in discussions of informed consent for youth undergoing puberty suppression.[47]

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[43] Klipstein et al. (2020).
[44] Practice Committee of the American Society for Reproductive Medicine (2019).
[45] Chen et al. (2017); Chiniara et al. (2019); de Nie et al. (2024); Nahata et al. (2017).
[46] Pang, Peri, et al. (2020).
[47] Shrier (2021b). It has been questioned "whether even highly intelligent children who have not had sexual experiences can meaningfully comprehend the loss of future sexual function and reproductive abilities" (Levine et al., 2022a, p. 720).

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Despite these concerning clinical observations, there is a striking paucity of research on sexual function outcomes in this population.[48] The potential for anorgasmia and sensory dysfunction merits serious consideration, especially given the irreversible nature of some interventions and the centrality of sexual health to overall quality of life.

There is a lack of published research regarding sexual function outcomes in females who underwent PMT with PBs followed by CSH.

7.4 Cross-sex hormones and gender dysphoria

Testosterone for females and estrogen for males are routinely used in PGM to induce changes in the secondary sex characteristics that resemble those typical of the opposite sex. In males, estrogen is frequently used alongside a testosterone blocker or PB to enhance estrogen's effects.

7.4.1 Physical effects of cross-sex hormones

As described above, puberty involves the maturation of primary sex characteristics—the male and female genitalia—and the entire reproductive system, enabling the production of mature gametes: sperm in males and ova in females. The ES guidelines for PMT describe titration of testosterone for females and estrogen for males as the "Induction of Puberty," a term that is misleading.[49] Under the influence of high doses of testosterone, females may develop facial and body hair, cystic acne, male pattern scalp hair distribution, clitoral growth, changes in musculature, thickening of vocal cords leading to voice deepening, and alterations in fat deposition. Similarly, males receiving high doses of estrogen may experience significant breast tissue growth (gynecomastia), reduced muscle mass, change in skin texture, and may develop a more typically female pattern of fat distribution. These physical changes reflect the body's response to unusually high levels of sex steroids, not actual opposite-sex pubertal development. In fact, development of reproductive capacity—definitionally, the purpose of puberty—may be

[48] Two Dutch studies have published data from one small patient cohort: Bungener et al. (2020); van der Meulen et al. (2025). Although the researchers found that for the males, sexual function outcomes after vaginoplasty were similar regardless of which Tanner Stage of puberty PBs had been started in, experts pointed out that the small study was methodologically limited due to sample size (therefore unable to reliably compare different subgroups) and that the patients frequently reported serious sexual difficulties/dysfunction (orgasm difficulties, pain, shame about genitalia) (Clayton et al., 2025).

[49] Hembree et al. (2017, p. 3884), for example. See also Coleman et al. (2022, p. S115), and Chapter 2.

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hindered. The physiological end point of puberty—sexual maturation that makes possible reproduction—is not and cannot be obtained via PMT.

7.4.2 Dosing of cross-sex hormones

In WPATH and ES guidelines, the principal goal of CSH administration is to induce physical characteristics typical of the opposite sex. When hormone levels rise beyond the typical reference range for a person's sex, they are considered supraphysiologic. ES guidelines suggest that the sex an individual identifies as—as opposed to their biological sex—should determine the target reference range for hormonal concentrations.[50] Critics have argued that perceived identity does not alter physiological processes and that such a belief can result in inappropriate and potentially dangerous hormone dosing.[51]

7.4.3 Hyperandrogenism in females

Hyperandrogenism refers to the condition of abnormally elevated androgen levels—most commonly testosterone—in the bloodstream. Among adult females, typical serum testosterone levels range between 2–45 ng/dL. In certain pathological conditions, testosterone may rise well above this range.

ES guidelines for cross-sex hormone administration in females recommend testosterone between 320–1000 ng/dL, comparable to, or exceeding levels found in endocrine disorders.[52] These concentrations represent a six to 100-fold increase above physiologic norms for females, inducing hyperandrogenism. Hyperandrogenism is also associated with health risks, discussed below.

7.4.4 Hyperestrogenemia in males

Hyperestrogenemia is defined as elevated blood levels of estrogens, such as estradiol, above the normal physiological range. In males, the standard reference range for estradiol is approximately 60–190 pg/mL. Certain disease states are known to cause

[50] Rosenthal et al. (2019).
[51] Laidlaw et al. (2021).
[52] Hembree et al. (2017).

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excess estrogen. For instance, certain adrenal tumors can elevate estrogen levels by a factor of 3 to 10.[53]

In PMT, supraphysiologic estrogen levels are intentionally induced through the off-label use of high doses of estrogen. ES guidelines advise titration of estradiol to levels between two and 43 times higher than the typical male range to induce the development of female-typical secondary sex characteristics such as breast tissue.[54]

7.4.5 Effects of testosterone on the female reproductive system

Testosterone use causes histopathological changes in the female reproductive tract.[55] Given the potential—though not well-defined—risk of cancer in the female reproductive tract, ES guidelines recommend that "health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer."[56] WPATH's clinical practice guideline[57] has not adopted the same recommendation, but there is limited reliable evidence regarding the long-term cancer risks associated with testosterone use in the female reproductive tract. Testosterone can cause reproductive organ atrophy, including thinning and atrophy of vaginal epithelium,[58] persistent pelvic pain and discomfort,[59] and pelvic floor dysfunction.[60]

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[53] Cavlan et al. (2010).
[54] Hembree et al. (2017).
[55] A review of 11 histopathologic studies of resected ovaries found that 34.9% exhibited polycystic-appearing ovaries, and 0.7% had benign ovarian neoplasms (Toland et al., 2023). In another study of females aged 18-56, 57% of 35 ovariectomy cases showed multiple bilateral cystic follicles, and 80% of 40 uterine resections displayed endometrial stromal fibrosis. Abnormal tissue growth was also noted in the vagina and cervix following hysterectomy and vaginectomy. The most common findings included transitional cell metaplasia and the development of prostatic-type glands (Lin et al., 2022). A separate study found that 100% of vaginectomy specimens contained abnormal prostatic tissue growth (Xu et al., 2022).
[56] Hembree et al. (2017).
[57] Coleman et al. (2022).
[58] In 2020, a whistleblower from Washington University in St. Louis clinic described a case in which a female minor taking testosterone called the clinic due to vaginal bleeding: "In less than an hour she had soaked through an extra heavy pad, her jeans, and a towel she had wrapped around her waist … We found out later this girl had had intercourse, and because testosterone thins the vaginal tissues, her vaginal canal had ripped open. She had to be sedated and given surgery to repair the damage" (Reed, 2023a). Reportedly, multiple patients at this clinic had problems with vaginal lacerations.
[59] Patients have sought hysterectomies due to these symptoms; e.g., Zwickl et al. (2023).
[60] Da Silva et al. (2024); Tordoff et al. (2023); Zwickl et al. (2023).

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7.4.6 Effects of estrogen on the male reproductive system

Testicles have two primary functions: producing testosterone and generating sperm capable of fertilizing an ovum. The use of estrogen in accordance with the ES and WPATH guidelines results in impairment of normal testosterone production and significant abnormal histologic changes to the male reproductive system.[61] These findings point to widespread structural reconfiguration of testicular tissue in response to prolonged exposure to the high levels of estrogen used in medical transition.

7.4.7 Cardiovascular and metabolic risks

Among the most significant long-term risks associated with CSH is an increase in cardiovascular risk factors. A 2018 review found that patients taking CSH had an elevated risk of heart attack and CV mortality compared to controls.[62]

Several studies and reviews have found increased risk of CV events like heart attacks and strokes in females taking testosterone.[63] This is thought to result from testosterone's effects on underlying metabolic factors related to CV risk. In females, testosterone can cause elevated blood pressure, polycythemia, and atherogenic

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[61] In one study of 99 testicle specimens, Leydig cells (crucial for producing testosterone) were completely absent or extremely diminished in 80% of cases. There was a significant average decrease in the diameter of the seminiferous tubules (site of spermatogenesis) when compared with controls, with 82% showing peritubular fibrosis, which interferes with tubular function (Matoso et al., 2018). In another study, 74% of specimens had abnormal basement membrane thickening (Riva-Morales et al., 2025). This mimics findings seen in conditions like cryptorchidism (undescended testes), which are associated with infertility (Mittal et al., 2017). In one of the abovementioned studies, all 125 testicular specimens showed atrophic changes and decreased spermatogenesis, with 71.2% having no sperm production at all (Riva-Morales et al., 2025). In another study, 80% of testicular tissue samples from males on estrogen showed maturation arrest, meaning that although the early stages of the sperm development may have begun, maturation to fully functioning spermatozoan did not occur (Matoso et al., 2018). These findings point to widespread structural reconfiguration of testicular tissue in response to prolonged exposure to high levels of estrogen used in medical transition. Other structures affected by estrogen (and/or androgen deprivation) include the epididymis, rete testes, and prostate (Crowley et al., 2023; Matoso et al., 2018). A long-term analysis involving 86 patients who underwent orchiectomies after a median duration of 7.5 years on estrogen therapy found a clear correlation between the length of hormonal treatment and the degree of tissue abnormality (Marins et al., 2024). This study discussed "[c]ompromise in integrity of blood-testis-barrier with *increased vulnerability to cytotoxic and immune damage*; impaired adhesion with premature detachment of spermatids from Sertoli cells, causing altered shaping in spermatids; germ cells phagocitation" as theoretical mechanisms of impaired spermatogenesis (emphasis added).

[62] Irwig (2018).

[63] E.g., Nota et al. (2019). A systematic review found moderate and high certainty evidence of some incidence of cardiovascular events in young females under 26 years old (Miroshnychenko, Ibrahim et al., 2025).

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changes in the lipid profile.[64] Longitudinal studies of PMT have reported increases in BMI (and/or fat mass) after initiation of CSH[65] and PBs.[66] Atherogenic changes to the lipid profile have also been reported.[67]

With respect to polycythemia, elevated hematocrit levels are known to increase blood viscosity, raising the risk of thromboembolic and CV complications. Among females, even modest elevations in hematocrit levels have been independently associated with heightened risks of CV disease, coronary events, and CV-related mortality.[68]

In males taking estrogen, studies have shown increased risk of CV events like venous thromboembolism and stroke.[69]

7.4.8 Other risks associated with cross-sex hormones

In both sexes, CSH use may be associated with early mortality.[70] In females taking testosterone, breast tissue undergoes structural remodeling, often with increased fibrous connective tissue and decreased glandular volume.[71] There is also some concern about possible increased risk of breast and ovarian cancer.[72] In males, some studies suggest that estrogen may increase risk of developing multiple sclerosis[73] and thyroid cancer,[74] and that it may lead to a decrease in brain volume.[75] However, research in these areas is still preliminary. While breast cancer is uncommon in natal males, data suggest that high-dose estrogen therapy increases this risk.[76] Other effects

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[64] Glintborg et al. (2024); Safer & Tangpricha (2019).
[65] Boogers et al. (2024); Jarin et al. (2017); Klaver et al. (2018, 2020).
[66] Carmichael et al. (2021); Ciancia et al. (2024); Delemarre-van de Waal & Cohen-Kettenis (2006); Fisher et al. (2024).
[67] Klaver et al. (2020); Olson-Kennedy, Okonta, et al. (2018). Millington et al. (2021) found atherogenic changes only in females, not in males.
[68] Gagnon et al. (1994). In a longitudinal cohort study of 1,073 adult females taking testosterone (Madsen et al., 2021), approximately 24% of participants developed hematocrit values ≥50%, a threshold commonly used to define severe erythrocytosis. While the study did not report prevalence in the intermediate range (hematocrit levels between 45% and 50%) it is reasonable to infer that a similar or greater proportion of individuals would fall within this bracket.
[69] Nota et al. (2019) reported a nearly five-fold (4.6x) elevation in risk of venous thromboembolism, and Getahun et al. (2018) reported a nearly ten-fold (9.9x) elevation in risk of stroke.
[70] C. J. de Blok et al. (2021).
[71] Grynberg et al. (2010).
[72] Hembree et al. (2017).
[73] Papkoor et al. (2016); White et al. (2022).
[74] Derwahl & Nicula (2014).
[75] Pol et al. (2006); Seiger et al. (2016); Zubiaurre-Elorza et al. (2014).
[76] C. J. M. de Blok et al. (2019).

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of estrogen may include diminished libido, erectile dysfunction, and loss of spontaneous erections.[77]

7.5 Surgery and gender dysphoria

WPATH provides an extensive list of surgeries it considers appropriate treatments for GD.[78] All surgeries carry risks,[79] some of which are amplified when surgery follows PBs and CSH. Further, surgeries to remove healthy and functioning organs introduce a unique set of iatrogenic harms not encountered in other areas of medicine.

7.5.1 Surgical problems related to early pubertal blockade

Males who initiate PBs at Tanner Stage 2 and then proceed to estrogen have narrowed options for future genital surgery, should this be desired. PBs arrest development of male genitalia. If PBs are started in Tanner Stage 2 and estrogen is started some time thereafter, the male genitalia will never develop beyond the prepubertal or early-pubertal state. For patients who proceed with vaginoplasty later in life, this may foreclose the surgical option of penile inversion vaginoplasty due to lack of sufficient genital tissue for this procedure. This issue was recognized in the original Dutch papers,[80] but over subsequent decades almost no research has been published on this topic. A single Dutch study found greatly increased odds of receiving intestinal vaginoplasty (compared to penile inversion) in male patients with history of pubertal blockade.[81] Intestinal vaginoplasty is a more technically complex and risky procedure.[82] One notable and tragic case involved a member of the original Dutch Protocol research cohort who died

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[77] Hembree et al. (2017). Of note, some or all of these effects on sexual function (diminished erections, for example) may be desired by certain patients.
[78] According to WPATH's SOC-8, even highly unusual surgeries such as non-binary mastectomies (where female breasts are reshaped to resemble gynecomastia in males), penis-preserving vaginoplasty, and vagina-preserving phalloplasty (to provide patients with both sets of genitals), and genital nullification procedures (involving genital removal) are considered medically-necessary procedures for some patients. Only phalloplasty for females has a minimum recommended age of 18 (Coleman et al., 2022). In 2024, a Canadian patient successfully sued a provincial health insurer, who had declined to cover "penile-preserving vaginoplasty" surgery, considering it experimental. Media coverage noted that "…the court decided that [this] procedure…[was] consistent with the World Professional Association for Transgender Health (WPATH) Standards of Care, the leading authority on gender-affirming medical and surgical care, especially as it recommends individualized treatment plans" (Arsenych, 2024).
[79] E.g., bleeding, infection, scarring, and risks related to anesthesia.
[80] Delemarre-van de Waal & Cohen-Kettenis (2006).
[81] van de Grift et al. (2020).
[82] Lee et al. (2023).

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from necrotizing fasciitis at age 18 following an intestinal vaginoplasty conducted because of inadequate genital tissue.[83]

7.6 Other risks associated with hormonal interventions or surgeries

The use of endocrine interventions affects multiple organ systems beyond the reproductive tract. In addition, there are psychological risks associated with PMT.

7.6.1 Adverse psychiatric effects

The FDA-mandated labeling for testosterone cautions about abuse potential, noting: "Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication ... Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions." These effects have been reported in males and females, including adolescents.[84]

Research on anabolic steroid misuse has demonstrated associations with severe psychiatric problems, including mood instability, psychosis,[85] and dependence.[86] The most frequently observed symptoms include irritability, aggression, euphoria, inflated self-perception, impulsivity, and risk-taking behaviors. Additional manifestations may include acute psychotic episodes, worsening of tic disorders or depression, and delirium-like states. One study assessing medium (300–1000 mg/week) and high (>1000 mg/week) anabolic steroid use found that 23% of users met diagnostic criteria for a major mood disorder, including mania, hypomania, or depression, while 3.4-12% developed psychotic features.[87]

In an analysis of the FDA's Event Reporting System (FAERS) database for people using CSH for medical transition, 88% of adverse drug reactions were classified as serious.[88] Without an idea of denominators, individual risks are not possible to quantify. Among the 83 reports regarding females using testosterone, 87.8% of the events were deemed

[83] Negenborn et al. (2017).
[84] Actavis Pharma, Inc. (2018).
[85] R. C. W. Hall et al. (2005).
[86] Skauen et al. (2023).
[87] R. C. W. Hall et al. (2005).
[88] Gomez-Lumbreras & Villa-Zapata (2024).

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serious, with two reported deaths (2.4%) and 25 hospitalizations (30.5%).[89] Reported psychological harms included anxiety, depression, mood swings, suicidal ideation and behavior, aggression, dissociation, and self-harm. More extreme symptoms, such as antisocial behavior and homicidal ideation, were also documented.[90]

A separate study from Sweden found an elevated rate of criminal convictions in natal females who had taken testosterone and undergone gender-transition surgery, compared to age-matched controls. This study also found that adults who had undergone medical and surgical transition had 19 times the rate of suicide deaths and nearly three times the rate of all-cause mortality and inpatient psychiatric care compared to age and sex-matched controls.[91] Elevated suicide rates (compared to the general population) have also been reported in other studies.[92] It is impossible to determine causation based on this data, in part due to presence of confounders like co-occurring mental health conditions.

7.6.2 Detransition and regret

In males, estrogen causes breast growth and infertility that may be irreversible even with cessation of CSH.[93] In females, irreversible virilizing effects of testosterone include face and body hair growth, deepening of the voice, clitoral growth, and male-pattern baldness.[94] Patients of any age may experience regret regarding the permanent physical and physiologic effects of CSH, regardless of how they identify. For example, stably transgender-identified patients may regret loss of fertility. Developing baldness, or chafing/discomfort caused by clitoromegaly, may lead a patient who identifies as a transgender man to regret taking testosterone.

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[89] Laidlaw & Jorgensen (2024).
[90] Laidlaw & Jorgensen (2024).
[91] Dhejne et al. (2011).
[92] C. J. de Blok et al. (2021) found that the standardized mortality ratio for suicide among transgender adults was 3.1 compared to the general population of the Netherlands. In Van Cauwenberg et al. (2021), five out of 177 adolescent patients died by suicide. All suicide deaths were in patients who had been started on CSH (Society for Evidence-Based Gender Medicine, 2024a). Biggs (2022) reported that four out of 15,032 patients referred to the U.K.'s pediatric gender medicine (PGM) clinic died by suicide over a ten-year period. Two of the suicides were in waitlisted patients (i.e., probably not taking CSH). A recent U.S. study reported a suicide rate of two out of 315 patients taking CSH over a two-year period (Chen et al. 2023).
[93] Cheng et al. (2019); Deutsch (2020a).
[94] Deutsch (2020b).

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If patients do detransition,[95] they may experience regret,[96] but some patients may integrate the physical changes into their self-concept and not experience regret.[97] Even proponents of PMT acknowledge that regret is a risk (e.g., the phrase "Some adolescents may regret the steps they have taken" in WPATH's guidelines).[98]

This serious issue has been minimized with the claim that detransition and regret rates are vanishingly low. In fact, the detransition rate is unknown.[99] The ubiquitous claim that the detransition and regret rates are vanishingly low is unsupported by the evidence.[100] A U.K. population-based study not focused on minors found that about one-fifth of patients discontinued hormonal interventions within five years, with more than half of them reporting experiences of detransition and/or regret.[101] Reasons for detransition are complex[102] and can be related to external[103] or internal[104] factors. With respect to

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[95] Detransition refers to reverting back to living as one's sex after having medically and/or surgically transitioned. For discussion of detransition as a phenomenon see Butler & Hutchinson (2020); Irwig (2022); MacKinnon, Expósito-Campos et al. (2023). For research based on survey data from detransitioners or their parents, see Bailey & Diaz (2023); Littman (2018), (2021); Vandenbussche (2022).

[96] Some detransitioners have described adverse experiences with CSH as well as regret; e.g., in a recent court case (DH v. Snyder Case: 21-15668, 07/07/2021, ID: 12164749, DktEntry: 22, n.d.) one patient described that testosterone "exacerbated her anxiety and depression" in addition to prompting increased aggression, risk-taking, and suicidal ideation (p. 22); another patient experiencing depression after several months of euphoria, (p. 24) and another described ongoing regret and distress due to a permanently deepened voice from testosterone and numb scars and absent breasts from mastectomy surgery (p. 18).

[97] MacKinnon et al. (2022).

[98] Coleman et al. (2022, p. S47).

[99] Cohn (2023).

[100] The detransition rate after PBs and CSH has been described as very low, but this is backed by little evidence. A few sources are frequently cited. One is an SR of surgery studies with limited (if any) relevance to PMT, which reported a regret rate of around 1% (Bustos et al., 2021). This SR had methodological problems, calculation errors, and included mostly studies of poor or moderate quality, many with follow-up times that were inadequate for capturing regret (Cohn, 2023; Expósito-Campos & D'Angelo, 2021). Additionally, there were issues with the ways included studies defined regret; in Wiepjes et al. (2018), for example, patients needed to report regret to their clinician and ask to start natal sex hormones. Another study was based on survey research of individuals who identified as transgender *at the time of survey completion*. Some respondents had detransitioned in the past (usually due to factors like stigma or other external difficulty) before re-identifying as transgender (Turban et al., 2021). A survey of surgeons found respondents had rarely been asked to perform reversals (Narayan et al., 2021); Cohn (2023) noted that these findings were hard to interpret because of "unclear follow-up time, loss to follow-up, and even measurement instrument (Were questions about regret routinely asked and was there a consistent definition of regret in use?)" (p. 1944). Another study of surgical regret partly quantified regret via request for surgical reversals (Jedrzejewski et al., 2023), which Cohn pointed out would have excluded patients who do not return to their surgeons.

[101] Boyd et al. (2022).

[102] MacKinnon, Gould et al. (2023).

[103] Turban et al. (2021).

[104] Littman (2021); Littman et al. (2024).

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clinical research studies of children and adolescents, one study reported a 7.1% regret rate,[105] two found low rates of CSH discontinuation or reidentification with birth sex (<5%),[106] and one found a higher rate of CSH discontinuation (25%).[107]

7.7 Mortality risk

Four population-based cohort studies have found that transgender individuals appear to have higher mortality risk when compared to members of the general population of similar age and sex. In the U.S., private insurance data from 2011 to 2019 indicated that transgender persons were nearly twice as likely to die as age- and sex-matched controls.[108] A Dutch cohort study that included five decades of data found that compared to their natal sex peers, transgender people had an elevated standardized mortality ratio (higher risk of death).[109] A 2023 cohort study from the U.K. found that compared to their natal sex peers, transgender people had higher risk of mortality (34 % higher for females, 60% higher for males).[110] Finally, a Swedish study that included three decades of data found that the mortality risk for transgender persons was 2.8 times that of age and natal sex matched population controls.[111]

This Review does not assess the methodological quality of these epidemiological studies or quantitatively synthesize their findings. The magnitude of the mortality risk for maintaining a transgender identity remains uncertain, as do the underlying causal factors (causes of death found to be elevated among transgender persons included suicide, cardiovascular disease, and HIV[112]). Moreover, in light of ongoing epidemiological shifts (see Section 4.3.1.1), it is unclear whether these findings extend to children and adolescents with gender dysphoria (GD). These studies further support a cautionary stance toward PMT, however, especially insofar as the Dutch cohort study

[105] Crabtree et al. (2024).
[106] Cavve et al. (2024); van der Loos et al. (2022).
[107] Roberts et al. (2022).
[108] Hughes et al. (2022).
[109] de Blok et al. (2021).
[110] Jackson et al. (2023).
[111] Dhejne et al. (2011).
[112] See de Blok et al., 2021; Dhejne et al., 2011; Hughes et al., 2022; Jackson et al. 2023.

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found that despite changes in care of the transgender population over five decades, the elevated mortality risk has persisted, not declined.[113]

[113] de Blok et al. (2021).

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Chapter 8 Summary and Implications of Evidence Review

Medical and surgical interventions for children and adolescents with gender dysphoria (GD) are widely promoted as essential and even lifesaving, yet the evidence base does not support strong conclusions about their effectiveness in improving mental health or reducing GD. Analysis of the biological plausibility of harms is necessary, and suggests that some short- and long-term harms are likely (in some cases expected) sequelae of treatment.

The Food and Drug Administration (FDA) also looks at risks in this manner when making a risk/benefit determination:

> Benefit-risk planning is most valuable in cases where a challenging benefit-risk assessment can be reasonably anticipated, either because the extent of benefit is expected to be modest or is highly uncertain, or when serious adverse events of the drug can be anticipated (e.g., based on a suspected class effect, understanding of the mechanism of action, and/or early-phase or non-clinical safety findings).[1]

The FDA states that with respect to risks, it is important to understand suspected class effects, meaning the types of predicted effects that are known to occur within the same class of medications. For example, the class of diuretics called thiazides are known to cause hypokalemia (low potassium), and so this potential adverse effect must be taken into account when making a risk/benefit determination regarding thiazides.

The FDA also emphasizes the importance of understanding the physiological mechanism of action, meaning the known way in which a drug affects the body. For example, medications called beta blockers affect the beta-adrenergic receptor and by their known mechanism of action cause effects such as slowed heart rate and decreased cardiac contractility. These physiological mechanisms—and the potential adverse effects of bradycardia (slow heart rate) and reduced cardiac output (amount of

[1] Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) (2023).

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blood pumped by the heart)—must be taken into account when making a risk/benefit determination regarding beta blockers.

Similarly, risk/benefit determinations regarding PMT must take into account both class effects and known mechanism of action for these interventions. Moreover, as the FDA also emphasizes, when the risks of a treatment are serious, anticipated effects must be proportionate:

> In cases where serious risks are anticipated, it is important to consider whether the risk can be outweighed by a benefit of sufficient certainty, magnitude, and clinical relevance to patients.[2]

Some of the plausible harms of PMT are serious. The likelihood of infertility when puberty blockers (PBs) are provided at the early stage of puberty and followed by cross-sex hormones (CSH) does not have to be demonstrated in a clinical trial. This is because the mechanism is well-understood and conducting a trial would amount to an unethical "parachute test."[3]

Analysis of all available data described in this section of the Review suggests that the risk/benefit profile of medical and surgical interventions for children and adolescents with GD is unfavorable.

This has implications for decision-makers—ranging from individual clinical care to guideline development, health policy, and regulation.[4] The findings of this evidence review also underscore the importance of clearly distinguishing how values and preferences are incorporated at different levels of decision-making.

At the individual level, shared decision-making must be grounded in transparency. This means that patients and their families need to be fully informed—not just about available interventions, but also about their potential benefits, harms, alternative

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[2] Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) (2023). See Chapter 13 for discussion of ethical implications.
[3] Smith & Pell (2003). The paper highlights the limitations of "gold-standard" research designs such as randomized controlled trials (RCTs) by pointing out that no RCTs have been done on the effects of jumping from a plane without a parachute. Narrow (mis)application of EBM would conclude that there is "very low certainty evidence" of death, given the dearth of high quality studies.
[4] Zeng et al. (2023); Zhang et al. (2017).

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options, and the certainty or uncertainty of the supporting evidence. When this information is missing or inaccurate, the values and preferences people express may be influenced by incomplete understandings.[5]

At the level of clinical practice guidelines and health policy, values and preferences should reflect those of a population well-informed about the strength of evidence. Weak or uncertain evidence for benefits requires greater caution and flexibility, not stronger recommendations.[6]

At the regulatory level, because decisions must prioritize public health and safety, the strength of the evidence is especially important. When evidence for benefit is lacking or of very low certainty, regulatory frameworks should focus on ongoing evaluation, risk mitigation, and the collection of more robust data before allowing broad implementation. At all levels, responsible decision-making requires a clear grasp of what is known, what remains uncertain, and how this understanding informs ethical obligations of clinicians. Several of the other chapters in this Review explore these issues in greater depth.

[5] Zhang, Alonso-Coello, et al. (2019); Zhang, Coello, et al. (2019).
[6] Guyatt et al. (2008).

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PART 3

CLINICAL REALITIES

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Chapter 9 Review of International Guidelines

Like in other areas of medicine, clinical care for gender dysphoric (GD) youth is typically guided by clinical practice guidelines (CPGs). The aim of such guidelines is to promote practices that are proven to improve patient outcomes and reduce unwarranted variation in care. Although guidelines are not mandates and clinicians must still exercise professional judgment, they serve as important reference points that influence treatment decisions, institutional protocols, insurance coverage policies, and broader standards of medical practice.

This chapter provides an overview of CPGs that address care for youth with GD. Section 9.1 is a primer on the purpose and characteristics of trustworthy evidence-based guidelines. Section 9.2 provides an overview of the quality of the existing guidelines in the area of pediatric gender medicine as assessed by two systematic reviews (SRs). It also discusses the newest guidelines not included in the extant SRs. Section 9.3 profiles the clinical recommendations set out in the only two guidelines rated as trustworthy (both from Nordic countries).

9.1 The role and process of clinical practice guidelines

Clinical practice guidelines are a set of clinical care recommendations intended to optimize patient care.[1] While used primarily by healthcare providers, CPGs also guide hospitals in standardizing care, informing insurance coverage decisions, shaping health policy, and supporting medical education. Researchers use them to identify knowledge gaps, and legal professionals may cite them in malpractice cases. Informed patients and caregivers may also rely on CPGs to participate in shared decision-making and advocate for appropriate care.

The field of evidence-based medicine (EBM) provides several sources describing the characteristics of a trustworthy guideline.[2] According to the National Academy of Medicine (NAM),[3] trustworthy CPGs:

[1] Brignardello-Petersen et al. (2021).
[2] Brignardello-Petersen et al. (2021); Brouwers et al. (2010); Lima, Mirza et al. (2023).
[3] Formerly the Institute of Medicine.

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> should be *based on a systematic review of the existing evidence*; be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups; consider important patient subgroups and patient preferences, as appropriate; be based on an explicit and transparent process that *minimizes distortions, biases, and conflicts of interest*; provide a clear explanation of the logical relationships between *alternative care options* and health outcomes, *provide ratings of both the quality [certainty] of evidence and the strength of the recommendations*; and be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.[4]

Most guideline users will focus on two core elements of guidelines: the content of the recommendations, and their strength. One of the most widely accepted approaches to rating the strength of recommendations is the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. GRADE classifies recommendations according to their direction and strength into four categories: 1) strong recommendation for an intervention; 2) conditional or weak recommendation for an intervention; 3) conditional recommendation against an intervention; and 4) strong recommendation against an intervention.[5]

In addition, there is a GRADE recommendation known as "only in research."[6] It is used sparingly in situations in which an intervention may be promising but lacks sufficient evidence to support its general use. The "only-in-research" recommendation is appropriate when three conditions are met: 1) the available evidence is of low or very low certainty, making it unclear whether the intervention provides meaningful benefit; 2) further research has a large potential to reduce this uncertainty and produce more definitive evidence; and 3) conducting such research is deemed valuable given anticipated costs and risks. This recommendation may be accompanied by a second strong recommendation not to use the intervention outside the research context.[7]

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[4] Graham et al. (2011, p. 5, emphasis added).
[5] Andrews, Schünemann et al. (2013).
[6] Agarwal et al. (2020).
[7] Andrews, Guyatt et al. (2013, p. 724); Guyatt, Oxman, Kunz et al. (2008, p. 1051).

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In addition to interpreting evidence of benefits and harms, guideline panels that develop CPGs also must "trade off the benefits and risks, burden, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and values and preferences" to make their final recommendations and GRADE them for strength.[8] Guideline development groups must be free from or carefully manage financial, intellectual, and personal conflicts of interest, and should represent diverse and balanced views.

The credibility of guidelines should be assessed before their recommendations are accepted as trustworthy. A guideline's trustworthiness and authority depend on how closely the development group adhered to best practices for guideline development.[9] The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument is one of the most well-established validated tools for assessing the quality and methodological rigor of CPGs. The AGREE II instrument evaluates guidelines across six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Each domain is rated on a standardized 7-point scale, with higher scores indicating greater methodological quality and trustworthiness. AGREE II further provides two overall assessments, one summarizing the guideline's overall quality and another evaluating whether the guideline should be recommended for implementation in clinical practice. By promoting transparency and consistency in guideline appraisal, AGREE II helps healthcare providers, policymakers, and patients identify guidelines most likely to improve patient outcomes and quality of clinical decision-making. Other approaches for evaluating the trustworthiness of CPGs emphasize related but distinct dimensions.[10]

9.2 Summary of systematic appraisals of clinical guidelines and guidance documents

At least two SRs have evaluated the quality (trustworthiness) of CPGs addressing the care of patients with GD. One focused on guidelines applying to all age groups,[11] and

[8] Guyatt et al. (2015).
[9] Graham et al. (2011).
[10] Brignardello-Petersen et al. (2021); Lima, Mirza et al. (2023).
[11] Dahlen et al. (2021).

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the other on guidelines devoted specifically to the care of youth.[12] Both relied on AGREE II.[13] This section focusses on the SR that assessed guidelines for pediatric GD, which was conducted by researchers at the University of York to inform the development of the Cass Review.[14]

The York analysis identified 23 and appraised 21 clinical guidelines and clinical guidance documents for their methodological rigor and quality. York's analysis revealed three main findings: 1) all the guidelines, with the exception of two (from Sweden and Finland), were found to be untrustworthy due to serious deviations from the methodological standards for trustworthy guideline development; 2) most international guidance documents have relied heavily on WPATH and Endocrine Society (ES) guidelines,[15] which were themselves closely linked through overlapping authors and with WPATH acting as a sponsor for the development of ES guidelines; and 3) none of the three guidance documents that have shaped the United States's approach to pediatric GD are trustworthy due to serious problems in their development methodology.[16]

9.2.1 Methodological quality of existing guidelines and guidance documents

All guidelines and guidance documents appraised by the York SRs were evaluated across AGREE II's six domains. The SR authors also provided two assessments, one on quality of the guideline overall, and the other on whether the guideline can be recommended for clinical implementation.

The reviewers noted that while generally most guidelines scored well in the domain of "clarity of scope and purpose," most scored poorly in the domains of "rigour of development," "editorial independence," and "applicability," the domains that tend to

[12] Taylor, Hall, Heathcote et al. (2024a, 2024b).
[13] Brouwers et al. (2010).
[14] Taylor, Hall, Heathcote et al. (2024a, 2024b). In this chapter, as in this two-part systematic review (SR), the word "guidelines" will be used to refer to the various documents that were appraised, some of which were not formal clinical practice guidelines (CPGs). The reviewers included "published articles or documents that [provided] at least one specific recommendation for the assessment and/or care of children and/or adolescents (age 0–18) experiencing gender dysphoria/incongruence, and which were developed by or for a professional, healthcare or government organisation or from a research study" (Taylor, Hall, Heathcote et al., 2024a, p. s66).
[15] Coleman et al. (2012); Hembree et al. (2009); Hembree et al. (2017).
[16] See Taylor, Hall, Heathcote et al. (2024a).

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most strongly influence the overall rating and the recommendation for use in clinical practice.[17]

Only the Swedish and the Finnish guidelines were rated as "recommended for implementation" by all reviewers; they also received the highest overall quality score, with Sweden rated as 6 and Finland rated as 5 (out of 7).[18] The Swedish and Finnish guidelines were the only guidelines that described how the evidence base was reviewed and that linked the evidence to clinical recommendations. All other guidelines and guidance documents scored between two and four and were not recommended for implementation by one or more reviewers.[19]

Overall, the reviewers described existing guidance documents that recommend pediatric medical transition (PMT) as "[lacking] an independent and evidence-based approach," noting that it was difficult to detect what evidence had been reviewed and how this informed development of recommendations. Moreover, they reported that the links between specific recommendations and evidence were often unclear or missing.

[17] Hoffmann-Eßer et al. (2018).
[18] See Figure 9.1 below.
[19] Taylor, Hall, Heathcote et al. (2024a, p. s65).

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Figure 9.1[20]

Guideline ID	OQA1	R1	OQA2	R2	OQA3	R3
AACAP 2012	3	No	3	No	4	Yes (mod)
American Academy of Paediatrics 2018	2	No	3	No	1	No
American Psychological Association 2015	3	No	2	No	3	No
Council for Choices in Healthcare Finland 2020	5	Yes (mod)	5	Yes	5	Yes (mod)
de Vries 2006	2	No	3	No	2	No
Endocrine Society 2009	3	No	4	No	4	Yes (mod)
Endocrine Society 2017	4	Yes (mod)	4	No	4	Yes (mod)
European Society for Sexual Medicine 2020	3	Yes (mod)	2	No	3	No
Fisher 2014	2	No	3	No	1	No
Health Policy Project 2015	2	No	1	No	2	No
Norwegian Directorate of Health 2020	3	No	3	Yes (mod)	4	Yes (mod)
Oliphant 2018	2	No	3	No	1	No
Pan American Health Organisation 2014	2	No	2	No	1	No
Royal Children's Hospital Melbourne 2018	3	No	3	No	2	No
Society for Adolescent Health and Medicine 2020	2	No	2	No	1	No
South African HIV Clinicians Society 2021	3	No	3	No	2	No
Strang 2018	3	Yes (mod)	2	No	2	No
Swedish National Board of Health & Welfare 2022	6	Yes (mod)	6	Yes	6	Yes
University California San Francisco 2016	3	No	2	No	3	No
WPATH 2012	3	Yes (mod)	3	No	2	No
WPATH 2022	3	Yes (mod)	3	No	3	No

OQA: Overall quality assessment - 1-7 where 1 is lowest possible score and 7 is the highest possible score

R: Recommend guideline for use - Possible responses are Yes, Yes with modifications (Yes (mod)), No

The numbers 1-3 refer to the three reviewers who appraised the guidelines

Abbreviations
AACAP – American Academy of Child & Adolescent Psychiatry
WPATH – World Professional Association for Transgender Health

[20] Supplementary Table S3 in Taylor, Hall, Heathcote et al. (2024a).

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Figure 9.2[21]

Table 1 Critical appraisal domain scores

Guideline ID	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence
AACAP 2012	65	39	44	63	7	31
American Academy of Paediatrics 2018	70	26	12	30	6	69
American Psychological Association 2015	74	74	24	50	18	14
Council for Choices in Healthcare Finland 2020	91	69	51	72	56	0
de Vries 2006	63	31	10	74	17	6
Endocrine Society 2009	65	33	44	70	22	31
Endocrine Society 2017	63	33	42	72	21	92
European Society for Sexual Medicine 2020	63	52	39	70	7	58
Fisher 2014	65	20	12	35	17	44
Health Policy Project 2015	63	63	16	24	33	6
Norwegian Directorate of Health 2020	76	81	30	57	47	17
Oliphant 2018	44	39	12	33	21	0
Pan American Health Organisation 2014	52	44	13	31	21	0
Royal Children's Hospital Melbourne 2018	81	59	19	41	19	14
Society for Adolescent Health and Medicine 2020	41	24	17	41	7	0
South African HIV Clinicians Society 2021	59	59	21	43	24	69
Strang 2018	87	31	18	37	15	19
Swedish National Board of Health & Welfare 2022	91	87	71	83	25	36
UCSF 2016	70	41	23	37	26	0
WPATH 2012	85	61	26	56	17	17
WPATH 2022	83	63	35	56	24	39

≥70%, 31%–69%, ≤30%.
AACAP, American Academy of Child & Adolescent Psychiatry; UCSF, University of California, San Francisco; WPATH, World Professional Association for Transgender Health.

9.2.2 Interdependence of the existing guidelines and guidance documents

The SR authors noted an unusual interdependence between much of the published guidance supporting the management of children and adolescents with GD.[22] There was a marked pattern of "circular referencing and mutual endorsements"[23] between guidelines recommending PMT for routine care, with WPATH and the ES guidelines influencing all other guidelines and guidance documents.

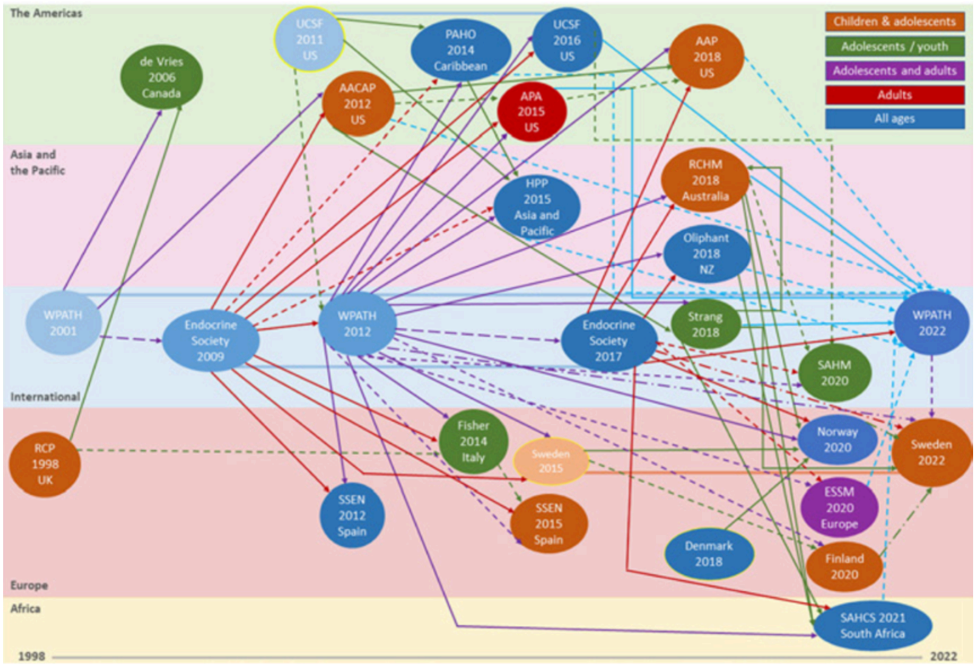
The pattern of "links and influences between guidelines"[24] had been established early in the field's tenure with the ES 2009 and WPATH 2012 guideline versions.[25] The pattern persisted as both ES and WPATH updated their guidelines in 2017 and 2022 respectively.[26] Moreover, the 2009 and 2017 ES guidelines state that WPATH was a guideline sponsor.[27] The University of York reviewers noted that this represents

[21] Taylor, Hall, Heathcote et al. (2024a, Table 1).
[22] Taylor, Hall, Heathcote et al. (2024a, pp. s69-s70).
[23] Donkin et al. (2025, p. 3).
[24] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[25] Coleman et al. (2012); Hembree et al. (2009).
[26] Coleman et al. (2022); Hembree et al. (2017).
[27] Hembree et al. (2009); Hembree et al. (2017).

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problematic circularity, "with WPATH adopting Endocrine Society recommendations in its own guideline and acting as a cosponsor for and providing input on drafts of the Endocrine Society guideline."[28]

Figure 9.3[29]



The Cass Review emphasized the interdependence and circularity of the guidance documents:

> The circularity of this approach may explain why there has been an apparent consensus on key areas of practice despite the evidence being poor … the guideline appraisal raises serious questions about the reliability of current guidelines.[30]

9.2.3 WPATH, Endocrine Society, and the American Academy of Pediatrics (AAP) guidelines and practice statements

The most influential sources of clinical guidance for treating pediatric GD in the U.S. are the WPATH and ES CPGs and the American Academy of Pediatrics' (AAP) guidance

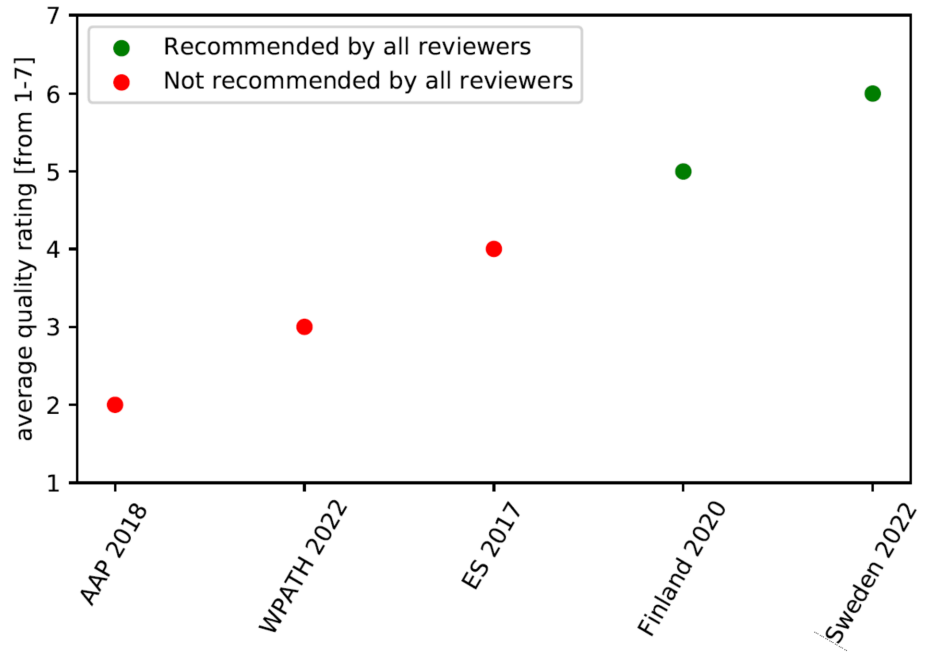
[28] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[29] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[30] Cass (2024a, pp. 129-130).

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document.[31] The York SR assessed all three documents as very low quality and did not recommend them for implementation.

Figure 9.4 plots the overall rating of the quality of these three guidance documents relative to the only two guidelines that have been recommended for implementation by the York SRs.[32]

Figure 9.4[33]



Legend**:** AAP: American Academy of Pediatrics; WPATH: World Professional Association for Transgender Health; ES: The Endocrine Society

The York appraisals found that WPATH's guideline, *Standards of Care*, Version 8 (SOC-8) and the ES guidelines were both "[lacking] in developmental rigour." SOC-8 was given an overall score of 3 out of 7; the ES guideline scored 4 out of 7. The extensive problems in the SOC-8 development process, which included the failure to base recommendations on SRs and numerous other serious limitations in the process,

[31] The American Academy of Pediatrics' (AAP) 2018 Policy Statement was reaffirmed in 2023 (Rafferty et al., 2018); the Endocrine Society's (ES) published in 2017 represents the most recent published version (Hembree et al., 2017); the World Professional Association for Transgender Health's (WPATH) most recent clinical practice guideline is *Standards of Care*, Version 8 (SOC-8) (Coleman et al., 2022).
[32] Taylor, Hall, Heathcote et al. (2024a).
[33] Figure 9.4 plots data from Supplementary Table S3 in Taylor, Hall, Heathcote et al. (2024a).

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ultimately led to this low rating and the status of "not recommended for implementation." These problems are discussed in more detail in Chapter 10.

The ES 2017 guideline, which used the GRADE framework, has been criticized for making strong recommendations for hormonal interventions in the setting of a weak evidence base.[34] Notably, none of the systematic reviews that supported the ES guidelines were based on outcomes for children or adolescents.[35] The ES recommendation to initiate puberty blockade using GnRH as was derived by putting a higher value on achieving a "satisfactory physical appearance" while putting the lowest value on avoiding physical harms.[36] The ES recommendation for the initiation of cross-sex hormones no earlier than age 16 was justified by placing a higher value on adolescent's purported ability to meaningfully consent to cross-sex hormones (CSH) and placing a lower value on avoiding harm from potentially prolonged pubertal suppression.[37]

The AAP 2018 policy statement is not technically a CPG but has been widely cited in the U.S. as influential in establishing how pediatricians respond to children and

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[34] E.g. Block (2023c). If such recommendations are made, which the GRADE framework allows in specific circumstances, the reasoning for this must be clear. The ES guidelines did not do this.

[35] Maraka et al. (2017); Singh-Ospina et al. (2017); Of note, the only study of adolescents included in these systematic reviews, Klink et al. (2015), concluded that puberty blockers impede the development of bone mass density (BMD) and cross-sex hormones fail to bring up BMD to its pretreatment potential: "Between the start of GnRHa and age 22 years the lumbar areal BMD z score (for natal sex) in transwomen decreased significantly from 0.8 to 1.4 and in transmen there was a trend for decrease from 0.2 to 0.3. This suggests that the BMD was below their pretreatment potential and either attainment of peak bone mass has been delayed or peak bone mass itself is attenuated" (Klink et al., 2015, p. E270).

[36] Full quotation: "These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression" (Hembree et al., 2017, p. 13). Published gender-affirming care literature has also described a prioritization of aesthetic outcomes, e.g., a research paper noted gender-affirming care can be beneficial because (among other reasons) "The combination of pubertal suppression and cross-sex hormones] may … increase the concordance of youths' appearance with cisgender norms …" (McGregor et al., 2024, p. 5).

[37] Full quotation: ""The recommendation to initiate pubertal induction [cross-sex hormones] only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/ harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers" (Hembree et al., 2017, p. 3885).

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adolescents with GD.[38] Because the document offers extensive clinical recommendations regarding every step of PMT—from social transition to PBs, CSH, and surgery—the York team assessed the trustworthiness of the AAP guidance using the same criteria they applied to CPGs. Using the AGREE II criteria, the AAP policy statement received the second-lowest average score among all international guidelines: 2 out of 7.

As noted in Chapter 2, the AAP's policy statement's use of "gender diverse" casts a very wide net regarding which patients the organization considers eligible for medical intervention. The statement has been heavily criticized in peer-reviewed articles, which have pointed out that it is rife with referencing errors and inaccurate citations.[39] Despite persistent advocacy among its members, who have petitioned the organization to release updated, evidence-based guidance for treating pediatric GD,[40] the organization chose to reaffirm their policy statement in 2023.[41]

9.2.4 More recent international guidelines

Since the publication of the York reviews, several new European guidelines have been issued in final or draft form, including those from the German AWMF, the French Society of Pediatric Endocrinology and Diabetology, the Polish Sexological Association, the European Society for Paediatric Endocrinology (ESPE), and the forthcoming final version of the French National Authority for Health (HAS) guidelines.[42] These reviews have been developed amid growing international awareness of the weaknesses of WPATH's SOC-8 and the outdated nature of the Endocrine Society's guidelines,

[38] Rafferty et al. (2018).
[39] E.g., Cantor (2020); McDeavitt (2025).
[40] See description of efforts led by pediatrician Julia Mason in Block (2023c).
[41] Block (2023c).
[42] The AWMF German guidelines (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy [DGKJP], 2025) are comprehensive; the guidelines by the French Society of Pediatric Endocrinology and Diabetology (SFEDP; Brezin et al., 2024) are limited to hormonal interventions and is currently available only as a preprint; the Polish guidelines, supported by the Polish Sexological Association, the Polish Psychiatric Association, and the Polish Society of Paediatric Endocrinology and Diabetology cover most aspects of PMT but are almost entirely derivative (Gawlik-Starzyk et al., 2025); the ESPE guidelines (Hannema et al., 2024) primarily focus on endocrine (medical/hormonal) interventions; the draft French national HAS guidelines became publicly available when a French newspaper published a draft in November 2024 (Sugy, 2024); the final version has not yet been released.

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reflecting the need to have defensible, localized, up-to-date guidelines that set the standards of care for youth with GD.

Unfortunately, these recently-published (or as yet to be finalized) guidelines suffer from the same or similar methodological weaknesses that have rendered the WPATH and the Endocrine Society's guidelines not trustworthy and not recommended for implementation. All suffer from non-evidence-based approaches to guideline development and exhibit one or more of the following problems: 1) guideline development groups are composed of individuals with unmanaged conflicts of interest relating to the provision of pediatric gender transition services; 2) the guideline takes an a priori WPATH-aligned position that medicalized pathway of hormones (and surgery) is the recommended treatment approach;[43] 3) the recommendations are not based on rigorously-conducted systematic reviews of evidence[44] 4) individual studies that drive treatment recommendations are not appraised for quality, and their conclusions are accepted at face value; 5) the recommendations are not graded for strength, resulting in ambiguity in clinical decision-making.

While some guidelines, in response to criticism of the draft version, have added references to systematic reviews of evidence, it is apparent that SRs were not utilized to make treatment recommendations, with apparent and unreconciled contradictions between the findings of the SRs and the treatment recommendations. [45] Alternatives such as psychological support are in nearly all cases marginalized or even entirely absent. Ongoing reliance on the "consensus-based" non-evidence-based process

[43] For example, the German AWMF guidelines state that the members of the guideline development group adhere to the WPATH positions (Society for Evidence-Based Medicine, 2025).The Polish guideline explicitly bases itself on WPATH SOC-8, without independent review, stating, "This document is based on the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (2022) [1] and an Endocrine Society Clinical Practice Guideline … The person conducting psychological or sexological assessment and care should be familiar with the content of the current standards of care of the World Professional Association for Transgender Health and comply with them" (Gawlik-Starzyk et al., 2025, pp. 4, 8).

[44] The German guidelines methodological report explicitly states that no evidence-based recommendations were developed (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP), 2025, p. 6).

[45] Society for Evidence-Based Gender Medicine (2025).

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underlines the trustworthiness of these guidelines, raising questions about the rigor of guideline development in pediatric gender medicine not just in the U.S., but worldwide.

9.3 Overview of recommendations in the high-quality guidelines

Of the 23 guidelines that were appraised in the systematic evidence review, only two were recommended for practice by all three reviewers: the guidelines from Finland (which were scored five out of seven), and those from Sweden[46] (which were scored six out of seven). Both guidelines recommend that psychotherapy—not hormones or surgeries—should be the standard of care for youth with GD, and that any use of hormones should be limited to nationally overseen research or exceptional circumstances. As described in the systematic review, the two Scandinavian guidelines were the only ones that based their treatment recommendations on systematic evidence reviews, a key element of trustworthy clinical practice guidelines.

9.3.1 Finland

In 2020, Finland's Council for Choices in Health Care (PALKO/COHERE) issued national guidelines for treating gender dysphoria in minors, representing a major shift away from the model endorsed by WPATH's *Standards of Care* Version 7.[47] Finland's guidelines emphasize that the first-line treatment for adolescents experiencing gender distress should be psychosocial support and psychotherapy, not early medical intervention.[48]

Following an SR, Finnish authorities concluded that the body of evidence supporting puberty blockers and cross-sex hormones for youth is inconclusive. Importantly, the guidelines explicitly state that "in light of available evidence, gender reassignment of minors is an experimental practice."[49] While medical transition remains possible, it is restricted to highly select cases—specifically, adolescents with persistent, childhood-

[46] In 2022, Sweden's healthcare authority, Socialstyrelsen, issued guidelines recommending that "Psychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures" (Socialstyrelsen, 2022b, p. 45).
[47] Council for Choices in Health Care Finland (2020a). There is an official English-language summary (Council for Choices in Health Care Finland, 2020c), as well as an unofficial English translation of the complete guideline document (Council for Choices in Healthcare Finland, 2020b).
[48] Council for Choices in Healthcare Finland (2020a).
[49] Council for Choices in Healthcare Finland (2020b, p. 8).

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onset gender dysphoria, no major psychiatric comorbidities, and stable identity development through adolescence.

Surgery is not offered to minors in Finland. Furthermore, the guidelines stress that psychiatric conditions must be treated and stabilized before considering hormonal interventions. Special caution is placed on the use of puberty blockers, given emerging evidence about their potential impact on brain maturation and long-term decision-making capacity.

Adherence to this strict protocol is assured because Finland has only two centres that provide assessments and approve treatment indications for youth with GD, with highly coordinated clinical teams that adhere to the Finnish strict protocol.

Since the publication of the Finnish guidelines, two major register studies have provided additional support for their cautious approach. One explored psychiatric needs among gender-referred individuals, finding high rates of psychiatric comorbidities and suggesting that the rising number of referrals includes increasingly complex clinical cases.[50] The second examined suicide mortality among individuals under 23 and found that, after adjusting for psychiatric needs, there was no statistically significant difference in suicide rates between gender-referred youth and matched controls from the general population.[51]

Finland's cautious, evidence-focused guidelines stand in stark contrast to the WPATH model. Rather than expanding access amid uncertain outcomes, Finland has re-centered pediatric care around rigorous assessment, psychotherapeutic exploration, and prioritizing long-term health.

9.3.2 Sweden

In 2022, Sweden's National Board of Health and Welfare (Socialstyrelsen) issued an update to its national guidelines for the treatment of children and adolescents with

[50] Kaltiala et al. (2023).
[51] Ruuska et al. (2024).

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gender dysphoria.[52] This update was motivated in part by shifts in epidemiology and uncertainty about the recent rise in cases, and limited data regarding rates of detransition or regret among young adults. Grounded in a systematic review of the evidence,[53] the new framework departs sharply from the SOC-8. Unlike WPATH's affirmation-based model, Sweden's guidelines conclude that the risks associated with puberty blockers and gender-affirming treatments likely outweigh the expected benefits for young people. As with Finland, such interventions are now restricted to research settings, with exceptions permitted under strict clinical oversight.

The Swedish guidelines prioritize a comprehensive psychosocial evaluation and support. Clinicians are instructed to conduct thorough assessments of psychological, psychosocial, and psychiatric factors, utilizing validated instruments, investigative interviews, and detailed life histories from both the young person and their guardians.[54] Rather than presuming a fixed outcome, the guidelines emphasize the importance of supporting the open-ended exploration of gender identity.[55] Systematic screening for neurodevelopmental conditions, including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), is required early in the evaluation process, with full neuropsychiatric assessments initiated when indicated.[56] Moreover, concurrent psychiatric conditions must be identified and addressed as early as possible, ensuring that psychosocial support and psychiatric interventions are available to bolster overall mental health throughout the evaluation.

Medical and surgical interventions are subject to equally rigorous restrictions. Treatment with puberty blockers (GnRH analogues) is confined to the context of clinical research. Until such research protocols receive ethics board approval, puberty blockers may be administered only in exceptional cases under the updated guidelines.[57] Similarly, the use of cross-sex hormones—testosterone or estrogen—is permitted solely within

[52] The official Swedish-language guidelines are Socialstyrelsen (2022c). Page numbers in this section refer to a certified, complete, unofficial translation that was submitted as evidence in a U.S. court case (Socialstyrelsen, 2022b). There is also an official English-language summary (Socialstyrelsen, 2022a).
[53] Swedish Agency for Health Technology Assessment and Assessment of Social Services (2022).
[54] Socialstyrelsen (2022b, p. 63).
[55] Socialstyrelsen (2022b, p. 66).
[56] Socialstyrelsen (2022b, p. 69).
[57] Socialstyrelsen (2022b, p. 85).

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research studies, with narrowly defined exceptional cases allowed.[58] Only adolescents who meet stringent eligibility criteria for gender-affirming hormone therapy may be considered for surgery, again under exceptional circumstances.[59] Across all interventions, the emphasis is on minimizing risk and ensuring that treatment decisions are based on the best available evidence.

Sweden's 2022 guidelines represent a marked shift away from affirmation-driven PMT model. Anchored in a systematic review of the literature, they embody a precautionary approach grounded in the principles of evidence-based medicine. Sweden's approach signals an important recalibration in gender medicine, reinforcing that interventions involving youth must be guided by systematic evidence appraisal, ethical responsibility, and a focus on long-term health trajectories.

9.3.3 United Kingdom

Currently, there is no finalized clinical practice guideline for pediatric gender medicine available from the National Institute for Health and Care Excellence (NICE) for England and Wales, or the Scottish Intercollegiate Guidelines Network (SIGN) for Scotland.[60]

NICE was commissioned by NHS (National Health Service) England[61] to perform a systematic evidence review evaluating treatments for gender dysphoria among children and adolescents. NICE's evidence reviews identified significant limitations in existing research, concluding that the available evidence was of very low quality (as assessed by the GRADE methodology) [62] and therefore insufficient to support the development of a formal clinical guideline.

These two SRs were cited as part of the Terms of Reference for an independent review that NHS England commissioned, led by Dr. Hilary Cass.[63] Released in 2024, the Cass Review aimed to thoroughly evaluate pediatric gender medicine services in the U.K. and provide clear recommendations on clinical practices and service delivery. Rather than

[58] Socialstyrelsen (2022b, p. 90).
[59] Socialstyrelsen (2022b, p. 95).
[60] Silver et al. (2025, p. 2).
[61] On March 13, 2025 it was announced that NHS England would be merged with the Department of Health and Social Care (DHSC).
[62] National Institute for Health and Care Excellence (2020b, 2020a).
[63] Cass (2024a, Appendix 1).

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providing explicit clinical guidelines, the Cass Review is a detailed, independent, investigative assessment based on multiple, commissioned, peer-reviewed systematic reviews.[64]

The Cass Review identified critical issues within the existing pediatric gender services, such as inadequate clinical assessments, insufficient long-term outcome data, and significant concerns over rapidly increasing referrals of young people with gender incongruence. Overall, it identified a significant gap between the available evidence and the clinical justifications for medical interventions for gender dysphoria in young people[65] and emphasized the necessity for comprehensive psychological support and thorough, individualized assessments.

In response to the Cass Review, NHS England introduced major policy changes. Puberty blockers are no longer routinely commissioned due to insufficient evidence regarding their long-term safety and effectiveness. Instead, they will only be accessible through structured clinical research trial, which is currently being designed. Additionally, CSH (masculinizing or feminizing hormones) are available to young people around the age of 16, contingent upon strict eligibility criteria and detailed assessment protocols by specialist multi-disciplinary teams and a new national Multi-Disciplinary Team (MDT) review process.[66] As reported most recently, no adolescent was prescribed cross-sex hormones in the last year. The NHS recently revealed that since the Cass Review was published, no minor has been found eligible to receive CSH according to the updated policy.[67]

Without a finalized clinical practice guideline, clinicians must follow the current policies directly informed by the Cass Review. These interim standards prioritize patient safety, rigorous clinical evaluation, ongoing research, and holistic care approaches, significantly revising the clinical pathways for young individuals experiencing gender incongruence.

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[64] Archives of Disease in Childhood (2024).
[65] Cass (2024a, pp. 22, 29, 32-35).
[66] National Health Service England (2024a); a review of adult services was also announced (National Health Service England, 2024b).
[67] Spencer (2025).

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9.4 Conclusion

The current landscape of CPGs for treating youth with GD underscores significant variability in methodological rigor and trustworthiness. Rigorous appraisals consistently demonstrate that only a select few guidelines, notably those from Finland and Sweden, meet high standards for evidence-based clinical decision-making. These Scandinavian guidelines emphasize cautious approaches grounded firmly in systematic evidence reviews, advocating psychotherapy and psychosocial interventions as first-line treatments, and restricting medical interventions to carefully monitored research settings or exceptional circumstances.

In contrast, many internationally influential guidelines, including those from WPATH, the Endocrine Society, and the American Academy of Pediatrics, have been criticized for substantial methodological shortcomings and conflicts of interest, resulting in recommendations not reliably supported by rigorous evidence. This pattern of circular referencing and mutual endorsement among these guidelines further compromises their credibility and has likely perpetuated a perceived consensus in pediatric gender medicine that belies the actual paucity of high-quality evidence.

Given the ethical implications and lifelong consequences of medical interventions in youth, it is imperative that future guidelines in pediatric gender medicine adhere strictly to established standards of evidence-based medicine. Guideline developers must prioritize transparency, methodological rigor, independence from vested interests, and systematic evidence appraisal. Only through such disciplined approaches can clinical practice guidelines fulfill their intended role of safeguarding the health and well-being of youth with GD, promoting informed decision-making among clinicians, families, and policymakers alike.

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Chapter 10 WPATH's *Standards of Care* 8

As shown in Chapter 9, the guidelines issued by the World Professional Association for Transgender Health (WPATH) have been rated among the lowest in quality and have not been recommended for implementation by systematic reviews of guidelines. Despite their lack of trustworthiness, for more than a decade WPATH guidelines have served as the foundation of the healthcare infrastructure for gender dysphoric (GD) youth in the United States. The WPATH *Standards of Care* guidelines are embedded in nearly all aspects of healthcare including clinical education, delivery of care, and reimbursement decisions by private and public insurers.

This chapter focuses on the current Version 8 of the WPATH *Standards of Care* guidelines (SOC-8),[1] published in 2022.[2] Section 10.1 describes WPATH's central role in shaping the treatment of youth with GD in U.S. healthcare settings. Section 10.2 provides a brief overview of the rationale for the development of SOC-8, highlighting how it differs significantly from earlier guideline versions with particular emphasis on the new Adolescent chapter. Section 10.3 examines the development process of SOC-8, considering both internal dynamics and external pressures, and analyzes its multipurpose role as a clinical guideline, a tool to secure insurance coverage, and a legal instrument aimed at promoting broad access to pediatric medical transition (PMT). Section 10.4 highlights one critical downstream consequence of the guideline's flawed development process: the elimination of all minimum age requirements for endocrine and surgical interventions (except phalloplasty) in minors. Section 10.5 discusses the implications of continued reliance on WPATH.

10.1 Influence of WPATH in the United States

There is no accredited subspecialty in "gender medicine" in the U.S. Instead, the practice of PMT typically involves a series of handoffs among different providers: a pediatrician or an adolescent medicine specialist[3] first assesses whether PMT may be

[1] Coleman et al. (2022).
[2] Portions of this evaluation necessarily rely on internal WPATH communications made publicly available through subpoena. See Boe v. Marshall, No. 2:22-cv-00184, (M.D. Ala.). Some material from Boe v. Marshall was previously released in Voe v. Mansfield, No. 1:23-Cv-00864: 100-1 (M.D.N.C.).
[3] American Board of Pediatrics (2024).

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warranted; mental health professionals diagnose GD or a related condition and recommend PMT; endocrinologists prescribe hormonal interventions (i.e., puberty blockers and cross-sex hormones); and various surgical specialties including plastic surgeons, urologists, and gynecologists perform a range of surgical procedures to alter the adolescent's sex-specific physical characteristics.

The multidisciplinary nature of PMT combined with the absence of a single medical specialty responsible for overseeing patient care has resulted in an oversight gap WPATH has filled. WPATH has successfully positioned itself as the leading authority in the field of gender medicine, including pediatric gender medicine. The first version of WPATH's Standards of Care was published in 1979. Subsequent updates followed in 1980, 1981, 1990, 1998, 2001, and 2012.[4] The most recent version, SOC-8, was published in 2022.[5] Chapter 3 provides a brief history of gender medicine and the role of WPATH, which was originally formed (under a different name, the "Harry Benjamin International Gender Dysphoria Association") to focus on the gender transition wishes of mature adults, but after pediatric transitions were pioneered in the Netherlands, increasingly shifted its attention to children and adolescents.

10.1.1 WPATH's role in clinical practice

Although some medical societies involved in providing PMT have issued guidance documents on specific aspects of care for youth with GD,[6] no professional society has published a comprehensive, up-to-date, evidence-based clinical guideline covering the full PMT pathway. Instead, medical societies have largely deferred to WPATH, adapting their own clinical positions to WPATH's most recent recommendations.[7] Unlike the U.K., Sweden, Finland, and other countries with centralized medical policymaking bodies that

[4] SOC-7 was released in 2011 and published in 2012.
[5] Coleman et al. (2022).
[6] The most notable documents are discussed in Chapter 9 and include the Endocrine Society's guidelines (Hembree et al., 2017) and the American Academy of Pediatrics position statement (Rafferty et al., 2018). Both are significantly outdated.
[7] In August 2024, WPATH was presented in a court case as "the leading association of medical professionals treating transgender individuals." It was further asserted that "[t]he Nation's leading medical and mental health organizations recognize [SOC-8] as reflecting the accepted standard of care for treating gender dysphoria." See U.S. v. Skrmetti (No. 23-477), Brief for the petitioner (2024, p. 3).

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issue independent, authoritative clinical care guidelines,[8] in the United States, WPATH's influence has been outsized and largely uncontested—primarily due to the fragmented healthcare system and the complexity of the U.S. regulatory environment.[9] WPATH's influence on clinical protocols for the care of youth with GD is pervasive within U.S. medicine. Its *Standards of Care* have become the primary framework embedded in clinical protocols and hospital operating procedures for the diagnosis and treatment of youth with GD.[10]

10.1.2 WPATH's role in medical education and training

WPATH has become the dominant influence shaping the education and training of U.S. healthcare providers who treat youth with GD. Indeed, it is virtually coterminous with the field itself. Because there is no officially accredited medical subspecialty in gender medicine in the U.S., and no formal board certification process as exists in fields like adolescent medicine, endocrinology, or psychiatry, training in PMT remains informal, variable, and largely organized through WPATH-affiliated medical education efforts.

WPATH's Global Education Initiative (GEI) offers certified courses that serve as the core curriculum for clinical training in the U.S. and worldwide. WPATH GEI's official collaborators include pediatric gender clinics and hospitals, the American Medical Student Association, and the World Health Organization (WHO).[11] Major U.S. hospitals and medical schools have embedded WPATH-aligned standards into their residency, fellowship, and continuing medical education programs.[12] Gender clinics reference

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[8] When NHS England moved to remove puberty blockers for GD from clinical practice, it received complaints that the decision was "not consistent … with the WPATH standards of care for trans children." NHS England responded: "The policy proposition has been developed following a review of peer reviewed published evidence as per NHS England Policy Development Methods. NHS England does not commission based upon guidelines or treatment protocols e.g. WPATH 8.0 [SOC-8] or practices in other countries. The not for routine commissioning position has been concluded based on 'insufficient clinical benefit to the patient of which evidence of harm is one aspect'" (National Health Service England, 2023, p. 4).

[9] The U.S. lacks a centralized medical policy-making body, resulting in what has been described as a "bewildering regulatory maze" (Field, 2008, p. 607).

[10] For an example, see Seattle Children's Hospital (n.d.). Note: it appears some pediatric gender clinics have recently removed public references to WPATH and have also removed the backups of the websites, making them inaccessible to citation.

[11] See World Professional Association for Transgender Health (n.d.).

[12] For example, Mt. Sinai's transgender psychiatry fellowship: "Fellows are provided time and financial compensation to attend the U.S. Professional Association for Transgender Health or World Professional

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WPATH's *Standards of Care* in clinical protocols and physician training.[13] WPATH-certified trainers further extend WPATH's reach into professional training at institutional and community levels.[14] WPATH certification not only is encouraged but also in some cases mandated.[15] This widespread integration has effectively established WPATH as the de facto authority for defining clinical competency, treatment eligibility criteria, and ethical frameworks across much of U.S. medicine.

10.1.3 WPATH's role in insurance reimbursement

Many U.S. public and private health insurers and regulatory bodies rely on SOC-8 when making coverage determinations. Requirements for credentialing, assessing medical necessity, and making coverage decisions almost universally reference WPATH's *Standards of Care*. Major U.S. private insurers, including Anthem,[16] Kaiser,[17] Aetna,[18] Cigna,[19] and UnitedHealthcare,[20] explicitly reference SOC-8 to define medical necessity, eligibility criteria, and coverage decisions.

Association for Transgender Health bi-annual conferences" (Icahn School of Medicine at Mt. Sinai, n.d.-b). Mt. Sinai's transgender surgery fellowship attending faculty includes Marci Bowers, the former president of WPATH (Icahn School of Medicine at Mt. Sinai, n.d.-a). Oregon Health and Sciences University's gender surgery fellowship program director is "the surgical lead for the World Professional Association for Transgender Health (WPATH) and the United States Professional Association for Transgender Health (USPATH) meetings" (OHSU School of Medicine Surgery, n.d.).

[13] For example, the Stanford Medicine Children's gender clinic website states, "the expert members of the Gender Clinic team consists [sic] of providers from pediatric endocrinology, adolescent medicine, pediatric urology and social services, supporting each child's or adolescent's gender identity. All our providers are members of the World Professional Association for Transgender Health (WPATH)" (Stanford Medicine Children's Health, n.d.). Fenway Health references WPATH as the authority in the field: "The World Professional Association of Transgender Health (WPATH) monitors current research and new knowledge about evidence-based medicine for transgender people. It publishes Standards of Care and Ethical Guidelines for health care providers, which 'articulate a professional consensus about the psychiatric, psychological, medical, and surgical management of gender dysphoria' to guide clinicians in providing quality care for transgender and gender diverse people, including children and adolescents" (Fenway Health, n.d.).

[14] See Harvard Medical School's continuing medical education (Harvard Medical School, n.d.), led by senior WPATH leaders involved in the production of SOC-8 (e.g., Sari Reisner, WPATH board member). Also see the following training initiatives: Gender Health Training Institute (n.d.); Silver Hill Hospital/World Professional Association for Transgender Health (n.d.).

[15] For example, the Washington State Department of Corrections mandates that physicians providing "gender-affirming care" must be WPATH-certified or obtain certification within two years (Washington State Department of Corrections, 2025). The Oregon Health Authority is another example (see following section).

[16] Anthem (2023). WPATH is referenced 35 times as the basis for all recommendations.

[17] Kaiser Permanente (2023). Transition and detransition policies require "WPATH letters."

[18] Aetna (2024). Adolescents are to meet "WPATH criteria" for hormonal interventions.

[19] Cigna (2025).

[20] Stroumsa & Kirkland (2020).

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Government payers, such as Medicaid programs, also commonly rely on WPATH guidelines as the primary basis for developing their medical policies. In 2024, Oregon became the first state to officially adopt SOC-8 as its standard of care, committing the Oregon Health Authority to cover treatments based entirely on WPATH guidelines. Oregon additionally requires that if a patient is denied coverage for medical or surgical intervention related to gender transition, the clinicians reviewing the patient appeal must complete WPATH-aligned training:

> health care providers reviewing adverse benefit determinations denying or limiting access to gender-affirming treatment complete the "WPATH SOC-8 Health Plan Providers Training," which is specifically designed for providers responsible for such reviews, or an equivalent training.[21]

This is notable as WPATH SOC-8 lists a wide range of procedures that should be provided to patients wishing to receive them. These include, in addition to puberty blockers, cross-sex hormones, mastectomy, and male-to-female or female-to-male genital surgeries, procedures such as vaginoplasty with a "retention of penis and/or testicle" (also known as penis-preserving vaginoplasty), removal of genitals entirely to create a "flat front" appearance, and uterine transplantation for male patients. Procedures listed as potentially necessary also include body contouring, liposuction/lipofilling, facelift, blepharoplasty, various implants, hair transplantation, vocal cord surgery, and a wide range of other appearance-modifying surgical procedures.[22]

10.2 The development of SOC-8 and the Adolescent chapter

Unlike most professional medical associations, WPATH does not require its members to be medical professionals. Full professional membership with voting privileges is also available to professionals in such fields as law, family studies, anthropology, and other areas. Reflecting the diverse aims of its broad membership, WPATH treatment

[21] Oregon Department of Consumer and Business Services (2024a). This position was further strengthened in the final ruling in Oregon Department of Consumer and Business Services (2024b).
[22] Coleman et al. (2022, p. S136).

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guidelines are designed to serve multiple purposes, ranging from clinical care to political advocacy.

Published in 2022, SOC-8 marked WPATH's first attempt to develop guidelines that were "evidence-based" and aimed to meet higher methodological standards through reliance on systematic reviews (SRs) of evidence.[23] The previous version, SOC-7, published in 2011 and described in Chapter 4, under which PMT began rapidly to accelerate, did not rely on SRs. Instead, its recommendations were based on "cultural shifts" and other factors.[24]

In pursuit of its goal to develop an evidence-based guideline, WPATH entered into a contractual agreement with the Evidence-Based Practice Center (EPC) at Johns Hopkins University (JHU), tasking JHU experts with conducting SRs and serving as methodological advisors to ensure a trustworthy guideline development process.[25] Given the sharp increase in the numbers of adolescents seeking PMT, and the rapid growth of pediatric gender clinics and PMT providers in the U.S., WPATH recognized the need to develop a robust adolescent section, acknowledging that "the Adolescent chapter is going to be one of the most scrutinized chapters in the entire standards of care."[26]

As the process of guideline development began, WPATH focused on two cornerstone issues for PMT: the evidence regarding the effectiveness of endocrine interventions in treating GD, and the evidence that adolescents have the capacity to consent to such treatments.

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[23] See Sinai (2022): "The World Professional Association for Transgender Health (WPATH) Standards of Care Version 7 (SOC7) are not evidence-based. The WPATH website clearly states that SOC8 is the first version being developed using an evidence-based approach."
[24] The prior version, SOC-7, stated that its recommendations were "based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender nonconforming people beyond hormone therapy and surgery" (Coleman et al., 2012, p. 166).
[25] Coleman et al. (2022, pp. S248-S249); Karen Robinson is named as the EPC lead and listed as a member of the SOC-8 Guideline Steering Committee.
[26] Boe v. Marshall, No. 2:22-cv-00184: 560-18 (2024, p. 42).

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10.2.1 Hope for evidence of effectiveness

At the outset of its collaboration with JHU's EPC team, WPATH leadership expressed confidence that an SR would yield "evidence-based statements" supporting both the benefits of PMT interventions and the capacity of adolescents to consent to them. SOC-8 Adolescent chapter co-chair Scott Leibowitz wrote:

> We are a unique chapter when it comes to the evidence based review because we do feel that there is a justification to do a literature review on what we postulate will be evidence based statements about the interventions (even though we expect the evidence to be graded low). Essentially the literature reviews on some of our statements—as we plan on submitting once I edit them to incorporate the feedback from our workgroup—are important for the following reasons:
>
> - Studies that demonstrate the psychological effectiveness of some of the interventions (blockers, hormones) in adolescence all included cohorts who went through a rather rigorous psychological assessment. We would like to talk this through as a group because it's a very important point.
> - There is also literature on adolescent decision making and capacity to make informed decisions that carry lifelong ramifications. Since our chapter is a new chapter for the standards of care, and it focuses in on a developmental age group/assessment, (as opposed to other chapters that are more intervention specific), we are going to want to justify certain statements with graded evidence in terms of looking at the literature on *decision making in the developmental cohort (adolescence)* in general.[27]

The JHU evidence evaluation team was presented with the expectation that their appraisal would support the "gender-affirming" medical approach WPATH had been advancing for over a decade. The original plan was for SOC-8 recommendations—asserting that treatment effects are beneficial and that adolescents possess sufficient capacity to consent to medical interventions—to be labeled "evidence-based," even if

[27] Boe v. Marshall, No. 2:22-cv-00184: 560-18 (2024, pp. 43-44).

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the quality of the evidence was low.[28] However, the evidence evaluation challenged WPATH's expectations on both fronts: adolescent capacity to consent, and the benefits of PMT overall.

10.2.2 Adolescent capacity to consent

In response to a request from JHU, Annelou de Vries, the leading Dutch developer of PMT and a co-chair of SOC-8's Adolescent chapter section, supplied the JHU team with publications she believed demonstrate adolescent competence to consent to PMT.[29] Upon reviewing these publications, however, the JHU team informed WPATH that they provided, at best, "limited indirect evidence" and were insufficient to support a statement asserting that adolescents possess the capacity to consent.[30]

Following the JHU team's findings, WPATH abandoned its original plan to base its claim about adolescent capacity to consent on evidence. Instead, the Adolescent chapter of SOC-8 features a section on consent that stresses the importance of careful assessment but cites the same studies that JHU had deemed insufficient to answer the question of competence. The section also features a discussion about the "unique situations in which an adolescent minor is consenting for their own treatment without parental permission."[31]

The section fails to acknowledge the dearth of reliable information about whether adolescents in a state of clinical distress can meaningfully consent to drastic interventions—with many known and some unknown risks—in the absence of

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[28] From a WPATH internal email exchange related to SOC-8: "Adolescent medical decision making literature is something that the Johns Hopkins team is able to help out in terms of a literature review and grading" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 116); for discussion of grading recommendations, see Chapter 9.

[29] The primary investigator of the Dutch Protocol and WPATH Adolescent chapter co-lead (de Vries) provided the relevant literature on adolescent consent for JHU evaluation, writing: "some articles on decision making in teens; these are review articles, but show that there is some evidence. I think we need this sort of evidence base on decision making capacity in adolescents, regarding medical affirming treatment" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 106).

[30] The JHU response to WPATH regarding the literature on adolescent consent to PMT stated, "The articles forwarded provide limited indirect evidence for this question. Please let me know if I missed something" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 106).

[31] Coleman et al. (2022, pp. S61, Section 6.12.c).

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demonstrable physical disease and without credible knowledge of their likely future identity trajectory.

The ethical challenges of obtaining informed consent from adolescents regarding the procedures that are expected to threaten their fertility is illustrated by a candid comment from a WPATH physician, who observed, “it’s always a good theory that you talk about fertility preservation with a 14-year-old, but I know I’m talking to a blank wall,” adding, “they’d be like, ew, kids, babies, gross.”[32]

10.2.3 Treatment effects

In contrast to WPATH’s early abandonment of efforts to evaluate minors' capacity to consent, SRs assessing the treatment effects of puberty blockers (PBs), cross-sex hormones (CSH), and surgeries were completed by the JHU team. As the following sections in this chapter detail, WPATH perceived the JHU evidence appraisals as unfavorable to its goals of promoting broad access to these interventions for minors. In response, WPATH leadership moved to suppress the findings, barring the JHU evidence evaluation team from publishing its results.

The Adolescent chapter does not disclose that the SR regarding the effects of PMT had, in fact, been conducted. Instead, the chapter claims that SRs are not feasible:

> Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible.[33]

Ultimately, SOC-8 recommended that adolescents wishing to undergo PMT be provided with PBs, CSH, and surgery. The recommendations are couched in cautious-sounding language, stating that GD should be “sustained over time,” particularly before administering CSH. However, no clear standard is set; the only guidance offered is the vague and clinically meaningless phrase “several years, leaving critical decisions open to broad and subjective interpretation”:

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[32] Hughes (2024, p. 12).
[33] Coleman et al. (2022, p. S46).

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> Given potential shifts in gender-related experiences and needs during adolescence, it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones or surgeries.[34]

As the following sections describe, the recommendations were deliberately crafted to allow any "willing" medical provider to prescribe hormones or perform surgeries on minors, even those with significant co-occurring mental health conditions.

10.3 The process of creating SOC-8

The creation of trustworthy, evidence-based guidelines requires first assembling a guideline development group (GDG) that is free from conflicts of interest (COI) or, at minimum, where COIs are transparently disclosed and rigorously managed. Only after this foundation is established should SRs proceed, addressing pre-specified guideline questions. Finally, recommendations should be based on SRs of evidence and should consider additional factors, with the aim of improving healthcare quality for individual patients and improving public health and access to care.

Although WPATH originally embarked on an evidence-based guideline development process, internal documents reveal significant deviations from internationally recognized clinical guideline development standards established by organizations such as the National Academy of Medicine[35] (NAM) and the World Health Organization (WHO).[36] These serious deviations from established standards meant that the GDG could not fulfill its promise of producing credible, evidence-based guidelines.

[34] Coleman et al. (2022, p. S60).
[35] Graham et al. (2011), published under its previous name, Institute of Medicine (IOM).
[36] SOC-8's reference to WHO's International Classification of Diseases (ICD) appears to have intended to be WHO's *Handbook for Guideline Development*, 2nd Edition. See Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 204).

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10.3.1 Conflicts of interest management

Managing COIs—both financial[37] and intellectual[38]—is essential for producing trustworthy clinical practice guidelines. Intellectual conflicts may even surpass financial ones in their influence,[39] especially when guidelines rely heavily on expert consensus. The selection of the GDG[40] chair plays a pivotal role in ensuring the integrity of clinical guideline development.[41] WHO recommends selecting a guideline chair who is free of significant conflicts and neutral between differing perspectives.[42] NAM advises using "unconflicted methodologists"[43] to lead recommendation development, working alongside clinical experts as advisors rather than panel members.[44] Both NAM and WHO stress that conflicted members should constitute no more than a minority of any GDG, emphasizing ongoing COI management throughout the entire guideline development process.[45] In 2022, the Endocrine Society adopted NAM's recommendations, prioritizing reduced conflicts even if it limits expert involvement.[46]

When the principal investigator of the JHU EPC team became involved in the SOC-8 process, she observed that they "would expect many, if not most, SOC8 members to have competing interests."[47] SOC-8's final COI statement reads as follows:

> Conflict of interests [sic] were reviewed as part of the selection process for committee members and at the end of the process before publication. No conflicts of interest were deemed significant or consequential.[48]

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[37] The WHO defines financial COI as any "paid work, consulting income or honoraria and travel stipends; support for research, including direct monetary contributions or donations of equipment, laboratory space, etc.;" "that is related to, or could be affected by, the outcome" of the guideline development process (World Health Organization, 2014, p. 63).
[38] NAM and WHO define intellectual COIs relevant to clinical practice guideline development as "academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation" (Guyatt, 2010, p. 739).
[39] Guyatt et al. (2015, p. 540).
[40] SOC-8's GDG comprised a guidelines steering committee with a chair and two co-chairs, who in turn appointed 26 chapter leads, 77 chapter members, and 16 stakeholders.
[41] Graham et al. (2011, p. 87).
[42] World Health Organization (2014, p. 61).
[43] Graham et al. (2011, pp. 81-82).
[44] World Health Organization (2014, p. 82).
[45] Graham et al. (2011, p. 7).
[46] McCartney et al. (2022).
[47] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 2).
[48] Coleman et al. (2022, p. S177).

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Based in part on correspondence between WPATH and the EPC team during the development of SOC-8, there are serious questions regarding the accuracy of this statement.

SOC-8 GDG members, including Chair Eli Coleman, had unmanaged financial and/or non-financial COIs that were plausibly "significant or consequential." Coleman had both financial and non-financial interests in the topic. He was the lead author of SOC-7[49] and had coauthored academic publications in support of expanded access to medical transition.[50] Using WHO criteria, his professional activities and academic profile, which were closely aligned with advancing medical transition, likely constitute both intellectual and financial COIs.[51]

Additionally, Coleman's academic work was supported with funding from the Tawani Foundation, chaired by Jennifer Pritzker, a philanthropist and advocate for transgender issues.[52] The foundation funded a research center at the University of Minnesota, and Coleman played a significant role in its development. Public statements confirm that the Tawani Foundation also funded the majority of the out-of-pocket costs associated with SOC-8's development.[53]

With Coleman as chair of the GDG, the importance of managing COIs appears to have been consistently misunderstood or undervalued. Coleman admitted under deposition that disclosure statements were not presented until at least six months *after* members had already been selected.[54] In a December 21 (2018) email sent to the SOC-8 education committee, EPC's Karen Robinson stated, "Disclosure, and any necessary

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[49] Coleman et al. (2012).
[50] Eisenberg et al. (2020); Rider et al. (2018).
[51] "Financial and nonfinancial interests can overlap. For example, intellectual interests related to career advancement obviously have a monetary component. Examples of roles or positions that might interfere with the objective assessment of a body of evidence include: prior publication of a study or SR that is part of the evidence base under consideration in the guideline; prior public declaration of a firm opinion or position, as in public testimony during a regulatory or judicial process, or in an editorial in a journal; or professional or personal affiliation with an organization advocating for products or services related to the subject of the guideline" (World Health Organization, 2014, p. 63).
[52] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 239).
[53] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 239).
[54] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, pp. 219-222).

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management of potential conflicts, should take place prior to the selection of guideline members. Unfortunately, this was not done here."[55]

For former WPATH president Marci Bowers, who played an influential role in shaping SOC-8, the idea of appointing an unconflicted professional to lead the project was outright nonsensical.[56] Another SOC-8 member wrote to the EPC to explain that "unlike other medical guidelines, trans health care is a socially and politically charged issue," and strongly recommended that the JHU team therefore rewrite their COI forms for this particular guideline.[57] Part of the justification for different treatment was that COIs were so prevalent within the GDG that it would be "impossible" for the group to be free of them.[58] One submitted COI form, on the question of non-financial interests, recorded that "everyone involved in the SOC process has a non-financial interest."[59]

Although WPATH later claimed that none of the SOC-8 members' COIs were significant or consequential, several members clearly met the internationally recognized definitions of COIs established by the NAM and WHO—the kind of conflicts known to bias clinical practice guidelines and erode their trustworthiness. For instance, SOC-8 chapter leaders Dan Karasic and Loren Schechter were paid expert witnesses in legal cases directly related to medical transition before and during the SOC-8 development process,[60] a role NAM explicitly identifies as a COI.[61] Schechter, co-chair of the surgery chapter and a plastic surgeon who derives part of his livelihood from performing gender

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[55] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 2).
[56] Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024, p. 121).
[57] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 3).
[58] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 3).
[59] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 8).
[60] Schechter provided testimony for Dekker v. Weida, No. 4:22-cv-00325 (N.D. Fla. filed Sept. 7, 2022); Willis v. Flagg, No. 17-cv-02754 (N.D. Ill. filed Apr. 10, 2017); Bruce v. South Dakota, No. 3:17-cv-03023-RAL (D.S.D. filed Oct. 5, 2017); Boyden v. Conlin, No. 17-cv-00264-WMC (W.D. Wis. filed Apr. 6, 2017); Kadel v. Folwell, No. 1:19-cv-00272 (M.D.N.C. filed Mar. 11, 2019); Toomey v. State of Arizona, No. 4:19-cv-00035-RM-LAB (D. Ariz. filed Jan. 23, 2019); and Fain v. Crouch, No. 3:20-cv-00740 (S.D.W. Va. filed Nov. 12, 2020).

Karasic provided testimony for C.P. v. Blue Cross Blue Shield of Illinois, No. 3:20-cv-06145 (W.D. Wash. filed Nov. 24, 2020); Kadel v. Folwell, No. 1:19-cv-00272 (M.D.N.C. filed Mar. 11, 2019); Fain v. Crouch, No. 3:20-cv-00740 (S.D.W. Va. filed Nov. 12, 2020); Brandt v. Rutledge, No. 4:21-cv-00450 (E.D. Ark. filed May 25, 2021); K.C. v. Individual Members of the Indiana Medical Licensing Board, No. 1:23-cv-00595-JPH-KMB (S.D. Ind. filed Apr. 5, 2023); Dekker v. Weida, No. 4:22-cv-00325-RH-MAF (N.D. Fla. filed Sept. 7, 2022); and Doe v. Ladapo, No. 4:23-cv-00114-RH-MAF (N.D. Fla. filed Mar. 23, 2023).
[61] Graham et al. (2011, p. 79).

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transition surgeries, voiced concerns to fellow GDG members about openly acknowledging insufficient evidence, noting the potential impact this would have on two federal court cases in which he was serving as a paid expert witness.[62] Despite this clear overlap of financial interest and guideline content, SOC-8 chair Eli Coleman considered it "ethically justifiable" for members involved in active litigation to advocate for guideline changes that could strengthen their legal positions.[63]

WPATH's process not only permitted significant financial and intellectual COIs among GDG members. It also allowed the creation of substantial panel composition bias—a phenomenon known as "panel stacking." This occurs when GDGs predominantly consist of members sharing similar viewpoints or vested interests, thereby threatening the validity and trustworthiness of clinical guidelines. Experts in evidence-based medicine describe panel stacking as a major threat, emphasizing that it can profoundly reduce the credibility of recommendations, particularly when, as in pediatric gender medicine, the evidence is limited, contentious, or unsystematically reviewed.[64]

Kepp et al. note that "recruitment specifically because of expressed viewpoints and allegiance is a recognized major problem for guideline development." In their own example from an appraisal of a consensus statement on COVID-19 recommendations, the authors characterized a panel with a "35% (or more) prevalence" of advocates of COVID-19 elimination ("Zero-COVID") as "extreme."[65] For SOC-8, WPATH required that all members of the GDG be "WPATH Full Members in good standing."[66] Marci Bowers explicitly stated that it was important for participants to be "advocates" for WPATH's "gender-affirming" approach to be considered for the GDG,[67] further underscoring the GDG's bias.

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[62] Boe v. Marshall, No. 2:22-cv-00184: 700-13 (2024, p. 56).
[63] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 158).
[64] Kepp et al. (2024, p. 5).
[65] Kepp et al. (2024, p. 6).
[66] Coleman et al. (2022, p. 248).
[67] Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024, pp. 119-120). This response came after it was pointed out to Bowers that selecting GDG members based on their "advocacy" for medical treatment was in "tension" with selecting GDG members who could be "impartial arbiters" on the evidence for those treatments.

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Internal documents revealed that WPATH actively monitored SOC-8 members and disciplined those who publicly questioned WPATH's "gender-affirming" approach, creating an environment that discouraged critical dialogue. Psychologist Laura Edwards-Leeper, chair of WPATH's Child and Adolescent Committee and a member of both the child and adolescent SOC-8 committees, co-authored a *Washington Post* opinion piece with Erica Anderson,[68] a psychologist and then-president of WPATH's U.S. chapter, arguing that WPATH "largely seems to be a dangerous echo chamber" resistant to constructive criticism. Edwards-Leeper privately warned WPATH leaders that their intolerance for dissent and attempts to "muzzle clinicians" risked damaging the organization's credibility among professionals, patients, and educated parents.[69] Anderson faced a formal reprimand[70] after criticizing (with Bowers) the quality and consistency of care provided under the SOC framework.[71]

This combination of poorly managed COIs and restrictive membership practices significantly undermines the credibility and scientific integrity of SOC-8 as a clinical practice guideline. The GDG's handling of the SRs of evidence WPATH commissioned for development of SOC-8 further highlights the serious threat to clinical integrity that plagued the guideline development process.

10.3.2 Suppression of evidence

NAM stipulates that trustworthy guidelines must be based on SRs of existing evidence. SOC-8 was promoted as the first to be "evidence-based,"[72] with its chair claiming it followed "the most rigorous protocol in the world to ensure these standards reflect scientific evidence."[73] The Methodology section states that SOC-8 "incorporated the recommendations on clinical practice guideline development set forth by the National

[68] Edwards-Leeper & Anderson (2021).
[69] Boe v. Marshall, No. 2:22-cv-00184: 560-26 (2024, p. 153).
[70] Boe v. Marshall, No. 2:22-cv-00184: 560-26 (2024, pp. 114-115).
[71] Shrier (2021b).
[72] "This version of the Standards of Care is the first to be developed using an evidence-based approach" (Radix, n.d., p. 13).
[73] Coleman (2023).

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Academies of Medicine and the World Health Organization, which addressed transparency, conflict-of-interest policy, committee composition, and group process."[74]

In 2018, as part of its development of a new clinical guideline, WPATH commissioned more than a dozen SRs from the EPC at JHU. SRs were completed and handed over to WPATH for its chapters on assessment, primary care, endocrinology, surgery, reproductive medicine, and voice therapy.[75]

These expert reviews had the potential to advance current understanding of the state of the evidence, but their usefulness cannot be evaluated because WPATH successfully suppressed them. In an email exchange from August 2020, a senior author from EPC, writing to the Agency for Healthcare Research and Quality (AHRQ),[76] stated that their SRs "found little to no evidence about children and adolescents" and that WPATH had been "trying to restrict our [JHU's] ability to publish."[77]

In a memo to all SOC-8 working group members, WPATH leadership reported that they "were caught on the wrong foot" when they learned that JHU wanted to publish reviews that would likely undermine WPATH's "gender-affirming" approach.[78] Despite their initial resistance, the JHU researchers ultimately capitulated to WPATH's new terms, allowing SOC-8's chair, co-chairs, a handpicked chapter member, and WPATH's Board of Directors to pre-approve manuscript content before any independent drafting could occur. Under WPATH's imposed process, researchers were required to submit a proposal form outlining the planned results and conclusions before drafting even began—and again once the manuscript was ready for publication—ensuring that leadership could steer findings to align with predetermined agendas rather than allowing an independent, evidence-driven process.[79]

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[74] Coleman et al. (2022, p. S247).
[75] Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 38).
[76] A unit of the U.S. Department of Health and Human Services.
[77] Boe v. Marshall, No. 2:22-cv-00184: 560-23 (2024, p. 23) The AHRQ official acknowledged the message: "Knowing that there is little/no evidence about children and adolescents is helpful." Nevertheless, two years later HHS released a memo in which it asserted that "[r]esearch demonstrates that gender-affirming care improves the mental health and overall well-being of gender diverse children and adolescents" (OPA: Office of Population Affairs, n.d.).
[78] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, p. 14).
[79] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, p. 8).

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Figure 10.1 WPATH approval process for manuscripts

1. The lead author submits a proposal of the publication to WPATH with the following headings: Background; Aim(s); Method; Results;

WPATH Policy Use of Data for SOC8 – Version 2
Approved by WPATH Board of Directors – August 2020

JHU_000003198

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Conclusion (Maximum 1 page and states which SOC8 chapter the publication is linked to);

2. It is WPATH's responsibility that the proposal is shared with the Chair and Co-Chairs of the SOC8, the members of the WPATH Board of Directors and all members of the SOC8 chapter linked to the proposed publication within 14 days after receipt of the proposal. The aim will be to identify an individual (s) from the chapter (maximum 2 individuals if a publication concerns more than one chapter) who will work with the lead author(s) of the proposed publication (unless the lead author is already working with one or more Working Group members); it is the responsibility of the Working Group as a whole to identify and to nominate one of their members, either by vote or general consensus within the Working Group.
3. WPATH will keep a record of the possible proposals with deadlines for draft submissions - in order to avoid the development of multiple papers with the same aims using the same data;
4. It is WPATH Executive Committee's responsibility to ensure that a vote is held within 30 days after the dissemination of the proposal.
5. It will be a blind vote and approval to write the paper is granted to the author(s) by majority vote. In case of a tie, the WPATH President will have the deciding vote.
6. It is the President's responsibility to respond to the author(s) with approval or disapproval within fifty-six (56) days of submission of the proposal to WPATH.
7. Once the manuscript draft is ready for publication, the lead author will submit the publication to WPATH
8. It is WPATH Executive Committee's responsibility to ensure that the manuscript is disseminated to the Chair of the SOC8, the Co-Chairs of the SOC8, and the members of the WPATH Board of Directors within 7 days after receipt of the manuscript.
9. It is WPATH Executive Committee's responsibility to ensure that a vote is held within 14 days after the dissemination of the manuscript to the Chair and Co-Chairs of the SOC8 and Board members.
10. It will be a blind vote and approval is granted to author(s) for publication by majority vote. The Chair and Co-Chairs of the SOC8 and Board members all have one equal vote. In case of a tie, the WPATH President will have the deciding vote.

Among the terms required for gaining WPATH approval was ensuring that the SRs' findings supported, or at least did not undermine, WPATH's goal of promoting greater access to medical interventions. Additionally, the SOC-8 chapter's working group leader or an appointed representative or the SOC-8 chair/co-chairs and at least one person

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who identified as transgender were required to oversee and approve the manuscript's design, drafting, and final content.[80]

Despite this close involvement and editorial control, all final documents were required to include a statement to the effect that "the authors are solely responsible for the content of the manuscript, and the manuscript does not necessarily reflect the view of WPATH."[81]

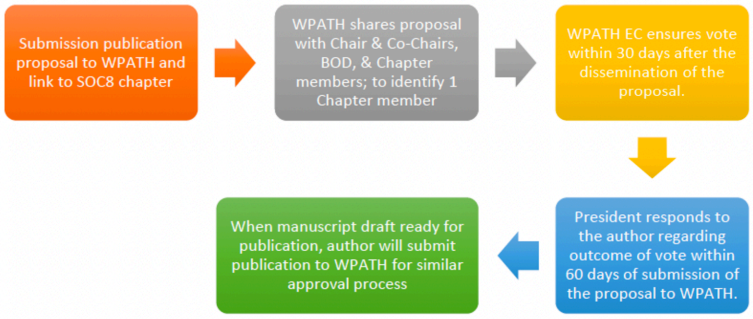
Figure 10.2 Pathway to manuscript approval

Pathway to approval for use of WPATH Data

WPATH grants approval to use the Data for publication to any interested party, when:

a. the directives outlined under the aim of this policy have been fulfilled and;
b. the author(s) have acknowledged that WPATH has sponsored the acquisition of the data in the publication and;
c. the author(s) have acknowledged that the authors are solely responsible for the content of the manuscript, and the manuscript does not necessarily reflect the view of WPATH in the publication and;
d. The publication ("manuscript") has been approved by WPATH via a designated approval process.

Designated approval process for publication of Data (see Figure 1)



WPATH's stated goal was to "ensure that publication does not negatively affect the provision of transgender healthcare in the broadest sense."[82] Following this

[80] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, pp. 5-6).
[81] Boe v. Marshall, No. 2:22-cv-00184: 523-1 Exhibit 1 (n.d., p. 8)
[82] Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 92).

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renegotiation, only one SR was published.[83] Internal WPATH documents reveal that Baker et al. complied with all the mandatory steps of WPATH's updated approval policy—from approving the conclusions before the manuscript was drafted to ensuring extensive WPATH engagement in the process and obtaining the final approvals. The Baker et al. SR was published with the mandatory disclaimer that "WPATH had no role in study design, data collection, analysis, interpretation, or drafting" of the SR, despite the checklist clearly recording that WPATH had engaged in the design, drafting, and final approval of the article.[84]

[83] Baker et al. (2021). Of note, only one other systematic review was published (Wilson et al., 2020), but its publication predates WPATH's updated policy.
[84] Wilson et al. (2020) includes the same statement but was published prior to the new agreement, so it is not possible to determine the degree to which WPATH influenced its drafting and design.

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Figure 10.3 Checklist for Baker et al.[85]

Checklist for JHU SOC8 systematic review papers

Title of Paper: Hormone Therapy, Mental Health, and Quality of Life among Transgender People: A Systematic Review

Supporting Chapter: initial question part of questions from Hormone Chapter

Proposed Authors: Kellan E. Baker, MPH, Lisa M. Wilson, ScM, Ritu Sharma, BSc, Vadim Dukhanin, MD, MHS, Kristen McArthur, BA, Karen A. Robinson, PhD

Acknowledged Authors: None

Yes or No	This paper provides data that advances the knowledge in the field of transgender health in a positive way
Yes or No	This paper will be published in a reputable, academic, peer-reviewed journal
	Journal proposed for first submission The Lancet Diabetes & Endocrinology
Yes or No	Involves the work group leader of the chapter or alternatively a designated representative of that specific SOC8 Chapter in the design, drafting of the article and final approval of the article
	Name of persons involved *chapter members provided original list of questions for reviews*
Yes or No	Involves at least one member of the transgender community in the design, drafting of the article and final approval of the article *chapter members provided original list of questions for reviews*
	Name of person if not open about trans status, if not open about trans status then enter N/A
Yes or No	Adheres to the WPATH language policy

WPATH's policy appears to have effectively blocked the planned[86] and completed[87] research—including critical evidence appraisals—from being developed into publishable manuscripts. As a result, important SRs addressing the safety of PBs, CSH, and surgery for adolescents were suppressed, keeping key findings out of the scientific record and shielding them from professional scrutiny.[88]

[85] Source: Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 41).
[86] Robinson, Sharma, Baker, et al. (2019); Robinson, Sharma, Wilson, et al. (2019); Sharma et al. (2018).
[87] In total, only 2 systematic reviews were published, and only one (Baker et al., 2021) followed the policy update.
[88] See Chapter 7 for a more extensive discussion.

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As established in Section 10.3.1, members of the GDG were committed to PMT and believed their positions to be grounded in evidence. Indeed, a central goal for SOC-8 was to deliver an updated version explicitly supported by robust evidence. However, once the GDG began working with methodological experts and applying evidence-based medicine (EBM) standards, it quickly became clear that their understanding of what constituted "strong evidence" was fundamentally at odds with established scientific criteria. Evidence that the GDG previously regarded as strong or compelling was frequently downgraded under EBM standards to low or very low quality, revealing a troubling gap between WPATH members' beliefs about evidence and the actual rigor of the underlying research. This process is clearly articulated by SOC-8 Chair Eli Coleman under points 6 ("Expert Consultation in Guideline Development") and 7 ("Research Agenda") of a 12-point draft following SOC-8's publication:

> As we faced challenges of developing and revising the methodology of SOC 8, we had to rely on Johns Hopkins, which while some degree helpful, was very constraining. We were able to consult with other experts and was [sic] able to learn that there were other ways of developing guidelines that were probably more appropriate for the state of our science. As a result, our methodology evolved and was improved—however, we were not able to be as systematic as we could have been … Now that we have reviewed the evidence, we are painfully aware of the gaps in the literature and the kinds of research that are needed to support our recommendations and strengthened [sic] the level of evidence in support of them.[89]

When confronted with SRs that did not adequately support its positions—particularly given their stated legal and advocacy concerns (see next section)—the GDG chose not to adjust its views but to find an alternative methodology to support its recommendations. As SOC-8 GDG Co-Chair Jon Arcelus explained in an email to other GDG members, "[t]here are many recommendations in the SOC that don't have direct

[89] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, pp. 8-9).

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evidence (most of the direct evidence is in the hormone chapter) but they have background evidence. This is why we have Delphi."[90]

A consensus-building process, Delphi is not a substitute for evidence-based recommendations but rather a method for GDGs to reconcile disagreement in the interpretation of SRs, or in deciding how evidence should inform treatment recommendations.[91] Guidelines that are not based on SRs inadvertently risk promoting suboptimal or even harmful care. This is why guidelines that rely only on consensus are not considered trustworthy.[92]

10.3.3 Redefinition of medical necessity

SOC-8 makes a strong recommendation that PBs, CSH, and surgery be considered "medically necessary" for eligible adolescents:

> We recommend health care systems should provide medically necessary gender affirming psychological, medical and surgical treatments for trans and gender diverse children, adolescents, and adults."[93]

The development of the "medical necessity" statement in SOC-8 starkly illustrates how many WPATH contributors prioritized goals other than ensuring the highest-quality care for adolescents with GD. A good example is WPATH's rewording of patient "wishes" as patient "needs" with the intent to frame them as "medically necessary." At first, the statement described the desired interventions as "wishes":

> There is strong evidence demonstrating the benefits in quality of life and wellbeing of gender affirming treatments, including endocrine and surgical procedures, properly indicated and performed as outlined by the Standards of Care (Version 8), in TGD people *wishing these treatments.*[94]

However, the final SOC-8 statement reads:

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[90] Boe v. Marshall, No. 2:22-cv-00184: 560-37 (2024, p. 101). Delphi is a structured consensus-building method in which a GDG iteratively reviews and rates statements to achieve agreement; SOC-8 utilized a 75% threshold for consensus.
[91] Djulbegovic & Guyatt (2019).
[92] Lima, Tangamornsuksan et al. (2023).
[93] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 32).
[94] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 38).

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> There is strong evidence demonstrating the benefits in quality of life and well-being of gender-affirming treatments, including endocrine and surgical procedures, properly indicated and performed as outlined by the Standards of Care (Version 8), in TGD people *in need of these treatments*.[95]

This consequential textual change was the result of WPATH members recognizing the implications of their word choice for insurance and legal contexts. The change was made based on the following request during the drafting phase:

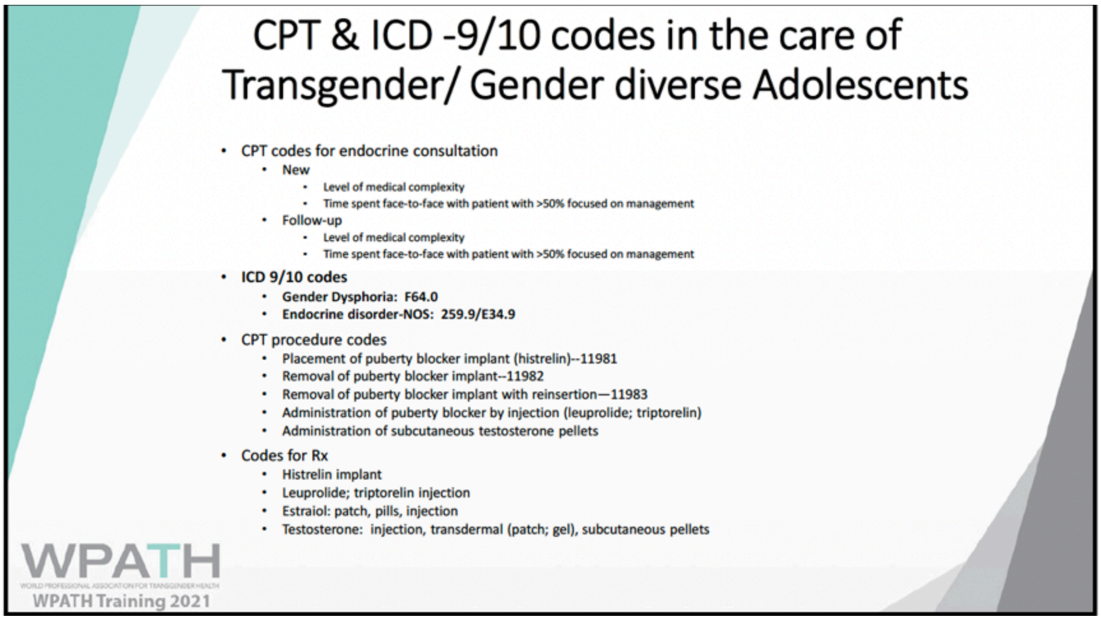
> Thank you, I also very much like this statement and the supporting write-up. There is one word, though, in the middle (on the right side of the page) of the last paragraph on the first page of the document: “wishing.” This word gives me pause, and perhaps I am being too sensitive, but one of the biggest obstacles trans people experience in getting support for coverage of our care is that we are told “you can't always get what you want" and “wishing does not make it so." Wishing makes the needed care seem optional, and we are often told we are imagining that we are not who we are and we should just suck it up. Would it be possible or advisable or prudent to replace “wishing” with “in need of” here? Thanks for your consideration, and for your great work on this.[96]

This was accompanied by WPATH’s explicit instruction to providers to use the “Endocrine Disorder” diagnosis as an alternative for the mental health diagnosis of GD[97]:

[95] Coleman et al. (2022, p. 18, emphasis added).
[96] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 28).
[97] Rosenthal (2021b, Slide 11).

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Figure 10.4 ICD codes for TGD adolescents



Together, these internal WPATH communications reveal that the "medical necessity" framing in SOC-8 was constructed to remove key safeguarding criteria and make patient desires central to treatment decisions. This was confirmed by another GDG member who candidly observed that the guidelines exist to allow any “goodwilling” clinician to meet patients’ wishes—however medically inappropriate they may be.

> I think it is clear as hell that the SOC8 refers to the necessity of treatment (in its broadest sense) of TGD people who pursue treatment (in its broadest sense) for their gender dysphoria (small "d": because it refers to the symptom of distress - which is a very broad category and one that any 'goodwilling' clinician can use for this purpose (or: in the unescapable medical lingo we, as physicians arc stuck with: those who fulfil a diagnosis of Gender Dysphoria and Gender Incongruence as per APA/WHO).[98]

The request to substitute “wish” for “need” and emphasize "medical necessity” was welcomed by WPATH leaders, who responded that the assertion of medical necessity

[98] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 37).

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would influence the “obtuse and unhealthy” U.S. healthcare system by compelling insurance coverage through the courts:

> Thank you for putting this together; you've done a great job with this. Indeed, it is important that such a statement is part of the actual SOC. And, indeed, the original Medical Necessity Statement was specific to the U.S. because this was where we were experiencing the problem with our obtuse and unhealthy system of healthcare "coverage" and we needed a tool for our attorneys to use in defending access to care here. I have long wanted this (and many of our other policy statements) to become part of the SOC because that gives them greater force.[99]

GDG Chair Eli Coleman stated that while WPATH had no definition of “medically necessary,” he understood this to be primarily a term used by insurance companies to determine which conditions or procedures to cover.[100] The SOC-8 legal and political goals are discussed in the next section.

10.3.4 Legal and political considerations

Internal documents reveal that SOC-8 authors manipulated guideline language with the explicit aim of shaping court rulings, legislative actions, and insurance coverage decisions, revealing a clear departure from the principles of unbiased, evidence-driven clinical guideline development. For example, contributors to the “Institutional Environments” chapter disclosed that “social justice lawyers” had advised them against rigorous evidence reviews, stating that such reviews might reveal limited or insufficient evidence, placing them “in an untenable position in terms of affecting policy or winning lawsuits.”[101] As discussed above, a key motivation for including a “medical necessity” statement in the guidelines was described as a strategic move to provide “a tool for our attorneys to use in defending access to care” within the U.S. legal context.[102]

[99] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, pp. 33-34)
[100] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 166).
[101] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 3).
[102] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, pp. 33-34).

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Schechter also expressed concerns about language, cautioning colleagues that terms such as “insufficient evidence” and “limited data” could strengthen legal arguments claiming medical interventions are experimental, and noting his own role as an expert witness in related federal cases.[103] Karasic, chair of the SOC-8 Mental Health chapter, highlighted the critical legal implications of defining treatments for adolescents as “medically necessary,” stating that this determination affects court cases, policy decisions, and insurance coverage.[104] Elsewhere, Karasic emphasized the urgency of addressing this issue clearly in SOC-8 given multiple ongoing lawsuits—some potentially reaching the Supreme Court of the United States—concerning whether medical gender interventions are “medically necessary” or “experimental or cosmetic.”[105]

One internal communication explicitly advised against using specific numerical age guidelines for treatments, stating, “I would avoid absolute numbers [for ages] that can be taken out of context or used in court” because they would disadvantage the people “we are trying to advocate for.”[106] Elsewhere, editorial input was provided specifically to help “Chase” [presumably a reference to Chase Strangio, Deputy Director for Transgender Justice with the ACLU’s LGBT & HIV Project].[107] GDG Chair Coleman urged the group to adopt a stronger defensive stance, stating, “we need a more detailed defense that we can use ... in the many court cases that will be coming up … especially around adolescence.”[108] One contributor even acknowledged prioritizing political advocacy goals explicitly over scientific accuracy, stating that SOC-8 should “land in such a way as to have serious effect in the law and policy settings...even if the wording isn’t quite correct for people who have the background you and I have.”[109]

Further, the U.S. healthcare context was clearly a specific focus of the SOC-8 authors. Karasic (SOC-8 Mental Health chapter chair) wrote:

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[103] Boe v. Marshall, No. 2:22-cv-00184: 700-13 (2024, p. 56).
[104] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 43).
[105] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 44).
[106] Boe v. Marshall, No. 2:22-cv-00184: 560-34 (2024, p. 25).
[107] Boe v. Marshall, No. 2:22-cv-00184: 591-24 (2024, p. 9).
[108] Boe v. Marshall, No. 2:22-cv-00184: 700-8 (2024, p. 40).
[109] Boe v. Marshall, No. 2:22-cv-00184: 560-34 (2024, p. 25).

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> But there are elements of the Medical Necessity statement that are critical to insurance reimbursement and access to care in the U.S., though not so in every country, and these should have a place somewhere in SOC 8. If WPATH SOC 8 fails to adequately support access to trans care in the U.S. by overgeneralizing wording, it may be globally applicable, but it is not globally useful, insofar as the U.S. is part of the globe. There should be room in SOC 8 to address concerns of national health systems, or other non-reimbursement focused systems without making SOC 8 less useful to U.S. trans care … Medical necessity is at the center of dozens of lawsuits in the U.S. right now over state actions to make trans care inaccessible, as well as being at the center of all reimbursement for trans care in the U.S. … it is critical that WPATH SOC 8 gets this right, which I think it does, currently."[110]

Incorporation of legal advocacy goals into guideline language, explicitly for purposes of influencing policy and litigation outcomes, conflicts sharply with accepted international standards emphasizing scientific rigor and impartiality.

Internal documents reveal that WPATH leadership was aware that the guidelines would be criticized due to the "continuing pressure in healthcare to provide evidence-based care." Coleman noted ongoing resistance from "academics and scientists who are naturally skeptical," "parents of youth who are caught in the middle of this controversy," and pressures arising from the "increasing number of regret cases and individuals who are vocal in their retransition process who are quick to blame clinicians for allowing themselves to transition despite an informed consent process."[111]

In response to anticipated criticism of SOC-8, Coleman drafted a "12-point strategic plan to advance gender-affirming care."[112] The plan acknowledged that all members of the GDG were "painfully aware that there are many gaps in research to back up our recommendations," and emphasized the importance of building consensus among

[110] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 65).
[111] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, p. 5).
[112] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, p. 6).

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medical groups in support of SOC-8. Coleman observed that the endorsement of medical organizations "has been an extremely powerful argument" in "legal battles":[113]

> As we are facing so many legal battles over trans health care and rights, the statement that the SOC has so many endorsements has been an extremely powerful argument. We need to be able to get the support of these important organizations and know how to indicate their support accurately or this argument in these court cases could be challenged.[114]

10.4 Elimination of age minimums

The handling of minimum age recommendations for clinical interventions for adolescents in SOC-8 exemplifies what happens when guideline development is compromised by ideological beliefs, COIs, and disregard for established evidence standards.

Initially, SOC-8 included age minimums for certain interventions: 14 years for cross-sex hormones; 15 years for mastectomy; 16 years for breast augmentation and facial surgery; 17 years for metoidioplasty, orchiectomy, vaginoplasty, hysterectomy, and fronto-orbital remodeling; and 18 years for phalloplasty. In July 2022, WPATH faced significant pressure from Admiral Rachel Levine, the U.S. assistant secretary for health, whose office communicated concern that listing specific, minor ages would trigger restrictive legislative actions. Internally, some SOC-8 members expressed discomfort about acceding to pressures from the federal government. "I don't know how I feel about allowing U.S. politics to dictate international professional clinical guidelines that went through Delphi," said one SOC-8 co-chair.[115] Another complained that it "is not appropriate to take any feedback from a nonmedical professional seriously."[116] Despite these reservations, WPATH's apparent investment in securing endorsement from the

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[113] Boe v. Marshall, No. 2:22-cv-00184: 560-40 (2024, pp. 6-8). Of note, although SOC-7 is now outdated, it was SOC-7 that was responsible for establishing the "gender-affirming" medical approach in the U.S. and internationally. The email from the lead author of both SOC-7 and SOC-8, Coleman, discloses that despite the widespread narrative that SOC-7 had been endorsed by all medical organizations, no such endorsements ever occurred. Coleman said he had "no idea how it was ever said that so many medical organizations … endorsed SOC 7" (Boe v. Marshall, No. 2:22-cv-00184: 700-3, 2024, pp. 262-264).
[114] Boe v. Marshall, No. 2:22-cv-00184: 560-40 (2024, p. 8).
[115] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 33).
[116] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 27).

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Biden administration led it to agree to downgrade age guidelines from "recommendations" to "suggestions," thereby circumventing the original consensus process by making these changes without conducting a new round of validation.[117]

The issue of minimum ages resurfaced when the American Academy of Pediatrics (AAP) threatened to publicly oppose SOC-8 unless all age thresholds were eliminated—further exposing how political pressure, rather than scientific evidence or clinical judgment, dictated the final content of the guidelines.[118] Under pressure and facing open opposition from a key ally, WPATH leaders capitulated and agreed to eliminate minimum age criteria for all hormonal and surgical procedures (except phalloplasty). They did so despite acknowledging privately that the individuals within the AAP who were issuing the demand were very junior and lacked the authority or expertise to credibly dictate clinical standards.[119]

In the process of removing minimum ages, WPATH's president wrote that it was "disappointing that politics always trumps common sense and what is best for patients."[120] Another WPATH leader confided that the deletion of age minimums "is a balancing act between what I feel to be true and what we need to say."[121] SOC-8 Co-Chair Jon Arcelus said that removing ages would "make a joke of our methodology."[122]

The rushed, 11th-hour changes—made outside any formal or transparent guideline development process—resulted in SOC-8 initially being published with its original age recommendations still intact. Only after publication did WPATH scramble to issue a correction via an erratum in their official journal, the *International Journal of Transgender Health*, quietly removing age restrictions to align with political demands rather than clinical evidence.[123] The current, published version of SOC-8 states that all

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[117] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, pp. 292-295); Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 33). SOC-8's final round of Delphi processing was in January 2022 (Coleman et al., 2022, p. S251).
[118] Coleman explains that removing ages "led to them [i.e. AAP] formally not opposing the SOC. Yes this is highly confidential" (Boe v. Marshall, No. 2:22-cv-00184: 700-17, 2024, p. 153).
[119] Boe v. Marshall, No. 2:22-cv-00184: 700-16 (2024, p. 201).
[120] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 26).
[121] Boe v. Marshall, No. 2:22-cv-00184: 700-6 (2024, p. 103).
[122] Boe v. Marshall, No. 2:22-cv-00184: 700-16 (2024, p. 110).
[123] Correction (2022).

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recommendations went through the Delphi process. However, Coleman later acknowledged that removal of age minimums did not go through Delphi.[124]

10.5 Continued reliance on SOC-8

It remains concerning that SOC-8 continues to exert substantial influence over U.S. healthcare. WPATH's misconduct during the development of SOC-8 was covered by major news outlets including the *New York Times*,[125] *Economist*,[126] *Boston Globe*,[127] *Fox News,*[128] and *National Review,*[129] as well as by the *BMJ*, a leading medical journal.[130] Despite these reports, with the exception of the American Society of Plastic Surgeons,[131] major American medical associations have not issued public statements addressing the concerns detailed in this chapter.

In an amicus brief submitted to the Supreme Court of the United States for the upcoming case *U.S. v. Skrmetti*,[132] the AAP and 21 other medical organizations describe SOC-8 as an "established, evidence-based clinical guideline." The brief does not address any of the concerns or revelations regarding the guidelines' development outlined in this chapter. Similarly, a group of 11 prominent "adolescent medicine specialists, pediatricians, clinicians, methodologists, professors, and researchers"—including professionals affiliated with the medical schools of Harvard University, Stanford University, and the University of Pennsylvania—asserts in a separate brief that SOC-8 has "all" the National Academy of Medicine's "hallmarks of reliability."[133]

The U.S. Department of Justice (DOJ) intervened in 2022 to challenge Alabama's age limit law in *Boe v. Marshall*, thereby becoming familiar with the subpoenaed documents from WPATH. Nevertheless, in August 2024—two months after the documents were unsealed—the DOJ in a merits brief filed in *U.S. v. Skrmetti* described WPATH as "the

[124] Boe v. Marshall, No. 2:22-Cv-00184: 700-3 (2024, pp. 294-295).
[125] Ghorayshi (2024b).
[126] The Economist (2024).
[127] Selin Davis (2024b).
[128] Joseph (2024).
[129] Whelan (2024a).
[130] Block (2024a).
[131] Sapir (2024c).
[132] U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024, p. 8).
[133] U.S. v. Skrmetti (No. 23-477), Clinical Practice Guideline Experts, Amicus curiae brief (2024, p. 22).

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leading association of medical professionals treating transgender individuals" and asserted that "[t]he Nation's leading medical and mental health organizations recognize [SOC-8] as reflecting the accepted standard of care for treating gender dysphoria."[134]

[134] U.S. v. Skrmetti (No. 23-477), Brief for the petitioner (2024, p. 3).

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Chapter 11 Collapse of Medical Safeguarding

When children or adolescents develop feelings of severe discomfort with their sexed bodies, parents understandably worry and consult pediatricians or therapists for advice. These frontline clinicians in turn refer them to specialists, believing that this requires special expertise. Both parents and the clinicians they initially consult likely expect that those with expertise in "gender" will conduct a comprehensive evaluation to rule out other, perhaps more common causes of such feelings. They may further assume that puberty blockers (PBs), cross-sex hormones (CSH), and surgery are offered only in rare cases, when less invasive alternatives are ineffective, and after careful consideration of the patient's unique developmental needs as well as the profound uncertainties and risks of the treatments.

This chapter documents how the original Dutch Protocol that underpins pediatric medical transition (PMT) has undergone transformation in the U.S. to become a "child led" process in which the patient's personal "embodiment goals" form the basis for the determination of "medical necessity." Section 11.1 revisits the Dutch Protocol (critically assessed in earlier chapters) and explores how the original safeguards on the practice of pediatric medical transition (PMT) have been systematically dismantled in the U.S. Section 11.2 evaluates the frequent assertion that PMT is "rare," questioning whether this claimed infrequency genuinely indicates rigorous assessment standards. Section 11.3 discusses a deeper shift in PMT objectives, highlighting how the concept and role of "assessment" have fundamentally changed. Section 11.4 introduces whistleblowers with direct experience in PMT who, similarly to their counterparts in the U.K.,[1] have revealed practices they consider unsafe and inconsistent with established clinical standards, providing additional evidence of expedited pathways to medical interventions in leading pediatric gender clinics across the U.S.

11.1 The Dutch Protocol and the relaxation of its criteria in the U.S.

According to WPATH SOC-8, the Dutch studies associated with the Dutch Protocol provide "[t]he most robust longitudinal evidence supporting the benefits of gender-

[1] Barnes (2023).

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affirming medical and surgical treatments in adolescence …"[2] In his testimony before the Florida Boards of Medicine and Osteopathic Medicine, Aron Janssen, vice chair of clinical affairs at Lurie's Pritzker Department of Child and Adolescent Psychiatry, who also serves as chair of the American Academy of Child and Adolescent Psychiatry's Sexual Orientation and Gender Identity Issues Committee, said that "the best longitudinal data we have on transgender youth comes primarily out of the Dutch clinic … The Dutch model of care [is] the prevailing model of care that most of the American clinics have based their care upon."[3] SOC-8 seems to acknowledge the guardrails recommended in the Dutch Protocol, contrasting the "detailed comprehensive diagnostic assessment process" of that Protocol with treatment based on "limited or no assessment." According to WPATH, the latter approach "has no empirical support and therefore carries the risk that the decision to start gender-affirming medical interventions may not be in the long-term best interest of the young person at that time."[4]

11.1.1 U.S. gender clinics' departure from the Dutch Protocol

In 2022, investigative reporters from Reuters interviewed "doctors and other staff at 18 gender clinics across the country" and found that "[n]one described anything like the months-long assessments [the Dutch clinicians] adopted in their research." Seven of the 18 clinics said they were comfortable prescribing hormones on an adolescent's first visit, provided clinicians saw no "red flags."[5]

The Dutch clinicians themselves recognized the divergence of the American model from their approach.[6] Noting the shift in age-of-onset, sex ratio, and mental health profile in the pediatric clinical population, Annelou de Vries wrote in 2020 that "[t]hese youth did not yet participate in the early evaluation studies. This raises the question of whether the positive outcomes of early medical interventions also apply to adolescents who more recently present in overwhelming large numbers for transgender care, including

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[2] WPATH is referring to de Vries et al. (2011) and de Vries et al. (2014), discussed in several earlier chapters.
[3] Florida Boards of Medicine and Osteopathic Medicine Joint Rules/Legislative Committee (2022), 47:45-48:03.
[4] Coleman et al. (2022).
[5] Terhune et al. (2022).
[6] For a study on how different countries have responded to the Dutch Protocol see Kozlowska et al. (2024).

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those that come at an older age, possibly without a childhood history of [gender incongruence]."[7] In 2021, Thomas Steensma complained that "the rest of the world is blindly adopting our research …"[8] Steensma reiterated this position in 2023, explicitly distancing his work from the child-led model prevalent in the United States, stating, "That's not our approach."

Of note, the Dutch Protocol did not recommend surgeries prior to legal adulthood, but according to WPATH guidelines, which are followed in the United States,[9] most surgeries, including most genital surgeries, may be deemed medically necessary for certain adolescents with GD.[10] Accordingly, adolescents with GD do undergo mastectomies[11] and (much less commonly) genital surgeries.[12] In the published research on mastectomies in adolescent females with GD,[13] some participants were as young as 12 years old.[14]

11.2 Is pediatric medical transition "rare"?

To bolster the perception that medical gatekeeping ensures patient safety, advocates of PMT frequently assert that medical interventions are "rarely prescribed" to minors. In 2022, for example, the president of the American Academy of Pediatrics (AAP) asserted in an opinion piece published in *The Wall Street Journal* that "for the vast majority of children," the "gender-affirming" approach recommends the "opposite" of medical interventions.[15] These claims are not supported by the data.

In 2025, a *JAMA Pediatrics* study utilizing insurance data reported that about 0.1% of American 17-year-olds, or one in 1,000, received CSH between 2018 and 2022. The authors concluded that hormonal interventions are therefore "rare" and decried the "politicization of gender-affirming care for transgender youth … driven by a narrative

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[7] de Vries (2020).
[8] Tetelepta (2021a). There is an English translation available: Tetelepta (2021b).
[9] Coleman et al. (2022).
[10] E.g., "A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical *and surgical treatments* (GAMSTs)" (Coleman et al., 2022, S45-S46, emphasis added).
[11] Wright et al. (2023); Ghorayshi (2022); Sapir (2024c).
[12] Milrod & Karasic (2017); Terhune et al. (2022).
[13] Ascha et al. (2022); Olson-Kennedy, Warus, et al. (2018); Tang et al. (2022).
[14] Tang et al. (2022).
[15] Szilagyi (2022a).

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that millions of children are using hormones and that this type of care is too freely given."[16]

Such claims ignore a number of critical facts. First, no serious critic or skeptic of PMT has claimed that "millions of children are using hormones." Second, whether a prevalence of 1 in 1,000 is "rare" is subjective. For context, the prevalence of Type 2 diabetes in less than one in 1,000—a rate that medical authorities have described as "high" and even as "an awakening epidemic."[17] Third, even medical interventions that are objectively "rare" can raise profound ethical concerns. For example, "only" about 600 out of millions of African American men were recruited into the highly unethical Tuskegee syphilis study.

A central question in the debate over the frequency of medical interventions, and by extension whether they are "rare" or "freely given," concerns the appropriate choice of denominator. The authors of the *JAMA* study calculated prevalence using the total population of American adolescents as the denominator. However, in a press release accompanying the study, one of the authors noted that access to hormones was "surprisingly low, given that over 3% of high school youth identify as transgender"—implicitly invoking a different denominator.

Another denominator, which yields an even higher estimated frequency, is the number of adolescents diagnosed with GD and/or referred to a gender clinic, where they ostensibly undergo an "assessment" to determine whether medical interventions are indicated. Data on the rate of medicalization among adolescents diagnosed with GD and/or referred to a gender clinic are lacking.

Reports from individual clinics suggest that medicalization is the norm, rather than the exception. For example, pediatric endocrinologist Daniel Shumer of the Comprehensive Gender Services Program (CGSP) at University of Michigan Health estimated that "65 percent" of pediatric patients referred to his clinic end up receiving CSH.[18] According to data collected by Jamie Reed, a case worker at the Washington University School of

[16] Hughes et al. (2025).
[17] Lawrence et al. (2021); Kingsbury & Greene (2025) and the research articles cited therein.
[18] Doe v. Horne, No. 4:23-cv-00185-JGZ: 265 (2025, p. 52).

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Medicine Pediatric Transgender Center at St. Louis Children's Hospital, 67 percent of the clinic's patients were prescribed endocrine interventions during her four-year tenure at the clinic.[19] Finally, WPATH has itself implied that medical interventions are appropriate for "most adolescents" who seek them. In its response to the release of the Cass Review in the U.K., WPATH issued a statement criticizing the Review as being "rooted in the false premise that non-medical alternatives to care will result in less adolescent distress for most adolescents…"[20]

11.3 Shift in objectives and the new meaning of "assessment"

The AAP and other American medical associations argue that transition-related medical decisions for minors are made in consultation with parents and only after a "robust diagnostic assessment."[21] Under the original Dutch Protocol, assessments were intended to predict lifelong transsexuality, with pubertal suppression conceptualized as part of the diagnostic process (buying "time to think"). By contrast, the "gender-affirming" model, as it has evolved in the United States, prioritizes the autonomy of children and adolescents, allowing their current "embodiment goals" to direct treatment decisions.[22]

A systematic review of recommendations for the management of GD in children and adolescents found an absence of "[d]etailed guidance" and "no consensus about the aim or clinical approach"[23] of assessment. Understanding the realities of clinical care for youth with GD in the U.S. requires appreciating the shift in the meaning of assessment, which reflects a deeper change in the goals of PMT. According to the Dutch approach, the goal was to predict lifelong "transsexualism." Mental health professionals were to ascertain whether a GD diagnosis was appropriate and if so, whether it was likely to persist through adulthood. Although advocates of this approach generally regard a

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[19] Broyles & Trakas (n.d.).
[20] Block (2024c). The original statement from WPATH/USPATH (2024, April 12) was deleted from WPATH's website (404 Not Found | WPATH, n.d.). The April 12 WPATH/USPATH statement was covered by the NPR station WBUR (Scheimer et al., 2024). WPATH subsequently changed the statement, removing the referenced passage (see World Professional Association for Transgender Health & United States Professional Association for Transgender Health, 2024a; 2024b).
[21] U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024).
[22] Block (2023d).
[23] Taylor, Hall, Heathcote et al. (2024b, s80).

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diagnosis of GD as a necessary condition for medical interventions, there is considerable disagreement about whether it is sufficient.

More recently, advocates of early intervention have argued that "trans kids know who they are"[24] and that the goal of treatment is to help them achieve their personal "embodiment goals."[25] If an adolescent's self-conception or embodiment goals later change, this is not considered a failure of treatment but part of a "gender journey."[26] In 2023, Jason Rafferty, the lead author of the AAP's 2018 policy statement, "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents," explained that PMT is about "affirming and validating the child's sense of identity from day one through to the end." If a child says, "I'm X, we operate under the assumption that what they're telling us is their truth, that the child's sense of reality and feeling of who they are is the navigational beacon to sort of orient treatment around." If patients later detransition, this does not mean that the treatments were inappropriate, even if the interventions' effects are partly or fully irreversible: "They're not treatment failures if that's what's affirming," Rafferty said.[27]

Of note, the more cautious approach, which seeks diagnostic and prognostic clarity and aims at improvements in mental health, has been found to be unsupported by evidence. No test can reliably predict the natural course of an adolescent's identity development. The U.K.'s Cass Review found that a gender dysphoria diagnosis "is not predictive that the individual will go on to have longstanding trans identity."[28] Clinicians who adopt the earlier diagnostic-oriented model might perceive their approach as more cautious relative to colleagues practicing the newer "affirming" model; however, research on outcomes from both approaches has been rated unreliable.

One indicator of the changing definition of "assessment" is that leading gender clinicians—who until recently characterized PBs as a "fully reversible" and temporary "pause button" intended to give patients "time to think"—now acknowledge that these

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[24] See Note 33 in Chapter 2.
[25] Ashley et al. (2023); Boskey et al. (2025, p. 2); Brennan et al. (2025, p. 5); Mosier-Mills et al. (2024).
[26] "Clinicians should see detransition as one of many possible steps in a person's gender journey" (Ashley et al., 2025, p. 7).
[27] Block (2023d).
[28] Cass (2024, p. 146).

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drugs function as the first step in a broader medical transition protocol and must be considered in conjunction with cross-sex hormones. For example, in an amicus brief submitted to the Supreme Court of the United States, a leading advocate for PMT, Meredithe NcNamara of the Yale School of Medicine, and colleagues, fault the University of York systematic reviews, commissioned for the Cass Review, for failing to conceptualize PBs and CSH as a single "consistent, well-organized standard of care." According to McNamara et al., if, as research suggests, "the vast majority of adolescents with gender dysphoria who receive puberty blockers progress to cross-sex hormone therapy," that is not because PBs interfere with the natural process of GD resolution but "because [the adolescents] are indeed transgender and because their diagnosis of gender dysphoria is accurate."[29] This explanation for the observed high persistence of GD lacks empirical support due to the absence of controlled prospective studies and raises concerns about motivated reasoning. Many of the brief's authors are actively engaged in the practice of PMT and therefore have intellectual and financial conflicts of interest.[30]

11.3.1 Ambiguity in SOC-8

On the surface, WPATH SOC-8 might appear to recommend a cautious approach toward assessment. Mental health providers are to conduct a "comprehensive biopsychosocial assessment" prior to initiating medical interventions in order "to understand the adolescent's strengths, vulnerabilities, diagnostic profile, and unique needs to individualize their care."[31] At the same time, however, WPATH recommends that clinicians use the *International Classification of Diseases* (ICD-11) diagnosis of "Gender Incongruence of Adolescence and Adulthood," which, unlike the DSM-5 diagnosis of "Gender Dysphoria," requires only "marked and persistent incongruence between an individual's experienced gender and the assigned sex." Because SOC-8 defines transgender in a similar way ("people whose gender identities and/or gender

[29] U.S. v. Skrmetti (No. 23-477), Expert Researchers and Physicians, Amicus curiae brief (2024, pp. 16-17).
[30] The lead author, McNamara, has positioned herself in media and court appearances as a provider of PMT to minors. However, in a deposition McNamara revealed that she does not in fact administer PMT to minors with GD. See Sapir (2024b).
[31] Coleman et al. (2022, Chapter 6).

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expressions are not what is typically expected for the sex to which they were assigned at birth") and provides no meaningful distinction between this meaning of transgender and gender non-conformity, SOC-8 effectively recognizes transgender identification as a medical condition justifying medical interventions.[32]

It is widely recognized that a fundamental tension exists between WPATH's desire to treat transgender identity (gender incongruence) as a normal and healthy variation of human development and its insistence that gender incongruence requires "medically necessary" treatment. This tension was explicitly acknowledged in medical literature supporting PMT contemporaneous with the preparation and publication of the fifth edition of the DSM. For example, in 2013, Jack Drescher, a prominent clinician-advocate of PMT, noted the significant difficulty in reconciling the "contradictory narratives" of "reducing stigma (which underlies the call for removal of the gender diagnoses [from the DSM]) and maintaining access to care (which requires the existence of a diagnosis in order to obtain needed medical treatment covered by third party payers)."[33]

In the lead-up to SOC-8's publication, *The New York Times* reported on disagreements among proponents of PMT concerning the proposed assessment recommendations for adolescents. One clinician told the *Times* it was "harmful and destructive and abusive and unethical and immoral" to require that a candidate for medical transition have longstanding GD since childhood—a key element of the Dutch Protocol. Another described the assessment recommendations as a "comprehensive inquisition of [an adolescent's] gender." The International Transgender Health Group criticized WPATH's draft chapter for its "harmful assertion of psychogatekeeping" and for "undermin[ing] patient autonomy." Asked whether it was appropriate to assess "the basis of a kid's gender identity," physician Colt St. Amand, a coauthor of SOC-8, told the *Times* that this "just reeks of some old kind of conversion-therapy-type things … People are who they say they are, and they may develop and change, and all are normal and OK." St. Amand was "less concerned with certainty around identity, and more concerned with

[32] See Chapter 13; The acronym "T/GNC" [transgender and gender-nonconforming] is commonly used in literature supportive of PMT.
[33] Drescher (2014, pp. 11-12).

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hearing the person's embodiment goals. Do you want to have a deep voice? Do you want to have breasts? You know, what do you want for your body?"[34]

11.3.2 SOC-8 guardrails abandoned

Although WPATH's guidelines do not necessarily discourage mental healthcare, they likewise do not require it as a precondition for PMT. Some guideline authors opposed even minimal requirements for mental health support, arguing that such provisions were analogous to "conversion therapy."[35] SOC-8's only formal recommendation is for a "comprehensive biopsychosocial assessment," although WPATH emphasizes that its guideline is "flexible," thereby leaving room for considerable variation in clinical practice.[36]

In 2024, leaked discussions among WPATH members illustrated the extent to which the organization's own members' practice is not always consistent with SOC-8 recommendations. Some WPATH members candidly acknowledged foregoing even minimal psychological evaluations and moving quickly toward hormonal interventions. The candid nature of these exchanges suggests that non-adherence to the guidelines is not a source of professional shame, and not an isolated phenomenon.[37] The flexibility embedded in SOC-8 has facilitated significant gaps between the guidelines' theoretical standards and the practical reality in clinical settings.

Further, this flexibility has effectively provided leaders in the field of PMT with a basis to argue that assessment should not serve the purpose of differential diagnosis or medical "gatekeeping" but rather should function primarily to inform patients and their caregivers about the nature and effects of medical interventions. In 2020, a Canadian conference presentation reported that among pediatric gender clinics surveyed, half did not require any mental health assessment prior to initiation of hormonal interventions.[38] As one group of clinicians recently stated:

[34] Bazelon (2022b).
[35] Bazelon (2022a).
[36] Coleman et al. (2022, p. S6).
[37] Hughes (2024).
[38] Lawson et al. (2020).

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> When a family comes to a mental health provider requesting a letter for a biopsychosocial assessment for pubertal suppression, work begins by explaining, in developmentally appropriate language, that this is not an assessment of whether they 'are actually transgender,' as many patients worry; rather this assessment is meant to help them understand the intricacies of pubertal suppression, so that they can make the best decision for themselves. The primary goal is to provide information, while identifying all potential avenues of support (social, educational, medical, and legal) related to gender.[39]

Jack Turban, the lead author of this statement and Director of the Gender Psychiatry Program at the University of California San Francisco, has said that differential diagnosis is pointless and may even be harmful. He disputes the notion that mental health assessment can reduce the risk of later regret, claiming that "there's not data [sic] that … any of these assessments make that [outcome] less likely."[40] According to Turban, children and adolescents "are just going to figure out the answers and then tell you what you want to hear. And you've set up this argumentative relationship with your patient or client."

Robert Garofalo of Lurie Children's Hospital in Chicago agrees that determining the causes of a child's feelings of alienation from their body through assessment is unnecessary.

> Sometimes parents will come in and be like, "I want to make sure that my young person, my child, is really trans … Can you help me with that?" And I'll turn to the child and be like, "yeah, so, you know, what gender identity do you have?" … You know, there's no form, there's no scale, there's no psychological battery of tests that needs to be done. Really, any young person can answer that question for themselves … Parents … think that they're going to come in and have this evaluation that is gonna help determine their child's gender identity, when really

[39] Turban et al. (2025, pp. 12-13).
[40] GenderGP (2021).

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> … our work sometimes is just getting them to recognize that anyone's gender identity … is a normal variation …[41]

Amy Tishelman, formerly of the Gender Multispecialty Service at Boston Children's Hospital, expressed discontent with the new model of assessment in an interview with *The Boston Globe*. "I've never been happy with that way of characterizing it. I feel like an assessment should encompass more than just, 'Should a person get medical intervention, or shouldn't they?'"[42] In contrast, physician A.J. Eckert, former medical director at Anchor Health Initiative in Connecticut, avowed: "If you are trans, I believe you." For Eckert, minors "are best equipped to make decisions about [their] own body." Eckert further clarified that while medical interventions at Anchor Health are not provided before puberty, psychological therapy is not mandatory because "being trans is not a pathology."[43]

11.3.3 Collapse of assessment times

The erosion of medical safeguarding practices within American gender clinics is evident in the significant reductions in patient assessment durations at prominent institutions.

11.3.3.1 Boston Children's Hospital

GeMS at Boston Children's Hospital is the nation's first pediatric gender clinic and is highly regarded internationally. Whereas in 2013 GeMS allocated a minimum of 20 hours for mental health assessments per patient, court records indicate that by 2021 the clinic had reduced these evaluations to approximately two hours per patient.[44] Laura Edwards-Leeper, the clinic's founding psychologist, characterized this change as "shocking." Amy Tishelman, a former GeMS psychologist and SOC-8 developer, described it as "reckless."[45] Tishelman's tenure ended following disagreements with colleagues, culminating in litigation. Current co-director Kerry McGregor defended the reduction in assessment times, stating that two-hour assessments were initiated around

[41] Figliolia (2025).
[42] Damiano (2024b).
[43] Edwards-Leeper & Anderson (2021); the quote from Eckert is in Eckert (2020).
[44] Alder (2024).
[45] Ryan (2024a).

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2017–2018 and are "appropriate" given the expanding patient load.[46] Endocrinologist and GeMS director Jeremi Carswell remarked in 2021 that puberty blockers were being prescribed "a lot like candy."[47]

11.3.3.2 Children's Hospital Los Angeles

Johanna Olson-Kennedy, medical director of the Center for Trans Youth Health and Development at Children's Hospital Los Angeles, has acknowledged that she approves some of her minor patients for endocrine interventions after "a couple of hours" of assessment.[48] In December 2024, Olson-Kennedy and the hospital were named as defendants in a lawsuit filed by a former patient whom Olson-Kennedy allegedly approved for PBs at age 12 following a single consultation with no involvement of a mental health professional. The lawsuit further alleges that Olson-Kennedy told the parents of the patient that the patient faced suicide risk without medical interventions, despite no prior suicidal history. Subsequently, the patient was put on testosterone at 13, underwent a double mastectomy at 14, and was recommended for hysterectomy at 17.[49]

11.3.3.3 Lurie Children's Hospital

In a webinar hosted by AMAZE, a producer of sex education content for students, Robert Garofalo of Lurie Children's in Chicago explained how his clinic handles parents who have doubts about the safety of medical interventions.

> Most of the young people who come in are wanting to figure out how fast they can get on hormones and what is the safest process to do that … 80% of the young people who come are often really activist [sic] in their mindset and come dragging their parents to the medical visit … The counterweight to that is the parents who are often coming in with questions about how can this be done safely, is this really the right decision, and so it's really a bit of a puzzle to put the pieces together to make sure that you are meeting the patient's needs but also

[46] Damiano (2024a).
[47] Lindquist (2022).
[48] Deposition of J. Olson-Kennedy in LB v Premera Blue Cross NO. 2:23:Cv-00953-TSZ (2024, p. 63).
[49] Complaint, Breen v. Olson-Kennedy, No. 24STCV32096 (2024).

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> moving the parents along … in a way that continues to get them educated so that they feel comfortable with the decisions they're about to make, because the truth is that these young people need their parents to be well and to do this well, and so it's our job as pediatricians to make sure that the entire family unit in some ways hopefully moves forward in an ideal situation in a way that feels supportive and nurturing. So, it's usually the young person who comes in knowing exactly what they want and us trying to navigate a process to ensure that's done safely and allaying parents' fears.

Garofalo went on to elaborate on his understanding of what shared decision-making means:

> If the medical provider thinks they have the answer [to whether medical interventions are appropriate] then they're the wrong medical provider. The answer lies within the young person and the family. Your job as a healthcare provider is to help them along that path, to find the answers and the solutions that feel authentic and healthy for them.[50]

11.3.3.4 Seattle Children's Hospital

In a response to Tordoff et al. (2022), a study conducted at Seattle Children's Gender Clinic,[51] one commentator pointed out that the control group, which received only psychotherapy, might have shown comparatively worse mental health due to selection bias: "patients with coexisting mental concerns may have been potentially discouraged from accepting the treatments until their coexisting conditions were addressed."[52] Lead author Diana Tordoff responded to the comment by pointing out that "youth who reported moderate to severe depression, anxiety, or suicidal thoughts were not precluded access to PB/GAH [puberty blockers and gender-affirming hormones], especially since initiating PB/GAH is known to improve or mitigate these symptoms."[53] Eighteen-year-olds "were provided care using an informed consent model and were not

[50] Figliolia (2025).
[51] Tordoff et al. (2022); see Section 6.2.2 for further discussion.
[52] Tordoff et al. (2022) [online comment; March 7, 2022].
[53] Tordoff et al. (2022) [online comment; March 13, 2022].

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required to complete a mental health assessment." Tordoff also noted that Seattle Children's practices were consistent with the (then draft) SOC-8 guidelines.[54]

11.3.3.5 UCSF Benioff

In 2018, the organization Gender Spectrum hosted a panel with Ilana Sherer, a pediatrician and gender clinician, and Diane Ehrensaft, a clinical psychologist at UCSF Benioff and one of the principal architects of the "gender-affirming" approach in the United States. Sherer said that she sees "lots and lots of kids" who "don't have [gender] dysphoria, that really don't have mental health issues, and so to say to them 'you have to go get a letter from a mental health provider' feels challenging to me." But since a letter of support is required for medical interventions, Sherer went on to explain that "what we've started to do in our clinics is have someone like Diane [Ehrensaft] ... go in and do a brief assessment, and give their rubber—I know you [addressing Ehrensaft] said you don't rubber-stamp, but basically in my mind that's what it feels like—and so then we can move on and say 'OK, now we can talk about what you're actually here for.'"[55]

11.3.3.6 Planned Parenthood

Specialized gender clinics are not the only institutions prescribing hormonal interventions to adolescents. According to a 2024 investigative report published in *The Free Press*, Planned Parenthood is "the country's leading provider" of hormones for young people. Approximately 40% of the more than 40,000 patients for whom Planned Parenthood prescribed hormones in 2023 were between the ages of 18 and 22. Some branches, however, "offer hormones starting at age 16 with parental approval." In recent years, Planned Parenthood clinics have adopted an expedited access policy on an "informed consent" basis. Nicole Chaisson, medical director of Planned Parenthood North Central States, told *The Free Press* that "Gatekeeping is not necessary. People are the experts of their own body and of their own journey, and as long as they can

[54] Tordoff et al. (2022) [online comment; March 13, 2022].
[55] Sherer (2018).

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make decisions, they should be the agent of their own healthcare." Chaisson said it was appropriate for teenagers to "leave the clinic with their prescription" after a single visit.[56]

Jamie Reed, the former case manager at the Washington University pediatric gender clinic in St. Louis, had previously worked at Planned Parenthood. Reed testified in a deposition that the St. Louis gender clinic would refer minor patients to Planned Parenthood "when we did not have consent from legal guardians" because Planned Parenthood would get "these kid's scripts [prescriptions] when they did not meet" diagnostic criteria. Although Planned Parenthood requires consent from an adult caregiver to prescribe hormones to minors, Reed said that Planned Parenthood "would not verify who the adult is that is bringing [the minor patient] to the building."[57]

11.4 The whistleblowers

In public statements, advocates and practitioners of PMT routinely imply that assessment functions as a form of medical gatekeeping, suggesting that PBs, CSH, and surgeries are offered cautiously and only to patients who genuinely require such interventions. Meredithe McNamara has argued that it is a "misconception" that "a child's disclosure of gender dysphoria leads to impulsive, irreversible decisions." Rather, "decisions on whether, when, and how to pursue medical interventions are slow-moving, rigorous, and individualized."[58] In his testimony before the Florida Boards of Medicine and Osteopathic Medicine in 2022, Aron Janssen, of Lurie Children's, said that treatments follow a "careful and thorough assessment of a patient's mental health including co-occurring conditions, history of trauma, substance use, among many other factors."[59]

In recent years, however, whistleblowers with firsthand experience working in gender clinic environments have come forward with compelling counterexamples. Their testimonies have often been dismissed, ignored, marginalized, or disparaged by colleagues. Several have also faced retaliation because of their disclosures.

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[56] Block (2024d).
[57] Noe v. Parson, No. 23AC-CC04530 (2024, p. 172).
[58] McNamara (2024).
[59] Florida Boards of Medicine and Osteopathic Medicine Joint Rules/Legislative Committee (2022), a 43:57.

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11.4.1 Laura Edwards-Leeper and Erica Anderson

In 2021, Laura Edwards-Leeper, the founding psychologist of the first pediatric gender clinic in the United States, and Erica Anderson, a clinical psychologist and former president of the U.S. Professional Association for Transgender Health (USPATH), became the first prominent whistleblowers in the United States. In an opinion piece for *The Washington Post,* Edwards-Leeper and Anderson warned that adolescents were "being rushed into" medical interventions without sufficient psychological assessment or deliberation. "A flood of referrals to mental health providers and gender medical clinics, combined with a political climate that sees the treatment of each individual patient as a litmus test of social tolerance, is spurring many providers into sloppy, dangerous care,"[60] they wrote.

Following publication in *The Washington Post*, USPATH sought to impose a moratorium on Anderson's ability to speak to the press while WPATH was finalizing its SOC-8. Anderson resigned from the organization in protest.[61]

In an interview with journalist Abigail Shrier, Anderson cautioned that the current PMT approach involved "sloppy healthcare work," which could result in young people making decisions they would later regret. Marci Bowers, a gynecologist and surgeon who, like Anderson, identifies as transgender, echoed these concerns in the same interview. Bowers observed that although medical interventions initially seemed promising, in practice they had not yielded better—or even equivalent—outcomes compared to earlier approaches. Bowers specifically voiced concern about the long-term implications of these interventions on reproductive capacity, sexual health, and the ability of patients to experience intimacy.[62]

Despite criticizing the "gender-affirming" approach now dominant in their field, Anderson and Edwards-Leeper continue to believe that at least some children and adolescents benefit from medical transition. Bowers issued a detailed letter of apology to WPATH

[60] Edwards-Leeper & Anderson (2021).
[61] Selin Davis (2022).
[62] Shrier (2021b).

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leadership[63] and remained with the organization, serving as its president from 2022 to 2024.

11.4.2 Jamie Reed

In 2022, Christopher Lewis and Sarah Garwood, then co-directors of the Washington University School of Medicine Pediatric Transgender Center at St. Louis Children's Hospital, testified before the Missouri House Judiciary Committee that "[m]edical interventions are done with a thorough and multidisciplinary team approach, which includes mental health assessment and requires consent from all custodial parents or caregivers."[64] Opening with the unfounded assertion that PMT is "literally lifesaving" (see 4.3.4 for discussion of suicide risk), Lewis, the Center's endocrinologist, emphasized that "[f]or pubertal transgender adolescents, medical services are started only after meeting strict eligibility criteria… [This] includes mental health professionals who have adequately documented and explored various aspects of gender and mental health exploration [sic], psychosocial medical concerns and conditions, and ability to understand their decisions and provide assent."[65]

These assertions were later disputed by Jamie Reed, who worked for four years at the Center as a case manager responsible for patient intake and oversight. In deposition testimony, Reed stated that Lewis had indicated at an early stage that he "[didn't] care" if patients met criteria for gender dysphoria. It was "not a requirement for [him] to prescribe hormones."[66] An investigation by *The New York Times* provided additional details about the clinic's practices and corroborated most aspects of Reed's testimony. According to the investigation, one patient, who subsequently detransitioned, received a prescription for testosterone following a single visit, without prior assessment by any mental health professional. When WPATH SOC-8 was published in September 2022, Lewis texted Karen Hamon, the Center's nurse, saying: "Right now I have no idea how to meet what would be the most intensive interpretations of the SOC."[67]

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[63] Boe v. Marshall, No. 2:22-cv-00184: 700-5 (2024, pp. 67-71).
[64] Lewis & Garwood (2022, 9:14:55).
[65] Lewis & Garwood (2022, 9:16:40).
[66] Noe v. Parson, No. 23AC-CC04530 (2024, p. 244).
[67] Ghorayshi (2023b).

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According to Reed, the Center responded to a 5-fold increase in its patient caseload by offering mental health providers a letter-of-support template for them to sign, in the hope that this would speed up the process of approval for endocrine treatments. It "was just copy paste," Reed testified in a deposition. Reed said that when she brought her concerns to Lewis, he "didn't care and was going to pass it [the letter] anyway".[68]

Concerned that the Center was not tracking patient outcomes, Reed and Hamon created a "red flag list," a private Excel spreadsheet in which they documented cases of patients with complex mental health presentations. As reported by the *Times*, the list included "a patient on testosterone [who] stopped taking schizophrenia medication without consulting a doctor and another [who] had visual and olfactory hallucinations. Another had been in an inpatient psychiatric unit for five months."[69] Reed also described an adolescent female from an "unstable family" who was in "an uncertain living situation and had a history of drug use" and was put on hormones at age 16, followed by a double mastectomy at 18. Three months later she regretted the surgery and informed the clinic, "I want my breasts back."[70] According to the *Times*, the patient contacted the surgeon at Washington University twice about her wish for breast reconstruction, but did not receive a response.[71]

Reed recalled a 17-year-old girl who was given testosterone and reported "bleeding from the vagina." The girl was advised to use a heavy pad to absorb the blood. "In less than an hour she had soaked through an extra heavy pad, her jeans, and a towel she had wrapped around her waist. The nurse at the center told her to go to the emergency room right away." The Center "found out later this girl had had intercourse, and because testosterone thins the vaginal tissues, her vaginal canal had ripped open. She had to be sedated and given surgery to repair the damage."[72]

Reed reported that when she raised concerns regarding inadequate mental health assessment and safeguarding with the Center's physicians, her objections were

[68] Noe v. Parson, No. 23AC-CC04530 (2024, p. 165).
[69] Ghorayshi (2023b).
[70] Reed (2023a).
[71] Ghorayshi (2023b).
[72] Reed (2023a).

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repeatedly dismissed and she was advised to “Get on board, or get out.” Individuals who expressed doubts frequently faced “being called a transphobe.”[73] A similar phenomenon of intimidation was documented at the Tavistock’s Gender Identity Development Service in the U.K.[74]

Reed, who is lesbian, profoundly regrets her past involvement in PMT, and has since become a leading advocate for restrictions on practices she regards as harmful, especially for youth with emergent same-sex attraction who are overrepresented among patients.[75] The Center stopped providing PMT following the enactment of Missouri's Senate Bill 49 (SB 49).[76] Lewis, the Center’s endocrinologist, accepted a job in Colorado, where he currently practices PMT at Children's Hospital Colorado.[77]

11.4.3 Tamara Pietzke

In February 2024, Tamara Pietzke, a licensed clinical social worker and therapist at MultiCare Health System in Tacoma, Washington, disclosed harmful practices occurring in her clinical environment.[78] Pietzke described patients with significant comorbid mental health conditions and complicated life histories, who, despite these vulnerabilities, were approved for hormonal interventions.

One patient, a 13-year-old adolescent female, had diagnoses of depression, anxiety, post-traumatic stress disorder, and intermittent explosive disorder. She had experienced childhood abuse, neglect, and sexual violence, and, according to Pietzke, reported that “horror and porn movies … were the only ones available in her house.” The patient also told Pietzke that her mother practiced bestiality. She communicated in therapy sessions by displaying extremely sadistic and graphic pornographic videos to Pietzke on her phone. The patient also was reported to have autism spectrum disorder, a factor that may have contributed to her communication difficulties. Pietzke noted that the girl would “age-regress” by “watching *Teletubbies* and sucking on a pacifier.”[79] A restraining order

[73] Reed (2023a).
[74] Barnes (2023); Cass (2024).
[75] Reed (2023b).
[76] Washington University (2023).
[77] University of Colorado Anschutz Medical Campus (n.d.).
[78] Pietzke (2024a).
[79] Pietzke (2024a).

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was also in place against the patient's mother, who had previously attempted to harm the girl's sister in her presence. The girls were being raised by their mother's former boyfriend.

In addition to these obvious red flags, Pietzke noted that her 13-year-old patient never asked for testosterone and failed to demonstrate an understanding of the hormone when the subject was raised. Nevertheless, the gender clinic at Mary Bridge Children's Hospital, part of MultiCare, approved the teenager for testosterone on her first visit. The clinic requested that Pietzke sign a letter of support clearing the patient of any mental health contraindications. Pietzke refused, and the case was referred to the hospital's risk management team. Instead of siding with Pietzke, however, the risk management team reassigned the adolescent to another therapist. Pietzke wrote to Amber Rolfe, MultiCare's in-house "gender-affirming care" expert, explaining her concerns and even citing Sections 6.3 and 6.12 from the Adolescent chapter of WPATH SOC-8 in support of her decision.

Rolfe disagreed with Pietzke's clinical judgment and citations from SOC-8, insisting that nothing in the patient's history, behavior, or concurrent diagnoses was a contraindication for hormone treatment.[80] "There is not valid, evidenced based, peer reviewed research that would indicate that gender dysphoria arises from anything other than gender (including trauma, autism, other mental health conditions, etc.)," Rolfe wrote to Pietzke.[81] "At it's [sic] core the diagnosis centers on an incongruence of gender identity and assigned gender at birth." Rolfe also suggested that Pietzke examine her biases and consider transferring the client "to someone who is comfortable with providing gender affirming care."[82] Pietzke resigned from MultiCare shortly thereafter and went public with her story.

11.4.4 Eithan Haim

Eithan Haim, a surgeon formerly affiliated with Texas Children's Hospital (TCH), became a whistleblower after discovering that TCH was performing medical transition

[80] Sapir (2024a).
[81] Rolfe (2023).
[82] Rolfe (2023).

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procedures on minors despite publicly announcing a cessation of such procedures.[83] In 2022, prompted by a Texas Attorney General's opinion describing PMT as potentially abusive, TCH declared it would pause hormone interventions for transgender-identifying youth.[84] Despite this declaration, Haim became aware of ongoing practices that he asserted contradicted these claims; three days following the public statement, an 11-year-old patient received a puberty blocking implant, and similar interventions continued throughout the subsequent year involving dozens of other patients.[85] In May 2023, Haim anonymously provided de-identified hospital records and related documents to journalist Christopher Rufo, which resulted in a public exposé. The released data suggested that TCH had misled the public about halting its PMT program.[86]

Haim was charged with four felony counts under the Health Insurance Portability and Accountability Act (HIPAA). Prosecutors argued that Haim was not authorized to access patient data and that he did so with intent to maliciously harm the hospital.[87] The charges carried penalties of up to 10 years' imprisonment. Haim pleaded not guilty, denying his access to patient records was inappropriate, and asserting his disclosures were whistleblower actions aimed at safeguarding children rather than malicious acts.[88] The allegations were unusual, as HIPAA violations are typically addressed through civil rather than criminal procedure. The choice to pursue criminal charges raised suspicion that the federal government's actions were retaliatory in nature.[89]

The DOJ's indictment against Haim had to be amended multiple times after it was revealed that the government was mistaken about Haim's involvement with TCH. A second indictment had to be revised again because Haim was charged with actions as crimes that are not criminal under the law. The third indictment, which was shorn of most of the initial factual allegations, was for unauthorized access to patient records with intent to cause harm to doctors and the hospital, not patients. In January 2025,

[83] Haim (2024).
[84] Campion (2022).
[85] Haim (2024).
[86] Alder (2025).
[87] Trombly (2024).
[88] Alder (2025).
[89] Trombly (2024).

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after months of legal contention and growing public criticism of the prosecution as "lawfare," federal prosecutors dismissed all charges against Haim with prejudice, effectively exonerating him.[90]

In November 2024, Haim's lawyers informed the DOJ that the lead prosecutor in the case, Tina Ansari, and her family, had "substantial financial and political ties" to Texas Children's Hospital and Baylor College of Medicine, resulting in a potential conflict of interest.[91] Shortly thereafter, Ansari withdrew from the case.[92]

[90] House Judiciary Committee (U.S. Congress) (2025).
[91] Patrick (2024).
[92] Whelan (2024b).

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Chapter 12 Medical Association Response

This chapter examines how, despite growing recognition of its problems, the 8th version of the World Professional Association for Transgender Health (WPATH) *Standards of Care* (SOC-8) continues to have substantial influence on the medical field. This can be better understood by examining the critical role that major medical and mental health associations (MMHAs) play within the U.S. healthcare system (Section 12.1). Section 12.2 explores the reasons why MMHAs have not properly responded to updated evidence, nor to serious ethical concerns; Section 12.3 is a summary conclusion.

12.1 The role of major medical and mental health associations

Given the decentralized and fragmented nature of the U.S. healthcare system, MMHAs play a central role in shaping clinical practice guidelines, healthcare policy, and medical practices. They educate clinicians on emerging research, develop authoritative clinical practice guidelines, publish peer-reviewed journals, facilitate interdisciplinary collaboration, and engage in professional advocacy on behalf of their members. Typically, MMHAs limit full professional membership to practitioners actively engaged in clinical medicine or the mental health disciplines and enforce professional codes of conduct under which members may face sanctions or loss of privileges for noncompliance. MMHAs derive their authority in large part from their perceived adherence to rigorous professional standards and to science.

However, despite their scientific orientation, MMHAs are not immune to institutional biases, including groupthink and the disproportionate influence of vocal, specialized subcommittees. These specialized groups may receive broad deference from the larger organization, especially when their initiatives are framed in the language of civil or human rights. Consequently, MMHAs can inadvertently become echo chambers where dissent is suppressed, confirmation biases go unchecked, and professional deference is exploited. This dynamic of institutional capture is hardly unique to MMHAs: it occurs whenever support for a particular viewpoint is concentrated within a small, motivated subgroup, while opposing views are diffuse, less attentive, and less organized. As a result of this dynamic, the general public may inaccurately perceive the wider membership of individual MMHAs as uniformly aligned with the professed position of

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their professional association. It is easy to overlook the fact that fundamentally, these organizations operate as trade associations, with a primary role of protecting their members' autonomy and professional interests. Although individual clinicians generally are motivated by altruism, it should not be assumed that the collective actions of an organization always reflect the values or intentions of its individual members.[1]

Historical examples demonstrate that despite their crucial role in safeguarding patients' interests, MMHAs have at times resisted necessary medical reforms, even when confronted with strong evidence of their urgency. For instance, the American Academy of Pediatrics (AAP) delayed rescinding its 2000 guidelines discouraging early peanut exposure for two years after evidence emerged linking the policy to increased rates of peanut allergies.[2] Similarly, professional organizations resisted evidence-based recommendations to limit arthroscopic knee surgeries, lobbying against healthcare reforms despite clear evidence of limited efficacy.[3] MMHAs may impede or even oppose evidence-based medicine when the professional or financial interests of their members are threatened by medical practice reversal.

The reliance of MMHAs on WPATH is exemplified by the Endocrine Society (ES) clinical practice guideline for the treatment of gender dysphoria (GD). As discussed in Chapter 9, the close alignment of these groups' guidelines suggests a lack of robust, independently derived frameworks for care, potentially limiting critical appraisal and alternative perspectives within the field. Notably, Joshua Safer, who is leading the 2024 revision of ES guidelines, is himself closely associated with WPATH and is a prominent advocate for pediatric medical transition (PMT).[4] His leadership role raises concerns about compliance with the National Academy of Medicine's standards for trustworthy guideline development, in particular with regard to conflict of interest management (see 10.3.1).[5]

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[1] For a discussion of this phenomenon and its consequences for medical policy, see Patashnik et al. (2017).
[2] See Section 1.2.2.
[3] Patashnik et al. (2017, Chapter 2).
[4] Sapir (2024d).
[5] Graham et al. (2011, p. 87).

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MMHAs have been reluctant to transparently address the weak evidence base underlying PMT. For example, the American Psychiatric Association's (APA) textbook *Gender-Affirming Psychiatric Care*[6] has faced internal criticism for failing to acknowledge the scientific debate and the policy shifts occurring internationally.[7] A petition with over 7,000 signatures, many from medical and mental health professionals, has called for the withdrawal or correction of the textbook,[8] yet APA leadership has not issued a substantive response.[9] Similarly, the American Academy of Child and Adolescent Psychiatry (AACAP) has rejected multiple proposals addressing important evidence and dissenting perspectives that were submitted to its conferences.[10] The AAP likewise has repeatedly declined to platform critical perspectives at its events.[11] This pattern of organizational defensiveness fosters environments in which clinicians feel compelled to self-censor.

The AAP has rejected multiple internal requests to conduct systematic reviews of the evidence underpinning PMT.[12] Although AAP leadership ultimately agreed in principle to a systematic review, it simultaneously reaffirmed the existing policy[13]—a move that evidence-based medicine experts have criticized as methodologically unsound and premature, as it presupposes the outcome of a review intended to impartially evaluate the evidence.[14] To date, there is no evidence the AAP has begun the review.

After the National Health Service (NHS)-commissioned Cass Review was published in April 2024, several affiliates of the American Psychological Association (APA) prohibited its very discussion on their professional listservs. When a San Francisco-area psychologist posted information about the Cass Review on a listserv of Division 39 of the APA, the listserv moderator blocked the post, citing a 2020 "Letter of Apology to

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[6] Goetz & Keuroghlian (2023).
[7] Satel (2024).
[8] Foundation Against Intolerance & Racism (2024).
[9] Posner (2024).
[10] Sibarium (2023).
[11] Shrier (2021a).
[12] Block (2023c).
[13] Wyckoff (2023). AAP policy statements automatically expire after 5 years unless readopted, revised, or revoked.
[14] Ghorayshi (2023a).

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LGBTQ+ Communities" that forbids "speech that is injurious to LGBTQ+ members."[15] The Pennsylvania Psychological Association (PPA), a state affiliate of the APA, sent an email to all its members informing them that the Cass Review was "no longer welcomed for discussion" on its professional listserv. The PPA explained that the Review "fail[s] to meet" the PPA's "professional standards," and that "LGBTQIA+" members and their "allies" might feel "targeted, harmed, and hurt by this literature being repeatedly shared."[16] A clinical psychologist who describes herself as "a liberal feminist" and who has "marched in Pride marches" told the *BMJ* that she was "reprimanded" by the Illinois Psychological Association after posting about the Cass Review on a therapist listserv.[17]

12.2 Factors contributing to neglect of evidence and open debate

Hilary Cass, past president of the Royal College of Paediatrics and Child Health and leader of the U.K.'s comprehensive review of pediatric gender medicine services, has stated that American physicians are "out of date" in their approach to pediatric gender medicine.[18] Several factors may help explain the reluctance of American MMHAs to engage fully with the shifting perspectives on evidence and ethics in this area of practice.

First, in managing unusual or complex conditions, primary care providers and generalist clinicians often rely on the expertise of specialists to inform their clinical decisions.[19] When the former also hold leadership positions in medical organizations and are tasked with shaping policies for the treatment of youth with GD, they often defer to specialized committees—such as committees devoted to LGBT issues—whose members they regard as the organization's content experts. These committees typically are composed of professionals whose careers are closely tied to supporting or delivering medical transition, limiting their ability to impartially evaluate the evidence due to significant intellectual and financial conflicts of interest. While reliance on specialist committees

[15] Selin Davis (2024a).
[16] Ryan (2024c).
[17] Block (2024b).
[18] Ghorayshi (2024a).
[19] Tzartzas et al. (2019).

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poses fewer risks in well-established subspecialties with decades of robust research,[20] pediatric gender medicine remains a new, highly controversial field characterized by a limited and low-certainty evidence base.

Second, the framing of PMT as a civil rights matter[21] may have contributed to premature and uncritical support at both the individual and institutional levels. Most medical professionals are broadly supportive of civil rights.[22] U.S. specialty committees often frame PMT as a morally righteous or progressive cause, leading many professionals reflexively to adopt supportive positions. Given that transgender identification is relatively common among youth—estimated at 2–5%, though precise figures remain uncertain—many clinicians and policymakers also may have personal connections, such as friends or loved ones who identify as transgender. These personal ties, combined with a genuine desire to be compassionate and supportive, may understandably make it more difficult for professionals to critically and objectively evaluate the evidence base or ethical considerations underlying PMT.

Third, by the time the weak evidence and growing international retreat from the practice became difficult to ignore, several major U.S. MMHAs had been actively promoting PMT and denouncing its critics.[23] As a result, some organizations responded to international developments defensively rather than reflectively, viewing the shifts as a potential challenge to their institutional credibility.[24] The only notable exception to this pattern appears to be the American Society of Plastic Surgeons which, following the publication

[20] It should be noted, however, that with respect to developing reliable clinical practice guidelines the role of clinicians with intellectual conflicts of interest should be minimal: see Graham et al. (2011); McCartney et al. (2022).
[21] In 2016 psychologist Diane Ehrensaft, leading proponent of the "gender-affirming" approach, explicitly conceptualized her work as having “finally created a civil rights movement” (Ehrensaft, 2016, p. 355). Some medical guidelines in this field also call for specific political activism on the part of clinicians; e.g., the AAP policy statement (Rafferty et al., 2018). The editorial board of *The Washington Post*, recognizing the failure of pediatric gender specialists to self-regulate in the U.S., recently called for “new research of maximum possible rigor, overseen by scientists *who are not gender medicine practitioners*” (Washington Post Editorial Board, 2024, emphasis added).
[22] Levine & Abbruzzese (2023).
[23] Szilagyi (2022b).
[24] E.g. Endocrine Society (2024); Hoffman (2024).

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of the Cass Review, publicly adopted a more cautious stance regarding the use of surgical interventions for treating pediatric GD.[25]

Experts within pediatric gender medicine hold sharply divergent views about best practices.[26] However, the absence of professional consensus is often obscured, as dissenting voices are seldom included on specialty committees responsible for policy development. Researchers who study detransition, investigate social influences underlying epidemiologic changes in GD presentations, express concerns about PMT, or advocate for a more cautious approach to pediatric GD frequently encounter hostility and a lack of support from major publishers, medical societies, and academic institutions.[27] Organizations advocating for higher evidentiary standards, journalists reporting on the controversies, and academics writing about issues related to sex and gender have also faced hostility and attempts at public shaming.[28] Activist organizations have contributed significantly to this dynamic, often targeting individuals and groups that question or critically examine prevailing practices in gender medicine.[29]

When MMHAs update their treatment guidelines and position statements, experts who question the evidence supporting PMT are excluded from guideline development

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[25] American Society of Plastic Surgeons (2024).

[26] As the Cass Review found, "clinicians who have spent many years working in gender clinics have drawn very different conclusions from their clinical experience about the best way to support young people with gender-related distress. Some feel [they should] access a medical pathway at an early stage. Others feel that we are medicalising children and young people whose multiple other difficulties are manifesting through gender confusion and gender-related distress" (Cass, 2024a, p. 13). Examples of divergent clinical opinions can be found by comparing two papers on the role of mental health assessments: Levine (2024); Turban et al. (2025). Differing treatment approaches are also described in Levine et al. (2022a) and two follow-up articles: Drescher (2023); Levine et al. (2022b).

[27] For some examples, see Barnes (2023); Bazelon (2022a); Brown University (2019); Byrne & Gorin (2025); Edwards-Leeper & Anderson (2021); Gecsoyler (2024); Jenkins & Panozzo (2024); Keenan & Lovett (2025); LGBTQIA+ Coalition (2022); Pietzke (2024a, 2024b); Reed (2023a); Schenck (2022); Society for Evidence-Based Gender Medicine (2023d); Turley (2024).

[28] 100 signatories (2023); GLAAD (2023a, 2023b); Hansford (2024); Hooven (2023); Singal (2023a, 2023b); Weale (2025).

[29] In addition to the examples above, a recent article recounted therapists' experiences of attending a training workshop where the representative of the political activist group Southern Poverty Law Center (SPLC) spoke about efforts to "hunt" therapists who practice exploratory therapy, with the goal of leveling complaints leading to licensure revocations. Another therapist reported having been formally investigated by her graduate school for sharing information about new pediatric gender medicine evidence from Europe, an investigation which remains on her permanent record (Jenkins & Panozzo, 2024). SPLC also chose to wield the emotional power of the "hate group" label on several groups that have engaged in evidence-based evaluation of PMT or the development of alternative approaches.

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committees.[30] Efforts to exclude dissenting perspectives from conferences and publications have been documented.[31] In addition, there is growing evidence of self-censorship among clinicians and researchers, driven by concerns about professional repercussions and reputational risks.[32] Some proponents of PMT explicitly endorse the use of silencing tactics and reputational attacks:

> The point of activism is sometimes 'silencing,' if by that one means destroying the credibility of professionals that activists deem dangerous.[33]

Medical professionals' years of training and social status leave them acutely aware of and sensitive to reputational risks. Fear of online attacks and social disapproval within professional medical societies may have contributed to widespread self-censorship among clinicians, mirroring similar trends observed across academia.[34] This dynamic is further reinforced when PMT is framed as a civil rights issue or a struggle against discrimination and oppression. Under this framing, critics—even those raising evidence-based concerns—are labeled "anti-trans" or intolerant by reputable, influential sources.[35] As Hilary Cass observed in the introduction to the Cass Review,

> There are few other areas of healthcare where professionals are so afraid to openly discuss their views, where people are vilified on social media, and where name-calling echoes the worst bullying behaviour. This must stop. Polarisation and stifling of debate do nothing to help the young people caught in the middle of a stormy social discourse, and in the long run will also hamper the research that is essential to finding the best way of supporting them to thrive.[36]

The American healthcare system relies heavily on MMHAs to create, organize, and disseminate knowledge and to referee scholarly dialogue through journals and

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[30] Marci Bowers, president of WPATH when its 2022 guidelines were published, acknowledged that it was "absolutely" important for someone to be an "advocate" of the "gender-affirming" approach to be considered for the committee. See Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024). Furthermore, most members of the guideline development committee had conflicts of interest, which were poorly managed.
[31] Curlin (2024); Kaliebe & Johnson (2024); Kaltiala (2023); Mason (2021); Sapir (2025).
[32] Clark et al. (2024); Pfaus (2023).
[33] Nichols (2008).
[34] Clark et al. (2024); Curlin (2024); Pfaus (2023).
[35] E.g., Endocrine Society (2024); Szilagyi (2022b).
[36] Cass (2024, p. 13).

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conferences. Regardless of the underlying causes, major MMHAs have issued advocacy-driven recommendations prematurely, without adequate scientific support.[37] This contributed to a degradation of the norms of open inquiry and constructive disagreement—norms that are essential for the credibility of MMHAs and their capacity to issue trustworthy, evidence-based guidance.

12.3 Conclusion

The significant influence MMHAs exert over professional opinion, clinical practice, and healthcare policy extends broadly across the healthcare landscape. In the area of pediatric gender medicine, prominent MMHAs have aligned their clinical guidelines and policy statements with WPATH SOC-8. This reliance on WPATH guidelines effectively imported into MMHAs many of the methodological and ethical deficiencies documented in WPATH's guideline development process. Consequently, problems originating within WPATH have not remained isolated but have instead propagated through influential MMHAs, contributing to a broader erosion of clinical standards, scientific rigor, and open academic discourse.

Today, MMHAs wield considerable influence over both public and professional perceptions of medical practices through statements frequently cited in the media. These shape broader societal attitudes toward both the medical field generally and the practices within that field specifically. The implicit social contract underlying MMHAs' self-regulatory privileges rests on the expectation that these organizations will prioritize the best interests of patients and society. However, MMHAs' handling of issues related to PMT illustrates how institutional biases, reliance on external guidance from advocacy-oriented groups, and internal political dynamics can undermine their regulatory effectiveness and scientific credibility.

[37] See also Chapters 6-8.

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PART 4

ETHICS REVIEW

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Chapter 13 Ethical Considerations

This chapter discusses central ethical issues in pediatric medical transition (PMT), which involves the use of puberty blockers (PBs), cross-sex hormones (CSH), and surgery to suppress or alter the development of sex- and age-typical sex characteristics in physically healthy children or adolescents.[1] These interventions are used as treatment for the conditions of "Gender dysphoria" (GD) in the *Diagnostic and Statistical Manual* (DSM-5-TR) or "Gender incongruence of adolescence or adulthood" in the *International Classification of Diseases* (ICD-11).[2] In assessing the effects of PBs, CSH, and surgery, researchers typically focus on conventional psychiatric outcomes such as depression, anxiety, and suicidality; recently, some have added novel outcome measures such as "chest dysphoria," "appearance congruence," and "gender euphoria."[3]

However, some clinician-researchers have called into question what they call the "logic of improvement," according to which PMT is justified only if it enables "a progression from 'doing worse' to 'doing better,' ultimately leading to an overall improvement in the individual's functioning and well-being."[4] Acknowledging that the evidence that PMT has this effect is weak, these clinicians argue that conventional outcome measures should be supplemented with—if not replaced by—patient-determined outcomes.[5] In the same vein, other advocates of PMT claim that focusing on clinical improvement is "pathologizing" and question the need for any clinical indication beyond the adolescent's "embodiment goals"[6] or mere desire for the intervention.[7] The guiding question of this chapter is whether the provision of hormonal or surgical interventions for these shifting and sometimes contradictory purposes is consistent with well-established principles of

[1] Patients may reach Tanner Stage 2 of puberty by age 8 or 9. An 8- or 9-year-old person is uncontroversially a child. However, for the sake of brevity the remainder of this chapter will use "adolescents" rather than "children and adolescents" in most cases to refer to this patient population.
[2] American Psychiatric Association (2022); World Health Organization (2022b).
[3] See, respectively, Olson-Kennedy, Warus et al. (2018); Chen et al. (2023); Blacklock et al. (2025).
[4] Oosthoek et al. (2024, p. 10).
[5] Oosthoek et al. (2024, p. 17).
[6] Ashley (2019, pp. 480-482).
[7] Chu (2024).

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medical ethics. Despite the high stakes—medical, social, political, and legal—this urgent question has received relatively little critical attention from bioethicists.

After a brief note on consent (Section 13.1), Section 13.2 summarizes how the medical profession's shift away from medical paternalism toward shared decision-making has strengthened patient protections against unwanted medical interventions via the mechanism of informed consent. This move toward greater respect for patient autonomy, however, does not negate clinicians' professional and ethical obligation to protect and promote their patients' health.

Section 13.2.3 turns to the pediatric context, where the latter obligation is especially strict due to the distinctive vulnerability of children and adolescents as well as their underdeveloped decision-making capacity. The best available evidence indicates an unfavorable risk/benefit profile for the prescription of hormonal and surgical interventions for adolescents with GD. The prescription of these interventions also raises justice-related concerns for members of this medically and socially vulnerable population.

Section 13.3 examines an alternative justification for PMT, one grounded in a purported right to access the medical resources needed to satisfy the patient's preferences for body modification. The shift to this alternative justification, which follows researchers' decades-long inability to demonstrate clear medical benefit, suggests that advocates of PMT have significantly altered the criteria for success.[8] The chapter then turns to a brief discussion of patient regret in Section 13.4 before concluding with some remarks on research ethics in Section 13.5.

13.1 Consent

Some disagreements in this field center on the question of whether adolescents have medical decision-making competence (MDC)—that is, whether they can provide

[8] "Clinicians remarked that there is no agreed fixed point of reference on which to judge the success of an intervention, let alone a societal consensus on the appropriate response" (Cass, 2024a, Appendix 3, p. 9).

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informed consent or assent to transition-related medical interventions.[9] Some proponents of these interventions believe they can.[10] In support of this position, some point to research showing that many adolescent patients have MDC as assessed using a quantitative semi-structured interview tool.[11] They also note that there are other invasive, life-shaping interventions to which adolescents and their guardians commonly and unproblematically assent or consent. For example, an adolescent may assent to treatment of leukemia, even when the treatment may cause future infertility. An adolescent also may assent to amputation of a limb that is diseased or damaged beyond repair. There are many similar situations in which assent by the adolescent, and legal consent by the parents, is given to an intervention necessary to preserve the adolescent's overall health but which also causes foreseen serious adverse side effects.

Some critics of PMT, on the other hand, maintain that patients—some of whom are only 8 or 9 years old when they reach Tanner Stage 2 of puberty and thereby become candidates for PBs[12]—are too immature[13] to adequately understand the full range of consequences of medical transition. These young people cannot deliberate about the relevant considerations in a manner that is appropriately attentive to the seriousness and complexity of the decision. Critics point out that even proponents of PMT recognize that children and adolescents lack the cognitive and social maturity to deliberate well about their future fertility.[14]

Moreover, critics assert—reasonably[15]—that providers of PMT often fail properly to inform patients and their guardians about the uncertainty of the clinical evidence for medical benefit and that they overstate the probability and magnitude of the harms of

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[9] "Consent" and "assent" here are technical terms. In the U.S. minors cannot provide *legal consent* for medical treatment (there are limited exceptions, e.g. for emancipated minors or for a narrow range of interventions such as treatment for sexually transmitted infections). Guardians provide legal consent while minors provide *assent*, or agreement to the intervention.
[10] Giordano et al. (2021); Mosier-Mills et al. (2024).
[11] Vrouenraets et al. (2021); See also Marino et al. (2024).
[12] See Chapter 7.
[13] Diekema (2020).
[14] Vrouenraets et al. (2022).
[15] See Chapter 11.

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non-medicalization.[16] Finally, as noted in Chapter 2, clinicians providing PMT routinely employ euphemistic and morally loaded language, which can mislead or unduly influence patients and their guardians. The concern, then, is that this combination of high pressure, low information, and reflexive "affirmation" undermines the possibility of genuinely informed consent or assent.

Informed consent is critically important, but before it is even a consideration, the intervention must be otherwise ethically permissible. For example, before asking whether patients can consent to any proposed intervention, from antibiotics to lobotomy, a clinician must determine whether the intervention has a favorable risk/benefit profile as a treatment for the patient's condition. Thus, while informed consent plays a central role in medical ethics and clinical practice and informs discussions about the distinctive challenges that attend decision-making in pediatrics, this Review's ethical analysis of PMT focuses primarily on the necessarily prior step. Namely: do these interventions have favorable risk/benefit profiles?

13.2 From paternalism to shared decision-making and patient-centered care

Over the course of the 20th century, advances in the biomedical sciences, expansion of healthcare delivery systems, increasing professionalization in medicine, and a series of medical scandals and seminal legal cases led to greater sensitivity among clinicians and researchers to the rights of patients and participants in medical research. Judges, regulators, lawmakers, and ethicists introduced constraints on the power of clinicians to impose their values, preferences, and perspectives on patients.[17] The "paternalistic model" in medicine, according to which "doctor knows best," gave way to a more egalitarian model of "shared decision-making" that emphasizes respect for the autonomy and authority of competent patients and research participants. There is now universal consensus that respect for patient autonomy requires clinicians to provide patients with information relevant to their medical options and to act on competent

[16] Reluctant parents have reported being asked by their child's clinicians whether they (the parents) preferred having "a dead son or a living daughter." In an interview, Dr. Johanna Olson-Kennedy stated, "We often ask parents, Would you rather have a dead son than a live daughter?" (ABC News, 2011).
[17] Faden et al. (1986).

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patients only with patients' consent. As the American Medical Association's *Code of Medical Ethics* puts it, patients have the right "[t]o make decisions about the care the physician recommends and to have those decisions respected. A patient who has decision-making capacity may accept or refuse any recommended medical intervention."[18] Patients are protected from unwanted medical interventions not only by professional and ethical norms but by the law. As Justice Cardozo famously wrote, "a surgeon who performs an operation without his patient's consent, commits an assault, for which he is liable in damages."[19]

13.2.1 Respect for autonomy vs *caveat emptor*

Crucially, the shift from medical paternalism to shared decision-making does not absolve clinicians of their ethical and professional obligation to protect and promote the health and well-being of their patients. Beneficence "undergirds all medical and health care professions and their institutional settings."[20] As mentioned in Chapter 1, clinicians have ancient but enduring ethical duties to avoid harming their patients and to promote their health and welfare: "The health and well-being of my patient will be my first consideration."[21]

The principle of respect for patient autonomy does not justify subjecting patients to interventions that pose medically unnecessary risks of harm, or which are otherwise nonbeneficial, even when patients prefer, request, or demand those interventions. An ethical analysis of PMT published by Finnish health authorities provides a succinct explanation:

> In healthcare, self-determination primarily manifests as the right to refuse treatments within the available service spectrum. This principle must be balanced against the freedom of individuals to express their own gender identity. Nevertheless, autonomy in healthcare does not imply unrestricted freedom to select treatments based purely on personal preference; rather, patient autonomy

[18] American Medical Association (2016).
[19] Schloendorff v. Society of New York Hospital (1914).
[20] Beauchamp & Childress (2019, p. 217)
[21] Parsa-Parsi (2017, p. 1971).

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> involves the choice among treatments *that are medically justified* and included within the recognized service options.[22]

The well-established moral and legal right of competent patients to refuse any medical intervention does not entail a corollary right to receive nonbeneficial interventions. The Institute of Medicine's Committee on Quality of Health Care in America warns clinicians against providing interventions based on this illicit inference, stating, "When a patient seeks inappropriate health care services, the challenge for clinicians is to find ways of reducing this conflict … If a conflict cannot be resolved through counseling, the clinician should refuse to provide nonbeneficial services."[23]

In refusing requests for nonbeneficial interventions, clinicians do not force anything upon their patients. They do not threaten, deceive, or mislead them. Nor do they withhold relevant information about risks, benefits, and available alternatives. In other words, withholding nonbeneficial interventions does not entail acting on patients without their informed consent. Conflating the right of patients to refuse medical intervention or to choose among the beneficial options offered by their clinicians with the wholly separate "right" to determine which interventions must be offered transforms the ethos of beneficent respect in medicine to the crude, responsibility-abdicating ethos of medical consumerism: *caveat emptor.*

> Using patient autonomy to justify acquiescence to patients' requests for nonbeneficial services violates professional integrity. Professional integrity requires physicians to adhere to standards of intellectual and moral excellence. Physicians achieve intellectual excellence by submitting clinical judgment to disciplined, evidence-based reasoning. Physicians achieve moral excellence by protecting patients' health-related interests as a primary concern, keeping self-

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[22] Saarni & Uusitalo (2020, p. 41, emphasis added). Original text: "Itsemääräämisoikeus terveydenhuollossa toteutuu ensisijaisesti oikeutena kieltäytyä palveluvalikoimaan kuuluvista hoitotoimista. Tämä on tasapainotettava sen näkökulman kanssa, että ihmiset saavat itse vapaasti ilmaista omaa sukupuolista identiteettiään. Autonomialla ei terveydenhuollossa kuitenkaan tarkoiteta vapaata oikeutta valita hoitoja omien preferenssien perusteella, vaan potilas voi valita palveluvalikoiman ja lääketieteellisesti perusteltujen hoitomuotojen sisällä."

[23] Committee on Quality of Health Care in America, Institute of Medicine (2001, p. 77). See also the "Physicians Charter" mentioned in Section 1.3.

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> interests systematically secondary. Commitment to professional integrity requires that physicians challenge requests for nonbeneficial interventions.[24]

13.2.2 Nonmaleficence, beneficence, and autonomy in pediatrics

Uncontroversially, then, the norms of medicine require clinicians to protect and promote the health and well-being of their patients. This means they must abstain from providing nonbeneficial interventions even when such interventions are requested by competent patients. In the domain of pediatrics, these norms limit the authority not only of patients (who in any case lack full decision-making capacity) but of parents as well. The American Academy of Pediatrics' (AAP) Committee on Bioethics puts it as follows:

> Pediatric health care providers have legal and ethical duties to provide a standard of care that meets the pediatric patient's needs and not necessarily what the parents desire or request. Parental decision-making should primarily be understood as parents' responsibility to support the interests of their child and to preserve family relationships, rather than being focused on their rights to express their own autonomous choices. It is important to note that parental authority regarding medical decision-making for their minor child or young adult who lacks the capacity for medical decision-making is constrained compared with the more robust autonomy in medical decision-making enjoyed by competent adults making decisions regarding their own care.[25]

The "constraint" on patient and parental authority is grounded in the medical best interests of the child:

> In pediatrics, the duties to protect and promote health-related interests of the child and adolescent by the physician are also grounded in the fiduciary relationship (to act in the best interest of the patient and subordinating one's own interests) between the physician and patient, but these duties may conflict with the parent's or patient's wishes …[26]

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[24] Brett & McCullough (2012, p. 149).
[25] Committee on Bioethics et al. (2016, p. e5). First published in 2016, this report was reaffirmed by the AAP in 2023.
[26] Committee on Bioethics et al. (2016, p. e2).

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In its influential policy statement, "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents," the AAP states that in navigating disagreements between parents and children clinicians should "maintain their primary responsibility to the welfare of the child."[27] Thus, while the statement recommends that "transgender and gender-diverse" youth have access to PMT, this recommendation is contingent not on the autonomy rights of patients or their guardians,[28] but rather on these interventions' purported contribution to patient health and well-being. [29] This affirms the longstanding, consensus view of medicine's fundamental aim as protecting and promoting the health and well-being of patients.

13.2.3 Risk/benefit in pediatric medical transition

To discharge their duties of nonmaleficence and beneficence, clinicians must ensure, insofar as reasonably possible, that any interventions they offer to patients have clinically favorable risk/benefit profiles relative to the set of available alternatives, which includes doing nothing.[30] As described in Chapter 5, systematic reviews (SRs) of the

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[27] Rafferty et al. (2018, p. 8).
[28] Bester (2024).
[29] It is worth noting, however, that while the AAP and WPATH support PMT, they do not promote intervening over a patient's objections. Neither group holds that a patient with gender dysphoria/incongruence who refuses puberty blockers, cross-sex hormones, or surgery should be strongly encouraged or, if necessary, forced to receive them. This distinguishes medical transition from other interventions claimed to offer great, potentially lifesaving benefit. In gender medicine and perhaps nowhere else, whether transition-related medical interventions are deemed medically necessary seems to hinge largely on whether the patient desires them. See Chapter 11 for more on this issue.
[30] An intervention has a clinically favorable risk/benefit profile when the expected medical benefits outweigh the expected medical harms. Expected benefits and harms are determined by their probabilities and magnitudes. This is a standard method for guiding action and policy, including in medicine, though the precise manner in which it is carried out can vary and depends on many variables, including risk tolerance, the way "benefit" and "harm" are defined and measured, the way probabilities are assigned, and the way uncertainty/ignorance is accounted for. Of course, it would not be difficult to adopt expected utility theory, defining "benefit" and "harm" and assigning values to the relevant variables, in a way that would render a verdict markedly different from the negative one reached in this Review. That said, the claims made here about the probability and magnitude of harms and benefits are grounded in the best available evidence. Sometimes, the probabilities are known with a high degree of certainty. For example, the probability that mastectomy will lead to an inability to breastfeed is 1.0 or close to it. Puberty blockers and cross-sex hormones threaten sexual function, though the precise magnitude of the problem and its distribution in the treated patient population is unknown. Where precise or even rough values are not available due to the absence of quality research, the analysis in this Review assumes plausible, if rough, estimates. As for the nature of medical benefits and harms and their relative weights, the Review's working assumptions cohere with common moral intuition, standard medical judgment as revealed in medical diagnostic criteria, and the outcomes of interest to clinicians and researchers, as well as the law. For example, the analysis would conclude that a minor improvement in depressive symptoms does count

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evidence for benefit of hormonal or surgical intervention in the treatment of GD in adolescents have concluded that this evidence is of low or very low certainty. This means that the true effects of the interventions may or are likely to be substantially different from the effects reported in the studies.[31] In other words, the best available evidence indicates that PBs, CSH, and surgery have not been shown to improve mental health outcomes.

At the same time, there is increasing recognition of the risks and harms associated with PMT, which are supported by clinical research or grounded in established biological theory.[32] While the value or disvalue of some outcomes, such as hirsutism in females, may be determined primarily by the preferences or tastes of patients, other possible outcomes, such as impaired cognitive function, greater susceptibility to hormone-sensitive cancers, cardiac disease, reduced bone density, sexual dysfunction, infection, and infertility[33] are objectively detrimental to health. Such medical harms, or plausible

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as a benefit but that such a benefit, even if assured, does not outweigh moderate or even low but non-negligible risks of infertility or serious sexual dysfunction, loss of breastfeeding function, or lifelong medical dependency, which the Review considers harms.

[31] Balshem et al. (2011).

[32] See Chapter 5 and Chapter 7.

[33] It may be objected that infertility is not necessarily a harm. One version of this objection is that for some young patients, perhaps those who have very clearly expressed that they do not want and will never want genetically-related children, infertility is not a harm since it is consistent with their chosen life plan. The response to this objection is that the medical profession does not ordinarily permit voluntary permanent contraception (sterilization) in children or adolescents and always takes the risk of infertility seriously in assessing the risk/benefit profile of any intervention that plausibly may impact reproductive health. That is to say that as a matter of well-established sociological fact, infertility is recognized by the medical profession as a harm (Geis et al., 2024). The second version of the objection relies on the claim that some patients are willing to accept infertility as a consequence of medical transition, even if they do not intend infertility. These patients prefer to remain fertile, all else being equal, but because all else is not equal they accept interventions that will undermine their fertility. The response to this objection is that such preferences reveal that these patients view infertility as a harm. The real question in the latter case is whether there is good reason to believe that the benefits of medical intervention outweigh this harm, and the answer to this question will depend on the evidence regarding benefits. Finally, research suggests that many transgender-identified people do want children and that some who medically transition experience decisional regret over their infertility. This suggests they also view infertility as a harm even if they do not regret their transition. See Asseler et al. (2024); Stolk et al. (2023).

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risks thereof,[34] should not be imposed on children or adolescents in the absence of a reasonable expectation of proportionate medical benefit.[35]

Although a favorable risk/benefit profile is necessary to justify an intervention, it is not sufficient.[36] The intervention must be favorable relative not only to doing nothing but also to other known alternatives. With respect to PMT, a relevant alternative is some combination of psychotherapeutic interventions.[37] Like the evidence for hormonal and surgical interventions, evidence regarding alternative approaches to GD is sparse and inconclusive,[38] though as Chapter 14 reveals there is good reason to believe that psychotherapy can be an effective intervention. Regarding the potential harms of psychotherapy for adolescents with GD, a systematic review of the evidence found no evidence of negative or adverse effects in any of the studies examined.[39]

One possible objection is that although the evidence supporting hormonal and surgical interventions is of low or very low certainty, this does not prove that the interventions are ineffective. For all we know, the interventions may be *more* effective than researchers have reported. The methodological weaknesses of the studies do not prove inefficacy—they tell us only that we cannot infer much of anything about beneficial effects. The same limitations apply to evidence on harms—after all, because there are no well-designed randomized controlled trials (RCTs) of PMT, it follows that there are no well-designed RCTs demonstrating sexual dysfunction, infertility, bone density loss, impaired cognitive function, susceptibility to hormone-sensitive cancers, and other potential harms. Some argue that in the face of uncertain evidence both for benefit and for harm, patients themselves (and their families), with expert clinicians providing relevant clinical

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[34] Sweden's National Board of Health and Welfare concluded that "the risks of puberty blockers and gender-affirming treatment are likely to outweigh the expected benefits of these treatments" (Socialstyrelsen, 2022a, p. 3).
[35] The "should not" here is a moral "should not." It does not entail any conclusions about what the law should permit or require. The relationship between ethics and the law is complex and is not taken up in this Review.
[36] If considerations not directly related to health are included in the risk/benefit analysis, there may be cases where an intervention that is marginally less effective in promoting health may be recommended (e.g. when the marginally more effective treatment is much more expensive). And of course, to say that the clinicians should offer the more favorable intervention is not to say that patients do not have the right (in most cases) to refuse it.
[37] See Chapter 14.
[38] Cass (2024a, pp. 153-154).
[39] Heathcote et al. (2024, pp. s19-s32, Suppl. 2).

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information, should decide how to proceed.[40] Medical decisions under uncertainty, the reasoning goes, should be made by those with the greatest personal stake in the outcome. In pediatrics, this means children and adolescents, supported (usually) by their families.

This objection properly expresses concern for patient health and well-being as well as respect for the developing decision-making capacity of children and adolescents (and the greater capacity of their guardians). But it fails, for two reasons.

First, the objection understates the cumulative case for evidence of harm. We can be certain in the ordinary sense of "certain" that these interventions cause harm, even if we do not have "high certainty" evidence in the technical sense employed in evidence-based medicine (EBM).[41] We do not need results from RCTs to be certain that removing an adolescent's breasts will eliminate or substantially impair capacity for breastfeeding. Nor do we need RCTs to establish that PBs and CSH stunt growth of the penis, increasing the risks associated with future surgery.[42] And apart from any systematic reviews of published studies, basic human physiology indicates that blocking puberty at Tanner Stage 2 and following with CSH will negatively impact fertility. That advocates of PMT recommend fertility counselling before undergoing these interventions is evidence that they, too, anticipate the risk of infertility and regard it as a harm. Other forms of evidence, such as indirect evidence from research on adults, also contribute to the case that these interventions cause harm.[43] Finally, research on PMT has focused largely on potential benefits to mental health, with less attention given to potential physical harms, compounding the problem of publication bias.[44]

Second, even granting that the uncertainty of the evidence makes it impossible to assign precise values to the probabilities or magnitudes of various potential outcomes, it does not follow that clinicians are dependent on their patients to guide clinical decision-

[40] Antommaria (2024).
[41] Smith & Pell (2003)
[42] Terhune et al. (2022).
[43] See Chapter 7.
[44] See Chapter 6 for discussion of publication bias.

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making.[45] Rather, the obligation to avoid serious harm justifies a precautionary approach, particularly in the absence of evidence for a proportionately serious threat to the patient's health without the intervention. In their seminal textbook on medical ethics, Beauchamp and Childress write:

> Depending on what is valued and what is at risk, it may be ethically justifiable and even obligatory to take steps, in the absence of conclusive scientific evidence, to avoid a hazard where the harm would be both serious and irreversible—that is, a catastrophe. Triggering conditions for these measures include plausible evidence of potential major harm where it is not possible to adequately characterize and quantify risk because of scientific uncertainty and ignorance. The process of developing precautionary norms should not be viewed as an alternative to risk analysis and scientific research. It should instead be viewed as a way to supplement risk appraisals when the available scientific evidence does not permit firm characterizations of the probability or magnitude of plausible risks.[46]

It seems clear that the triggering conditions for adopting a precautionary approach to the use of hormonal and surgical interventions for the treatment of pediatric GD have been met. When precautionary considerations are added to the cumulative case for harm, the ethical argument against PMT becomes compelling.

> The importance of avoiding harm is emphasized by the fact that many treatments (e.g., surgery, hormone therapy) can lead to relatively common and potentially serious long-term adverse effects. This necessitates particularly strong justification (i.e., clear evidence of benefits and the decision-maker's competence) before administering such treatments or accepting these risks. In practice, physically modifying healthy bodies is generally associated with potential harms or risks. Empirical evidence concerning the long-term benefit-to-harm ratio of these interventions is often limited. In other words, avoiding harm

[45] One would hope this would come as a relief to clinicians and especially to pediatricians, though some seem happy to let children lead the way. See Chapter 11.
[46] Beauchamp & Childress (2019, p. 250)

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> prompts considerations similar to those raised by competence: when evidence of benefit is uncertain, but risks are probable, the ethical imperative to minimize harm is further underscored.[47]

The unfavorable risk/benefit profile distinguishes PMT from many other off-label uses of drugs and medical devices. Advocates for PMT point to the prevalence of off-label prescribing in pediatrics,[48] but the legitimacy of some off-label uses does not license the prescription of any pharmaceutical to any patient for any reason. The favorable risk/benefit threshold, or, more minimally, the precautionary threshold, must be met irrespective of whether the intervention is approved by FDA. Off-label use of an intervention is sometimes justifiable based on studies of the intervention in a different patient population or for a different indication. Such use may be warranted when there is a reasonable expectation of benefit, when there are no superior alternatives, and when the prognosis, absent medical intervention, is predicted to be worse for the patient than the negative effects of the off-label drug.

This is decidedly not the situation with PMT. The natural history of pediatric GD is poorly understood[49] and decades of research has shown that early-onset GD usually resolves without medical intervention.[50] There is no compelling evidence that the same will not prove true in the case of adolescent-onset symptoms, and limited evidence suggesting it will.[51] And in any case, it is widely acknowledged that clinicians are unable to distinguish patients whose GD will persist from those whose GD will resolve.[52] Further,

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[47] Saarni & Uusitalo (2020, p. 41); our translation. Original text: “Haittojen välttämisen tärkeyttä korostaa se, että monista hoidoista voi seurata varsin yleisiä ja vakaviakin pitkän tähtäimen haittoja (esim. kirurgia, hormonihoidot), jolloin hoitojen antamiselle (eli näiden riskien ottamiselle) pitää olla erityisen hyvät perusteet (eli näyttö hyödyistä sekä päätöksentekijän kompetenssista). Käytännössä terveiden kehojen fyysiseen muokkaukseen voidaan katsoa useimmissa tapauksissa liittyvän haittoja tai riskejä. Empiirinen näyttö hoitojen pitkän tähtäimen hyöty/haitta-suhteesta on useissa tapauksissa vähäistä. Toisin sanoen haitan välttäminen johtaa siis samankaltaiseen pohdintaan kuin kompetenssikysymys: jos näyttö hyödyistä on epävarmaa mutta haitat todennäköisiä, haittojen minimoinnin tärkeys eettisenä periaatteena korostuu.”

[48] Meng et al. (2022).

[49] See Chapter 4.

[50] Ristori & Steensma (2016); Singh et al. (2021).

[51] Bachmann et al. (2024); Byrne (2024a); Rawee et al. (2024); Sun et al. (2023)

[52] “Although a diagnosis of gender dysphoria has been seen as necessary for initiating medical treatment, it is not reliably predictive of whether that young person will have longstanding gender incongruence in the future, or whether medical intervention will be the best option for them.” (Cass, 2024a, p. 29). The

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there are concerns about the role medicalization itself may play in contributing to the persistence of the conditions being treated,[53] and less invasive and less risky interventions are available.[54] Lastly, medical intervention has known and plausible harms,[55] and decades of research conducted by leading academic institutions have failed to produce reliable evidence of medical benefit.[56]

13.2.4 Justice

According to the Belmont Report, published in 1978 in the wake of the U.S. Public Health Service's Untreated Syphilis Study at Tuskegee, "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly."[57] While the Belmont report set out ethical principles to guide human subjects research, the principle of justice applies also to clinical medicine. Advocates for PMT sometimes claim it is unjust to withhold PBs, CSH, or surgeries from youth with GD.[58] They cite research finding that this patient population has significant healthcare needs and also suffers from social marginalization and stigma.[59] These patients indeed are vulnerable along multiple axes, and it would be an injustice to deny them safe and effective medical care. It would also be unjust, however, to subject them to serious hormonal and surgical interventions that lack a favorable risk/benefit profile. In fact, it seems particularly unjust to subject youth struggling with complex psychiatric, neurodevelopmental, and psychosocial challenges to the harms associated with these interventions. The justice principle has been rightly invoked but wrongly applied.

In both her Interim and Final Reports, Cass notes concerns brought to her by patients and families about "diagnostic overshadowing."[60] Diagnostic overshadowing is a form of

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recent German clinical guidelines note that its own review found no studies that could supply empirical criteria to determine whether GD or gender incongruence would persist into or beyond adolescence (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP), 2025, p. 188).

[53] Jorgensen (2023a).
[54] See Chapter 14.
[55] See Chapter 7.
[56] See Chapter 5.
[57] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (2010).
[58] Kimberly et al. (2018); Maung (2024).
[59] Hatzenbuehler & Pachankis (2016); Rider et al. (2018).
[60] Cass (2022a, p. 46; 2024b, p. 200).

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bias that leads clinicians to misattribute symptoms of one condition to a different previously diagnosed condition. This can happen, for example, when clinicians mistakenly attribute patients' complaints of physical discomfort to the patient's previously diagnosed psychiatric condition, a mistake that may lead to misdiagnosis and inadequate treatment.[61] Diagnostic overshadowing is especially salient in mental health care contexts, where a patient with psychiatric problems, neurodevelopmental challenges, or cognitive disabilities may be treated one-dimensionally as a "case" of some psychiatric diagnosis rather than holistically as a person susceptible to a range of health problems unrelated to that diagnosis.

In the context of PMT, the concern is that the diagnosis of GD tends to obscure causes of distress and crowd out other mental health care needs, particularly when patients are referred to specialty gender clinics. The gender clinic model of care becomes Maslow's hammer to which every problem appears as a nail. The risk of diagnostic overshadowing increases insofar as (1) clinicians fail to provide comprehensive psychiatric evaluations;[62] (2) clinicians face pressure from colleagues, patients, and parents to "affirm" patients prematurely, that is, prior to providing them sufficient time to develop and mature;[63] and (3) co-occurring mental health challenges or problem behaviors are reflexively assumed to be minority stress-mediated sequelae of the patient's GD diagnosis.[64] To neglect the mental health care needs of members of an already vulnerable population of youth with complex psychiatric, neurodevelopmental, and psychosocial challenges is to deny them a benefit to which they are entitled, and to expose them to medically unnecessary risk of harm is to impose a burden unduly.

There are additional problems related to justice. Compared to their age-matched peers, same-sex attracted youth are significantly overrepresented among patients presenting to gender clinics.[65] As noted in Chapter 3, this phenomenon has been observed from the beginning. Of the 70 patients recruited by de Vries and colleagues in the

[61] Hallyburton (2022); Jones et al. (2008); Reiss et al. (1982).
[62] Damiano (2024a).
[63] Edwards-Leeper & Anderson (2021).
[64] Papers claiming minority stress explains various health problems of transgender-identified adolescents include Delozier et al. (2020); Dolotina & Turban (2022); Hunter et al. (2021).
[65] Drescher & Yarbrough (2024); Singh et al. (2021); Wood et al. (2013).

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Netherlands from 2000 to 2008, 62 reported being exclusively same-sex attracted, six reported being bisexual, and one reported being exclusively opposite-sex attracted.[66] That is, the original Dutch Protocol patient cohort was comprised almost entirely of gay, lesbian, and bisexual patients[67]—one of whom died as a result of surgical complications from vaginoplasty following pubertal blockade and cross-sex hormones.[68] Reports of negative attitudes towards homosexuality, which may be internalized, are not uncommon in this field.[69] One of the earliest clinical reports on adolescent transition describes a family concerned that their son's gender nonconformity was a sign of homosexuality.

> It is of interest to note that [the patient's family] were all reassured to discover that George was not a *homosexual*. The diagnosis of 'transexual' provided an explanation for his feminine behavior and was, especially for the parents, psychologically relieving.[70]

Given the medical profession's history of pathologizing and medicalizing same-sex attraction,[71] serious justice-related concerns are raised by the overrepresentation of gay, lesbian, and bisexual adolescents among patients receiving unproven interventions that adversely impact fertility and sexual function.

13.3 Alternative clinical rationales

Clinical research on pediatric medical transition has focused primarily on its effects on psychiatric morbidity and to a lesser extent on psychosocial function. The original Dutch

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[66] de Vries et al. (2011, Table 1). The remaining one patient reported "don't know yet."
[67] Biggs (2023b).
[68] Biggs (2023b); de Vries et al. (2014); Negenborn et al. (2017) Bachmann et al. (2024); Sun et al. (2023).
[69] Barnes (2023); Sansfaçon et al. (2023); Littman (2021).
[70] Newman (1970). Given clinician reports of his self-reported sexual behavior and desires, it is almost certain that George was gay.
[71] Hodge (1950); Murphy (1992); Shidlo et al. (2001). From Hodge: "Male aged 37 years, who came voluntarily, being concerned by his definite homosexual bias which, though it had not since puberty found overt expression, was nevertheless a source of great worry and unhappiness … He appeared after close investigation to be a homosexual deviant of very long standing—an 'innate' pattern rather than one of traumatic 'level fixation'—and he failed to respond to psychotherapy. Treatment by oestrone has been followed by loss of sexual libido and he reports considerable 'mental relief.'" (p. 135) See also Chapter 3 for the influential case of George/Christine Jorgensen and the subsequent wave of lesbian and gay people who sought medical transition.

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Protocol required patients to have "Gender Identity Disorder" (GID), as GD was then called. The diagnostic criteria for GID and its DSM-5 successor GD include clinically significant distress and/or functional impairment.[72] While the diagnostic criteria for GD closely mirror the previous criteria for GID, the DSM-5 more explicitly emphasizes that cross-sex identity, by itself, does not constitute a pathology. The attendant distress, if present, is what is pathological. As such, medical interventions target the patient's distress or impairment, not the underlying identification.

That patients must have a mental health disorder to access medical resources has long troubled some patients and advocacy groups.[73,74] Some clinical protocols require patients to undergo assessment to determine if they meet (*inter alia*) the distress or impairment criterion—it is not enough that a patient attests to cross-sex identification or incongruence. These criteria thereby create an impediment[75] for people who do not suffer distress or impairment but who nevertheless wish to medically alter their bodies. To access the interventions they want, these patients may need to exaggerate or feign symptoms or else shop for clinicians willing to rubber stamp a diagnosis.[76]

One possible solution to this challenge is simply to eliminate any requirement for a medical diagnosis. Doing this would remove the obstacle of assessment from the path of patients seeking medical interventions. The problem with this solution for the DSM and the ICD working groups was that removing the diagnoses altogether would make reimbursement for medical intervention difficult or impossible. The tension between

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[72] Because GID and GD are DSM diagnoses and the DSM is a manual of mental disorders, this is not surprising. However, it does constrain the options available to clinician-researchers insofar as reimbursement requires a DSM diagnosis, i.e. the categorization of the patient as suffering from a mental disorder.

[73] Drescher (2017).

[74] Objections to medical "gatekeeping" and tensions between patients and clinicians regarding the pathologization of cross-sex identification predate the Dutch Protocol and the medicalization of pediatric gender distress by decades. Adults, wishing for hormones and surgeries to satisfy their longing to modify their bodies and to be perceived as members of the other sex, have butted heads with psychiatrists, psychologists, endocrinologists, and surgeons since the early 20th century when the first "sex change" procedures took place. Disciplinary turf wars between experts, with each field vying for authority over diagnosis and treatment, contributed to the ongoing professional uncertainty over the fundamental aims of medical intervention and the appropriate balance of power between patients and clinicians. See Meyerowitz (2009); Shuster (2021).

[75] Jacobsen (2024).

[76] For accounts of patients feigning symptoms and manufacturing histories in order to convince clinicians of their medical need, see Ashley (2019); Pimenoff & Pfäfflin (2011); Shuster (2021).

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ensuring reimbursement and thereby access, on the one hand, and satisfying the demands of patients and activist groups for depathologization, on the other, required compromises on the part of DSM and ICD developers.[77] The DSM developers depathologized incongruence and pathologized distress. The ICD-11 developers had more options because unlike the DSM, which is devoted exclusively to mental disorders, the ICD catalogues all diseases and health conditions. Having considered the various possibilities,[78] the ICD-11 working group decided to move the diagnosis out of the mental health chapter, where it was believed to contribute to stigma, and into a new chapter, "Conditions Related to Sexual Health," where it would be less stigmatizing but still useful for purposes of reimbursement.

Consequently, present DSM and ICD diagnoses comprise different frameworks shaped by historical contingencies—including, crucially, payment considerations.[79] According to the DSM-5, experiencing gender incongruence itself is not pathological, while associated distress or impairment are, rendering GD a mental disorder. Meanwhile, according to the ICD-11, gender incongruence (that is, being transgender according to contemporary understandings of what it is to be transgender) itself is pathological, but not a mental health disorder. ICD-11's diagnosis, Gender Incongruence of Adolescence or Adulthood, includes no requirement of distress or impairment for medicalization. Thus, DSM-5 and ICD-11 differ on whether hormonal and surgical interventions are treatments for a mental health problem or rather some other kind of pathology, on whether transgender identity itself is pathological, and on whether a patient must be distressed or impaired to receive reimbursable medical intervention. Despite these differences and inconsistencies, both diagnoses are employed to justify and reimburse the provision of hormonal and surgical interventions to adolescents.

The more permissive approach to medicalization is defended by some clinicians,[80] bioethicists, and activists.[81] For example, bioethicist Florence Ashley argues that the

[77] Drescher (2015).
[78] Drescher et al. (2012).
[79] See Drescher (2015); Drescher & Yarbrough (2024).
[80] See Chapter 11.
[81] Chu (2024).

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provision of hormonal and surgical interventions to adolescents is justified by the interventions' capacity to satisfy patients' "gender embodiment goals":

> Adolescent medical transition aims at preventing or altering the development of sexual characteristics to achieve the individual's gender embodiment goals. Given its purpose, the effectiveness of adolescent medical transition is defined by its ability to achieve the sought physiological outcomes—a standard undisputedly met.[82]

While the Dutch Protocol was designed to alleviate adolescents' psychiatric distress and improve psychosocial functioning, Ashley's approach drops the requirement of clinical improvement—achieving the patient's embodiment goals is enough.[83] Elsewhere, Ashley explains that some people seek hormonal or surgical interventions not because they are suffering from a pathology but rather because these treatments can deliver certain desired experiences such as "gender euphoria" and "creative transfiguration." Gender euphoria is a "distinct enjoyment or satisfaction caused by the correspondence between the person's gender identity and gendered features associated with a gender other than the one assigned at birth."[84,85] Creative transfiguration, Ashley writes, "is more difficult to capture in words. Foregrounding creativity and aspirational aesthetics, creative transfiguration sees the body as a gendered art piece that can be made ours through transition-related interventions."[86]

Because contemporary gender medicine countenances a multiplicity of "genders," this newer emphasis on embodiment goals moves beyond the "sex change" framework of previous decades, in which male patients acquired female-typical characteristics to "live as women" and female patients acquired male-typical characteristics to "live as men"

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[82] Ashley (2022a, p. 127).
[83] See Gorin (2024). It is notable that de Vries, the lead author of the two seminal papers (de Vries et al 2011 and 2014) that established the Dutch Protocol, has more recently questioned the "logic of improvement" that undergirds that original clinical rationale and has favorably cited the approach advocated by Ashley (Oosthoek et al., 2024).
[84] Ashley & Ells (2018, p. 24). The definition of gender euphoria offered by Ashley and Ellis entails that no one who does not experience incongruence can experience gender euphoria. According to other writers, however, gender euphoria is "quite common… among trans and cis folks alike." (Kukla, 2024, p. 288).
[85] Researchers recently have developed a scale intended to measure gender euphoria (Blacklock et al., 2025).
[86] Ashley (2019, p. 481).

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(see Chapter 3). Nothing in the newer "gender affirming" approach limits the number of bodily variations clinicians may be asked to create. Some girls or women want just a bit of stubble while others want full beards and flat chests; some boys or men want softer skin and breasts but wish to keep their penises intact. Expanding clinical offerings reflect these expanding embodiment goals. Surgeons provide penis-preserving vaginoplasty for patients who want both male and female genitals and offer "nullification" procedures for patients who identify as nonbinary and want no external genitals at all. There are at least as many physical combinations for patients to acquire as there are "gender identities"—indeed more, since presumably each gender identity can be embodied in different ways.[87]

While the ICD-11 does not mention "gender euphoria" or "gendered art pieces," the diagnostic criteria for Gender Incongruence of Adolescence or Adulthood implicitly formalize the "embodiment goals" approach to medical transition. The diagnosis is explained as follows:

> Gender Incongruence of Adolescence and Adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.[88]

According to Jack Drescher, a member of the World Health Organization's (WHO) Working Group on the Classification of Sexual Disorders and Sexual Health, which was tasked with making recommendations for the ICD's eleventh edition, to qualify for the diagnosis of Gender Incongruence of Adolescence or Adulthood, a patient need satisfy only two of the following four criteria:

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[87] James et al. (2015).
[88] World Health Organization (2022b).

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1. Strong dislike or disagreement with primary or secondary sexual characteristics due to incongruence with the experienced gender.

2. Strong desire to get rid of some of those sexual characteristics due to the incongruence with the experienced gender.

3. Strong desire to have the primary or secondary sexual characteristics of the experienced gender.

4. Strong desire to be treated and accepted as a person of the felt gender.[89]

It is hard to see how either of the first two criteria could be used to diagnose gender incongruence. ICD-11 says that gender incongruence is "characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex …"[90] Criteria (1) and (2) themselves include incongruence and so the diagnosis, when met by the first two criteria, suggests that a person has gender incongruence because they have attitudes or desires due to incongruence.[91]

Setting problems of circularity aside, an adolescent can be diagnosed with gender incongruence by satisfying (3) and (4),[92] which amount to having certain strong embodiment goals. A male who strongly desires to have (some? all?) the sex characteristics of a female and to be treated or accepted as such, or a female who strongly desires to have (some? all?) the sex characteristics of a male and to be treated or accepted as such, qualifies for the diagnosis. According to the ICD-11, a patient with such desires has a "condition related to sexual health" and, therefore, clinicians have a rationale for providing, and being reimbursed for, hormonal or surgical interventions.

It is noteworthy that the ICD-11 employs identical diagnostic criteria for adolescents and adults, despite the clear physiological and psychological developmental differences

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[89] Drescher & Yarbrough (2024, p. 2508).
[90] World Health Organization (2022a).
[91] The problem of circularity is also discussed in Chapter 2. It is also unclear what it could mean to be in a state of "disagreement" with one's sex characteristics. Perhaps the authors mean that one finds one's sex characteristics disagreeable, that is, unpleasant. This makes sense, as long as the unpleasantness does not rise to the level of distress, which would transform gender incongruence into something like gender dysphoria and thereby undermine the rationale for moving the gender incongruence diagnosis out of the mental disorder chapter of ICD-11.
[92] Whether the criteria must be met for a specific period of time is unclear. ICD-11 does not specify a time requirement; Drescher and Yarbrough say "several months" (Drescher & Yarbrough, 2024, p. 2508).

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between these populations and their respective capacities for decision-making and self-understanding. Neither DSM-5-TR nor ICD-11 provide any explanation for why children or adolescents might desire to modify their sex traits or to be treated or accepted as someone other than a member of their sex, and counseling approaches that might explore possible explanations with patients often are labeled "conversion therapy" by advocates of the "gender-affirming" approach.[93] As far as the DSM-5-TR and ICD-11 diagnoses are concerned, it makes no difference that a patient of 10 or 13 or 17 might wish to modify their body and be perceived and treated as someone other than a member of their sex for any number of reasons. These may include discomfort with one's homosexuality, a history of sexual trauma, pubertal distress, the rejection of perceived sex-based roles, and/or psychiatric comorbidities. For the ICD-11, desire alone is sufficient to justify a medical diagnosis and, within the "gender-affirming care" framework, set the adolescent on a course of PMT.

If using hormonal and surgical interventions to reduce psychiatric morbidity associated with gender dysphoria lacks a favorable risk/benefit profile, using these interventions merely to satisfy adolescents' embodiment goals veers from clinical error into clinical recklessness.

13.4 Regret

Patient regret has begun to receive significant attention in discussions of PMT. Proponents of PMT claim that regret is extremely rare.[94] Some also claim that since mental health assessments have not been shown to reduce regret rates, they should not be required prior to prescribing.[95] The tacit assumption is that absence of regret is an indication of medical benefit or at least of absence of harm. Other researchers point out that research on regret, like most research in PMT, is severely lacking and that we do not know the true prevalence of regret.[96] Whether implicitly or explicitly, proponents and critics alike consider the question of regret as central to the ethics of PMT.

[93] Ashley (2023). See Chapter 14.
[94] Crabtree et al. (2024); Kidd & Sequeira (2024); McNamara et al. (2024); Turban et al. (2021).
[95] Ashley et al. (2023); Wu & Keuroghlian (2023). See also Chapter 11.
[96] Cohn (2023); Jorgensen (2023b); MacKinnon, Expósito-Campos et al. (2023).

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That some patients report profound regret after undergoing invasive, life-changing medical interventions is clearly of importance. However, regret alone (just like satisfaction alone) is not a valid indicator of whether an intervention is medically justified. Not only is regret a complex phenomenon itself,[97] but its relation to ethical considerations in medicine, and to benefit and harm in particular, is tenuous. Patients sometimes come to regret consenting to interventions that were in fact well-justified, that is, interventions that did offer a favorable risk/benefit profile at the time the intervention was proposed. Patients may come to regret such interventions because they suffer harmful complications that were unlikely to occur but did occur in their case. Or they may come to regret the interventions for other reasons. For example, a woman may undergo a spine surgery for which there is compelling evidence of net benefit to her health and yet come to regret the surgery because the modest relief of pain seems to her retrospectively to have not been worth the cost or hassle involved in recovering from the surgery. Or perhaps the improvement in her health allowed her to take some course of action that turned out to make her life worse, all things considered. That she comes to regret the surgery does not mean that it was clinically or ethically unjustified, nor that her clinician violated medical ethics.

Conversely, humans have a remarkable capacity to incorporate suffering and loss into their life stories. A man may be paralyzed as the result of a spine surgery that did not prospectively offer a favorable risk/benefit profile, and which should never have been attempted by the surgeon. Yet months or years later the man may report that he does not regret undergoing the surgery, because the injury and debility it caused led him to focus more attention on the love and care of his family and friends. Or perhaps, as able-bodied, he was isolated and lonely but now, due to his greater physical dependency, he finds a supportive community within which he develops a new identity that imbues his life with structure and purpose. Or maybe as a result of his injury he simply comes to appreciate more deeply the gift of life in its fragility. That this man does not regret the surgery does not imply that his decision to consent to it was prudent, nor that the surgeon was justified in offering the surgery.

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[97] Landman (1987).

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The implications for PMT are complex. The provision of hormonal or surgical interventions to physically healthy adolescents cannot be vindicated by purportedly low rates of regret. Some patients who have suffered objective medical harm and then detransitioned nevertheless do not regret having been medicalized.[98] Nor can the interventions be condemned based on the fact that some adolescents who have undergone them do report regret. The central question for PMT is not: "Do these medically transitioned patients have regret?" A more fundamental question is, "Does medical transition provide health benefits proportionate to its harms?" The best available evidence, along with a risk/benefit analysis and precautionary approach ethically appropriate to pediatrics, shows that the answer to the latter question is almost certainly "no."

13.5 Research Ethics

Multiple SRs, commissioned by leading international health authorities and conducted by independent academic researchers, have concluded that the evidence underpinning the expected benefits of PMT is of low or very low certainty.[99] A natural response among researchers to the absence of higher quality evidence is to conduct more and better research. Whether and how such research should be conducted, however, is a matter of significant ethical controversy.

One controversy concerns RCTs, the "gold standard" for clinical research.[100] Some proponents of PMT claim that RCTs on the effects of PBs or CSH would be infeasible and unethical.[101] With respect to feasibility, because the effects of PMT interventions are so apparent, it is not possible to blind researchers and participants in an RCT for which the control group receives only psychotherapeutic support. Some worry that many adolescents would refuse to participate in a study that does not guarantee they receive hormonal interventions, or that they would drop out if randomized to the control group. These challenges may be harder to overcome in the current climate in which adolescents have been led to believe that hormonal and surgical interventions are well-

[98] For some real examples, see Sansfaçon et al. (2023).
[99] See Chapter 5.
[100] Hariton et al. (2018).
[101] Ashley et al. (2024, 407-418).

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supported by the evidence and even life-saving.[102] However, randomization does not require blinding, and until an RCT is attempted, speculation about how potential participants will respond is just that—speculation.

With respect to research ethics, one objection to conducting RCTs is that such research would violate the principle of equipoise. In their textbook, *Principles of Biomedical Ethics*, Beauchamp and Childress explain that "[t]he community of reasonable physicians is … in a state of 'clinical equipoise'" when "[n]o one knows, prior to conducting the research, whether it is more advantageous to be in the control group or in the experimental group … In this model, no patient, then, will receive something known to be less effective or to have a higher risk than an available alternative."[103]

Advocates for PMT allege that it would violate the principle of equipoise to conduct an RCT of PMT in which the control group receives only psychological counseling, "given the numerous studies associating adolescent gender-affirming interventions with improved mental health."[104] This allegation is unfounded, however, because it mischaracterizes the state of the science. Indeed, if equipoise were violated, it plausibly would be in the other direction, given the more certain evidence of harm. In the end, while their reasons differ, there may be a point of agreement between proponents of PMT and some of its critics concerning the impermissibility of conducting RCTs for hormonal or surgical interventions for pediatric GD.

It is not clear that hormonal or surgical interventions for GD can ethically be offered in a trial, irrespective of trial design. Currently, researchers in the U.K. are planning a PB trial. At the time of this Review's writing, the trial has not yet received official ethics approval, and details regarding the trial's design, which outcomes will be studied, what the inclusion and exclusion criteria will be, and so on, have not been published. Some critics of PMT already are raising concerns about the proposed study. They worry about prescribing PBs even in research settings given the recognized inability of clinicians to distinguish between patients whose GD will persist into adulthood from those whose GD

[102] Clayton, A. (2023).
[103] Beauchamp & Childress (2019), p. 365; See also Freedman (1987).
[104] Ashley et al. (2024, p. 408).

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will resolve on its own,[105] and the high likelihood that any patient who begins PBs will go on to CSH and possibly surgery.[106] Since most adolescents who take PBs go on to CSH, and since it is CSH and surgery that provide the sought-after physical characteristics in PMT, it is unclear whether PBs are a stand-alone treatment and should be studied as such.

Other critics point out that safer types of research—for example, research into various psychotherapeutic approaches—have yet to be explored with this population of patients. They also point out that U.S. gender clinics have yet to collect longitudinal data on existing patients.

There are other important ethical problems to consider. The Nuremberg Code is a foundational and internationally accepted statement of norms guiding human subjects research and it includes the following:

> The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results justify the performance of the experiment.[107]

This suggests that, insofar as PMT poses risks that can be explored through animal studies, such studies should be conducted before these treatments are further tested on humans. Animal studies could help clarify how hormonal interventions affect fertility, brain development,[108] bone development (including future risk of fracture), and cardiovascular outcomes. Such studies also could help clarify to what extent and under what conditions fertility can be recovered after suppression by hormonal interventions.

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[105] Feinmann (2025).
[106] E.g. Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[107] BMJ (1996).
[108] Chen and colleagues, for example, write, “studies in rodents show ovarian hormones, acting during puberty, program cognitive flexibility by exerting long-lasting effects on excitatory-inhibitory balance in the pre-frontal cortex . . . [and] testosterone, acting during puberty, programs the ability to adapt behavior as a function of social experience” (Chen et al., 2020, Table 2).

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The World Medical Association's Declaration of Helsinki is another foundational and internationally accepted statement of guidance for human subjects research. It includes the following:

> All medical research involving human participants must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimize the risks and burdens must be implemented. The risks and burdens must be continuously monitored, assessed, and documented by the researcher.
>
> Physicians and other researchers may not engage in research involving human participants unless they are confident that the risks and burdens have been adequately assessed and can be satisfactorily managed.[109]

It is not ethical to subject adolescents to hormonal and surgical interventions used in PMT, even in a research trial, until and unless the state of the evidence suggests a favorable risk/benefit profile for the studied intervention, *and* the researchers have well-grounded confidence that the foreseeable "risks and burdens have been adequately assessed and can be satisfactorily managed." As explained in this Review, the state of the science does not support a favorable risk/benefit profile, nor does it give researchers a basis for confidence that the risks of PMT can be satisfactorily managed.

Finally, the Belmont Report, authorized by the National Research Act of 1974 and published in 1979 by the United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, is a landmark statement of ethical principles to guide human subjects research in the United States. The Belmont Report affirms that research on humans should not be conducted until and unless that research is "justified on the basis of a favorable risk/benefit assessment" arrived at through "systematic, nonarbitrary analysis of risks and benefits." It continues:

[109] World Medical Association (2025).

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> Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible … It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies … [and] When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject …).[110]

As demonstrated throughout this Review, the presuppositions that guide PMT have not been shown to be valid; the nature, probability and magnitude of risks associated with PMT have not been distinguished with sufficient clarity; PMT proponents' estimates of the probability of harm and benefit have not been shown to be reasonable, as judged by known facts and available studies; and the risks of serious impairment that PMT involves have not been shown to be justified. For these reasons, administering PMT to adolescents, even in a research context, is in tension with well-established ethical norms for human subjects research.

[110] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (2010).

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PART 5

PSYCHOTHERAPY

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Chapter 14 Psychotherapy

This chapter reviews psychotherapy (talk therapy) for gender dysphoria (GD).[1] First, the chapter describes relevant trends in society at large and in the medical profession; specifically, trends in youth mental health (Section 14.1) and in diagnostic and social labels (Section 14.2). Section 14.3 discusses the role of mental health assessment in the care of youth with GD. Section 14.4 briefly recounts the re-emergence of psychotherapy as the primary treatment for this patient population in Europe, and Section 14.5 discusses psychotherapy and its specific application to GD.

14.1 Youth mental health

Puberty is the biological, developmental process during which a child becomes a sexually mature adult.[2] Puberty overlaps significantly with adolescence, the period between childhood and adulthood.[3] During puberty, hormonal fluctuations can affect mood and behavior.[4] The onset of puberty often coincides with heightened sensitivity to social dynamics and self-image along with increasing vulnerability to stress and anxiety. Emotional regulation can become challenging as adolescents navigate the complexities of identity formation and peer relationships. Cognitive development accelerates, allowing deeper abstract thinking and self-reflection, which can contribute to existential questioning and emotional instability.[5] Adolescence also involves learning to function independently, as part of identity formation and individuation from the family of origin. Rebellion and resistance to parents and other caregivers or authority figures frequently occur during this process. Adolescents often struggle with long-term planning and are more susceptible to risk taking, as drives for stimulation and affiliation increase but the prefrontal cortex, responsible for executive functions, is still maturing.[6]

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[1] Gender Dysphoria is a formal diagnosis in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5): see Appendix 2. In this chapter and throughout the Review the term “gender dysphoria” is used to refer to sex-related distress or discomfort, not the formal diagnosis (see Chapter 1, Note 1).
[2] See Chapter 7.
[3] According to the American Academy of Pediatrics (AAP), adolescence spans ages 12-21 (Hardin et al., 2017). See also National Academies of Sciences, Engineering, and Medicine (2019, pp. 22-23).
[4] Viner (2015).
[5] E.g., Reena (2015); Steinberg (2005).
[6] Steinberg (2009).

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14.1.1 Trends in youth mental health

In 2021, the American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry (AACAP), and the Children's Hospital Association declared a "National State of Emergency in Children's Mental Health."[7] In December of that year, U.S. Surgeon General Admiral Vivek Murthy issued an Advisory on Protecting Youth Mental Health, highlighting rising rates of depression, anxiety, hopelessness, and self-harm among youth—trends that worsened during the COVID-19 pandemic. The Lancet Psychiatry Commission on youth mental health noted a similar worldwide trend.[8]

In the U.S., there has been a significant increase in mental illness among teens and young adults since 2010.[9] Data reveal sharply increased rates of diagnosed depression and anxiety; some studies indicate that these rates have more than doubled.[10] Increases also have been documented in rates of suicidal ideation and behavior and self-harm,[11] emergency room visits and hospitalizations for self-harm,[12] and death by suicide.[13] Young people today experience weaker social connections and greater feelings of loneliness. Since 2010, adolescents have had fewer in-person social

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[7] American Academy of Child and Adolescent Psychiatry et al. (2021).
[8] McGorry et al. (2024).
[9] Twenge (2020).
[10] Data from a large national database showed that rates of major depressive episodes among adolescents aged 12 to 17 increased by 52% from 2005 to 2017 (from 8.7% to 13.2%) and by 63% among young adults aged 18 to 25 from 2009 to 2017 (from 8.1% to 13.2%) (Twenge et al., 2019). The "Anxious Generation" website, using Centers for Disease Control and Prevention (CDC) data, shows that rates of major depressive disorder from 2010 to 2022 more than doubled for both boys and girls, with major depression in boys increasing by 161% and in girls by 145%. Mental illness for college students increased, with a 134% increase in anxiety and 106% increase in depression over that same period (Rausch & Haidt, 2023). A cohort study of approximately 1.7 million individuals aged 5 to 22 years in Southern California revealed that from 2017 to 2021 the overall incidence of depression increased by approximately 60%, and anxiety by 31% (Xiang et al., 2024). A survey of a Midwestern school district found from 2012 to 2018 there was a 29% increase in youth screening positive for past-month anxiety (Parodi et al., 2022). See also Goodwin et al. (2020); Keyes & Platt (2024).
[11] See CDC trends report, 2013-2023 (Centers for Disease Control and Prevention, 2023).
[12] See Gutiérrez-Sacristán et al. (2022) for information about increase in psychiatric hospitalizations during the COVID-19 pandemic, for example. See also McGorry et al. (2024).
[13] Suicide death rates for children and young adults aged 10 to 24 years increased 62% from 2007 (6.8 per 100,000 individuals) to 2021 (11.0 per 100,000 individuals) (Curtin et al., 2023). Youth suicides began to rise in the 2000s, with a sharper upward trend starting around 2012; see Farah et al. (2023); Miron et al. (2019); Twenge (2020).

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interactions with peers compared to previous generations.[14] The deterioration in youth mental health has no one simple explanation. Researchers and theorists have identified several potential factors, including overprotective parenting,[15] the decline in free play,[16] and the ubiquity of smartphones and social media.[17] In 2023, the Surgeon General released an Advisory of Social Media and Youth Mental Health, which called attention to the potential risks associated with social media use for children and adolescents.[18]

14.2 Diagnostic and social labels

The rise in reported mental health problems may be partly attributable to overdiagnosis. Some argue that the rise in mental health awareness campaigns aimed at reducing stigma and increasing understanding may have led some young people to interpret normal behaviors and typical developmental challenges as a mental health disorder.[19] Being labeled with a mental health diagnosis can influence how young people see themselves, affect their belief in the possibility of change, and shape how others perceive them. The very act of classifying psychiatric conditions changes the behavior of patients and clinicians. Although diagnostic labels are important for research—where categorizing people or experiences is often necessary—they can oversimplify the

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[14] Twenge et al. (2021); Twenge (2023). Based on CDC data, adolescents have, over time, reported increased feelings of meaninglessness, as well as less willingness to engage in risk-taking behaviors. This includes behavior such as drug and alcohol consumption, but also encompasses developmental experiences such as working or learning to drive a vehicle (Haidt, 2024).
[15] Wang et al. (2024); Winnicott (1965); Zhang & Ji (2024).
[16] According to the AAP: "Children need to develop a variety of skill sets to optimize their development and manage toxic stress. Research demonstrates that developmentally appropriate play with parents and peers is a singular opportunity to promote the social-emotional, cognitive, language, and self-regulation skills that build executive function and a prosocial brain" (Yogman et al., 2018).
[17]Increased use of technologies, including social media, caused a displacement of other activities, such in-person socializing, schoolwork, sleep, sports, reading, and other hobbies. Heavy use of smart phones and social media is ubiquitous among teenagers today (Rothwell, 2023; Twenge et al., 2022; Twenge & Campbell, 2019; Vogels et al., 2022), and common among pre-teens (Rideout et al., 2022). Social media in particular may result in worsening mood and negative self-image in adolescent girls (Choukas-Bradley, 2024; Rodgers & Rousseau, 2022; Scott et al., 2023), and in some cases may play an etiologic role in increasing presentations of specific psychiatric and neurologic issues (Giedinghagen, 2023; Haltigan et al., 2023; Hull & Parnes, 2021; Padín et al., 2021; Pringsheim et al., 2021; Weigle & Shafi, 2024). Social media has introduced a new sociomedical phenomenon in which individuals may find a sense of belonging online through identification with an illness or condition, which may place them at risk of inappropriate or unnecessary medical care (Corzine & Roy, 2024). For a meta-analysis that found reasons for skepticism about the evidence for the effects of social media on mental health, see Ferguson (2025).
[18] Office of the Surgeon General (2023).
[19] Foulkes & Andrews (2023).

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richness and complexity of human experiences for the benefit of a standardized clinical language. To some extent, skillful clinicians can compensate for this reductionism,[20] but they cannot prevent diagnostic labels from escaping the clinic and being used in unintended ways in the wider culture.[21]

Overdiagnosis can lead to overtreatment; unnecessary tests, procedures or medical interventions may cause harm rather than helping. Loosening the diagnostic criteria for a condition will likely increase overdiagnosis and the risk of iatrogenic harm, so definitions should be formulated responsibly:

> … any changes [to diagnoses] should use a systematic, transparent approach where benefits and harms are explicit, especially when they lead to an increase in the prevalence of disease, and broadening of definitions should require evidence of clinical benefit.[22]

Although the term "gender identity" was used in the 1960s,[23] it did not appear in the *Diagnostic and Statistical Manual of Mental Disorders* until 1980 (third edition, DSM-III). "Gender Identity Disorders" was a subcategory of "Psychosexual Disorders," further divided into "Transsexualism" (for late adolescents and adults) and "Gender Identity Disorder of Childhood."[24] In the DSM-IV, published in 1994,[25] "Transsexualism" vanished, and "Gender Identity Disorder" (GID), covering both adults and children, appeared under "Sexual and Gender Identity Disorders." The DSM-5, published in 2013,[26] replaced "Gender Identity Disorder" with "Gender Dysphoria" and designated it as a separate category. This last change "focused the diagnosis on the gender identity-related distress that some transgender people experience (and for which they may seek

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[20] Johnstone (2018).
[21] Hacking (1998); Shorter (1993). See also Brossard (2019); Elliott (2000); Haslam (2016); Lindholm & Wickström (2020); Smids & Vasterman (2025).
[22] Kale & Korenstein (2018, p. 8). The field of psychiatry is no stranger to the phenomenon of misdiagnosis, overdiagnosis and overtreatment; see, for example, Harris & Carey (2008), Havens et al. (2022), and Moreno et al. (2007) for discussion of controversies related to overdiagnosis of pediatric bipolar disorder.
[23] See Chapter 2.
[24] American Psychiatric Association (1980).
[25] American Psychiatric Association (1994).
[26] American Psychiatric Association (2013).

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psychiatric, medical, and surgical treatments) rather than on transgender individuals or identities themselves."[27]

The intention of the DSM's linguistic evolution—from "Transsexualism," to "GID," to "GD"—was to reduce stigma. A parallel linguistic evolution in society at large has resulted in the increasing adoption of labels such as "nonbinary," "genderqueer," "queer," "gender-fluid," "two-spirit," and "transgender."[28] The individuals who identify with these labels—unlike historical or contemporary "transsexuals"[29]—are not a patient group of any kind. "Transgender," "nonbinary," and similar words are not medical terms: they apply to a diverse group of individuals, many of whom are neither dysphoric nor desire any medical or surgical interventions. If there is a common experience, it is "incongruence" between "experienced gender" or "gender identity" and "assigned sex." As the 2022 Text Revision of the DSM-5 explains, "not all individuals will experience distress from incongruence."[30]

As discussed in Chapter 4, social influences have plausibly contributed to the dramatic increase in adolescents presenting to pediatric gender medicine (PGM) clinics over the past decade.[31] Adolescents' need for belonging and acceptance[32] can be met by online communities and spaces centered around identity. The growing use of identity labels such as "transgender" and "nonbinary" among adolescents is an important topic for social science research. In the current U.S. healthcare environment, self-labeling of this kind increases the likelihood that a young person will seek input from a gender clinic,

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[27] Drescher (2017). According to a systematic review of cross-sex hormones and mental health outcomes commissioned by the World Professional Association for Transgender Health (WPATH), "[the diagnostic changes] clarify that the target of gender-affirming medical interventions is not the person's gender identity itself but rather the clinically significant distress that can accompany a misalignment between gender identity and sex assigned at birth" (Baker et al., 2021, p. 2). For the diagnostic criteria, see Appendix 2.

[28] See James et al. (2015), and also Section 13.4 of the previous chapter, on "gendered art pieces."

[29] Some individuals who have medically and surgically transitioned still claim this label: e.g., "I do consider myself more as a Transsexual person, which to me is somebody who wanted to switch genders. I always wanted to be a man, I identify as a man, that's what I am, I don't identify as a Transperson at all" (LOTL staff, 2014). See also American Psychological Association (2023), and Chapter 3.

[30] American Psychiatric Association (2022). See also Chapters 2 and 11.

[31] See also the discussion of rapid-onset gender dysphoria (ROGD) in the same chapter.

[32] Especially in girls, e.g., Archer (2019); Prinstein et al. (2005); Rose & Rudolph (2006).

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where medical transition may be recommended as early as the first appointment (see Chapter 12).[33]

14.3 Controversies regarding assessment and the role of the psychotherapist

In the Dutch research that underpins the contemporary pediatric medical transition (PMT) approach, the psychotherapist occupied an essential role. The original Dutch approach involved an intensive assessment process.[34] Adolescents who began medical transition were required by the protocol to continue to receive regular mental health care.[35]

When discussing contemporary applications of PMT in the U.S., providers often describe a similar approach: multidisciplinary, slow, careful, and methodical.[36] For healthcare providers, the term "multidisciplinary" may connote the lengthy, intensive deliberations that occur at "tumor boards"[37] or during organ transplantation assessments. In inpatient psychiatric units, it is considered preferable to have a multidisciplinary approach, for example involving nursing staff, psychologists, occupational therapists and social workers.[38]

However, in PGM, multidisciplinary teams (MDTs) often do not function like the collaborative model just described. They are more similar to the common healthcare scenario in which a patient sees a cardiologist for cardiac clearance before undergoing

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[33] Discussion of labels is also salient to the treatment of the prepubertal patient cohort with GD. As discussed in Chapter 2, the relatively recent practice of calling gender dysphoric youth "transgender children" may increase the likelihood these patients will be placed on a medicalized pathway.
[34] As described in Delemarre-van de Waal & Cohen-Kettenis (2006), "[In] the first diagnostic phase, information must be obtained from both the adolescent and the parents on various aspects of general and psychosexual development of the adolescent, the adolescent's current functioning and functioning of the family. Standardized psychological assessment is a part of the procedure. The patient is always seen by two members of the gender team. If a child and adolescent psychologist makes the diagnosis, the child is also seen by a child and adolescent psychiatrist and vice versa" (p. S132).
[35] Delemarre-van de Waal & Cohen-Kettenis (2006). Mental health visits were required every 3 months.
[36] E.g., from ABC News: "[Kellan] Baker [the executive director of the Whitman-Walker Institute, an LGBTQ research organization and care provider] said the decision to pursue gender-affirming care is often a lengthy process that includes teams of medical care providers and mental health professionals who work with families to talk about their child's experience, their needs, their choices, and more…'We're talking months of appointments with a mental health specialist. We're talking lots of conversations between providers, parents, and kids,' Baker said" (Alfonseca & Geho, 2024).
[37] Okasako & Bernstein (2022).
[38] Russ (2021).

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an orthopedic procedure. Under some models, the mental health professional (MHP) seeing the minor with GD writes a note or may just fill in a pre-written template; this is taken to an endocrinologist, who prescribes, or a surgeon, who operates.[39] Further, individuals who comprise the MDTs may all subscribe to the PMT model of care, which prioritizes administration of endocrine and surgical interventions to patients who desire them.[40] This is different from traditional MDTs where various specialties approach problem-solving from different perspectives, enhancing the accuracy of the diagnosis and identification of effective treatments.[41]

The MDT model in the context of PMT has created considerable uncertainty about whether the MHP or the physician providing the medical (and/or surgical) interventions bears the ultimate responsibility for the decision. This may have resulted in "diffusion of responsibility," a phenomenon in which "individuals can underperform in circumstances of shared accountability."[42] With respect to the U.K.'s National Health Service (NHS), the Cass Review's interim report provided some clarity by stipulating that the pediatric endocrinologist, as the physician providing the intervention, should be responsible for assessing the patient and formulating a full differential diagnosis. In other words, according to the interim report, receipt of a therapist's letter should not be sufficient for the prescription of hormonal intervention.[43]

In the U.S., no such clarity exists regarding which MDT professionals are ultimately responsible for medical interventions. Endocrinologists and surgeons may believe that the medical necessity of any intervention has been determined by the MHPs who made the diagnosis.[44] Whether the MHP "letter of approval" for hormones or surgery

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[39] See description of the university-based multidisciplinary clinic in Reed (2023a). See description of two-hour long assessments at Boston Children's Hospital in Damiano (2024a).
[40] To further mitigate the potential biases of established MDT teams who subscribe to the PMT model, the National Health Service (NHS) in England issued a new clinical policy for cross-sex hormones in 2024. It calls for independent oversight, specifying that new national MDTs must include "clinicians *not directly involved* in the formation of the individual's care plan," who must agree "on the suitability of the individual receiving [CSH]" (National Health Service England, 2024c).
[41] Morabito et al. (2024).
[42] Marcotte et al. (2020, p. 802).
[43] Cass (2022a).
[44] See, for example, the role of endocrinologists as described in Karakılıç Özturan et al. (2023b). The field of pediatric gender medicine is unusual in this respect: "It [is] not the norm for doctors to prescribe powerful medication to people—especially children—they themselves [did] not diagnos[e]" (Barnes, 2023, p. 337).

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constitutes a formal treatment indication will likely be determined by ongoing lawsuits brought by young people against the clinicians who treated them. In practice, these MHP approval letters may primarily serve to ease the ethical concerns of the physicians.[45]

Some prominent PMT advocates assert that children and adolescents should not receive *any* mental health assessment prior to initiation of hormonal interventions or surgeries.[46] As a principal investigator of NIH-funded research on PMT, Johanna Olson-Kennedy, a U.S. pediatrician and president-elect of the U.S. Professional Association for Transgender Healthcare (USPATH), likened the initiation of PMT to treating diabetes, asserting: "I don't send someone to a therapist when I'm going to start them on insulin."[47]

14.4 Psychotherapy for GD: Re-emergence in Europe

Three European countries—Sweden, Finland, and England—have conducted independent systematic reviews of evidence commissioned by their public health authorities.[48] All three concluded that the risks of medicalization may outweigh the benefits for children and adolescents with GD at the population level, and subsequently sharply restricted access to medical gender transition interventions for minors.[49] All three countries now suggest traditional mental health approaches and have begun efforts to de-exceptionalize GD. Psychotherapy is now the recommended first-line treatment, as it is for all psychological distress based on the conventions of "conservative management."[50]

Per England's National Health Service (NHS):

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[45] Levine (2024, p. 4).
[46] As described in McDeavitt (2025, p. 1298), "The argument for doing away with mental health assessments is often articulated alongside the opinion that the presence of a DSM-5 diagnosis of gender dysphoria (or indeed any type of psychological distress) should not have to be required in order for an adolescent to be initiated on PBs/GAH." See Mosier-Mills et al. (2024), for example, and similar arguments in Ashley (2022a, 2022b, 2023).
[47] Singal (2018).
[48] Ludvigsson et al. (2023); National Institute for Health and Care Excellence (2020b, 2020a); Pasternack et al. (2019); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024).
[49] See Chapter 4.
[50] Adhiyaman & Ambalavanan (2021).

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> The primary intervention for children and young people … is psychosocial (including psychoeducation) and psychological support and intervention; the main objective is to alleviate distress associated with gender dysphoria and promote the individual's global functioning and wellbeing.[51]

Per Finland's Council for Choices in Health Care in Finland (COHERE):

> The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.[52]

Per Sweden's National Guidelines:

> The psychosocial care of young people with gender dysphoria needs to be adapted to the needs of the individual adolescent. Psychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures. For those suffering from mental health problems, measures such as supportive counseling, psychotherapy, child psychiatric treatment, and suicide prevention need to be offered and adapted to the nature and severity of the mental health problem and the young person's overall situation.[53]

14.5 Psychotherapy and its application to gender dysphoria

Psychotherapy is the least invasive intervention for addressing psychological distress, regardless of its etiology, and it has been recognized as the international standard of care for a wide range of mental health diagnoses. However, the evidence for psychotherapy for GD is of very low certainty. As noted in Chapter 5, there are multiple reasons for the paucity of data, and "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[54]

[51] National Health Service England (2022, p. 2).
[52] Council for Choices in Healthcare Finland (2020b, p. 5).
[53] Socialstyrelsen (2022b, p. 45).
[54] Cass (2024a, p. 155).

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14.5.1 Psychotherapy for conditions frequently co-occurring with gender dysphoria

The etiology of GD in youth remains understudied. However, patients presenting to PGM clinics today have a range of neurodevelopmental disorders and mental health conditions, including comorbid depression, anxiety, eating disorders, self-harm, and suicidality.[55] Some studies suggest that in more than 70% of cases, other DSM diagnoses appeared before the GD.[56] Etiologically, the relationship between the GD and the high rate of co-occurring mental health conditions in this population is unclear. [57] As explained by psychologist Kenneth Zucker,

> it may be that the gender dysphoria has emerged as secondary to another, more "primary" mental health diagnosis, such as autism spectrum disorder or borderline personality disorder, or as a result of a severe trauma (e.g., sexual abuse). Another explanation is that gender dysphoria is inherently distressing, i.e., the marked incongruence between one's felt gender and somatic sex—even within psychosocial milieus that are largely "affirming/supportive"—which leads to clinically significant symptoms such as anxiety or depression.[58]

Regardless of its etiology, psychotherapy as an effective intervention for depression, the most common mood disorder, has been studied extensively and is supported by high-quality evidence. For example, cognitive behavioral therapy (CBT), an (often) manualized therapy that helps patients recognize the reciprocal relationships between

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[55] See Section 4.3.

[56] Becerra-Culqui et al. (2018); Kaltiala-Heino et al. (2015); Kozlowska et al. (2021).

[57] Littman (2021), a study that analyzed online survey data from a convenience sample of detransitioners, found that 40.6% of females and 25.8% of males reported that their "feelings of being transgender actually were the result of a mental health condition." 44.9% of females and 16.1% of males reported that "feelings of being transgender actually were the result of trauma" (p. 3364). The Cass Review reported that "Clinicians have described … how in patients with [body dysmorphic disorder, or BDD], the intense focus on appearance is most commonly on facial features, but that some experience distress about genitalia or breasts. In this situation it can be difficult to determine whether the distress is due to BDD or gender dysphoria. However, at the end of a treatment package for BDD some young people say they no longer feel ill at ease with their birth-registered gender, while some may have less distress about their genitalia or breasts but still have marked gender incongruence and proceed to a social or medical gender transition" (Cass, 2024a, p. 92).

[58] Zucker (2019). In addition to these two possibilities, a third theory is that "co-occurring mental health issues are simply secondary to factors such as family rejection or social ostracism within the peer group vis-à-vis the gender dysphoria" (p. 3). This "minority stress model" is discussed later in the present chapter.

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thoughts, feelings, physiology, and behaviors, has evidence for benefit across age groups.[59] Psychodynamic psychotherapy (PDT) focuses on relational interactions, the role of formative life events, and unconscious processes, with the aim of facilitating emotional expression and interpersonal effectiveness.[60] Research indicates that PDT is effective in adults with depression, and there is also evidence of benefit for younger populations.[61] Another approach for adolescent depression with evidence for benefit is family-based treatment (FBT).[62]

Anxiety disorders also are highly prevalent in children and adolescents. The AACAP clinical practice guidelines strongly recommend that children and adolescents (ages 6-18) be offered CBT to address social anxiety, generalized anxiety, separation anxiety, specific phobias, or panic disorder.[63] PDT is less-well studied for anxiety, but may also be effective.[64]

For suicidality and self-harm in adolescents, evidence suggests that dialectical behavioral therapy (DBT), an approach that combines CBT with mindfulness and

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[59] "Manualized" therapeutic approaches follow specific, standardized guidelines. CBT is the most well-studied. A recent meta-analysis of CBT for depression, including more than 50,000 patients across all age groups and 409 randomized controlled trials (RCTs), found that "CBT is effective in the treatment of depression with a moderate to large effect size, and that its effect is still significant up to 12 months (Cuijpers et al., 2023, p. 114). Other forms of psychotherapy were also found to be significantly beneficial. With respect to studies specifically focused on children and adolescents, evidence suggests CBT had modest positive effects on depressive symptoms (Espada et al., 2023).

[60] Opland & Torrico (2025).

[61] A systematic review of PDT for adults, which used the GRADE framework for evidence assessment, found "high quality evidence for depressive disorders and somatic symptom disorders, and moderate quality evidence for anxiety and personality disorders, that PDT achieves clinically meaningful effects in target symptoms and functioning compared to controls and is associated with low risk of harms and reasonable costs" (Leichsenring et al., 2023, p. 286). Midgley et al. (2021) is a narrative review of studies on PDT for children and adolescents (including some RCTs), finding "evidence of effectiveness for psychodynamic therapy in treating a wide range of mental health difficulties in children and adolescents" (p. 1).

[62] For example, attachment-based family therapy is an evidence-based approach to treating adolescent mood disorders, including depression, using a combination of separate (adolescent-only and parents-only) and joint family sessions (Diamond et al., 2021).

[63] This recommendation was based on a commissioned Agency for Healthcare Research and Quality (AHRQ)/Mayo Clinic systematic review and meta-analysis that included 60 RCTs and almost 7,000 pediatric patients. It found moderate-strength evidence that CBT improves primary anxiety symptoms and global functioning (Walter et al., 2020).

[64] Leichsenring et al. (2015); Midgley et al. (2021).

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interpersonal skills training,[65] is an effective treatment.[66] Guidance published by the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2020 found strong evidence that DBT was associated with reductions in suicidality (ideation, non-suicidal self-injury, and suicide attempts).[67] Another evidence-supported intervention, attachment-based family therapy, supports adolescents and parents as they rebuild trust and safety within their relational patterns, gradually reducing the risk of self-harm and suicidality.[68]

Eating disorders also frequently co-occur with GD.[69] CBT has shown some effectiveness as treatment for eating disorders in adults,[70] and CBT, DBT, and family-based treatment or family therapy for eating disorders (FT-ED) have shown effectiveness in adolescents.[71] Such approaches initially target the presenting issue by helping parents and caregivers support their children more effectively, while issues related to identity development are addressed as the condition improves. These family-based treatments are considered first-line interventions for treating adolescent eating disorders, particularly anorexia nervosa and bulimia nervosa.

Body dissatisfaction, which is common in adolescence, is treated with specific evidence-informed protocols. A combination of CBT and selective serotonin reuptake inhibitors (SSRIs) is recommended by the National Institute of Health and Care Excellence (NICE) in the U.K. for body dysmorphic disorder. It also recommends that parents and caregivers actively participate in the treatment process.[72]

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[65] DBT originated as a treatment for adults with borderline personality disorder with chronic suicidality. Its focus is on helping patients achieve mindfulness, interpersonal effectiveness, emotional regulation, and distress tolerance (Substance Abuse and Mental Health Services Administration, 2020).
[66] This is in direct contrast to hormonal interventions, which have *not* been shown to reduce suicidality or suicide in minors with GD. See Section 4.3.4 and Chapter 5.
[67] This SAMHSA guidance considered evidence to be "strong" if positive impact was demonstrated by two or more RCTs (or other controlled trials). Nine studies (of varying methodologies) of DBT for suicidality in adolescents were included in this evidence review; two were RCTs (Substance Abuse and Mental Health Services Administration, 2020).
[68] Diamond et al. (2010).
[69] From a theoretical standpoint, eating disorders and GD both have been conceptualized as arising, in some cases, out of a subconscious desire to avoid the development of adult sex characteristics, perhaps in part due to maladaptive coping strategies or to avoid sexual objectification (Nadrowski, 2023).
[70] Öst et al. (2024).
[71] Datta et al. (2023); Lock et al. (2010); Vogel et al. (2021).
[72] National Institute for Health and Care Excellence (2005).

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When discussing the broader issue of the high prevalence of GD in patients presenting with conditions like eating disorders, body dysmorphic disorder, and functional tic-like behaviors, the Cass Review noted that "[t]he distressing symptoms that occur in these 'body and mind' conditions are real, and like pain or discomfort that arises from other causes can be addressed and helped with psychological interventions. It is very important that gender-questioning young people are able to access these evidence-based treatments."[73] The Cass Review also observed,

> Some therapies, which are well proven for associated mental health problems, already have a strong evidence base. Where it is clear that children/young people have such problems, they should receive the appropriate therapies in the same way as any other young person.[74]

14.5.2 Psychotherapy for gender dysphoria

The overview of systematic reviews (Chapter 5 and Appendix 4) found a dearth of evidence for psychotherapeutic interventions for youth with GD. As summarized in the Cass Review,

> there is a lack of evidence about alternative approaches for managing gender-related distress, and it is difficult to obtain information about routine clinical practice or pathways of care for children and young people who do not receive medical interventions. An explicit clinical pathway must be developed for non-medical interventions, as well as a research strategy for evaluating their effectiveness.[75]

Although several studies suggest that psychotherapy for GD may effectively resolve the condition noninvasively,[76] the quality of the evidence is very low certainty.[77] At the same time, the overview identified two SRs deemed as trustworthy (i.e., at low risk of bias),

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[73] Cass (2024a, p. 93)
[74] Cass (2024a, p. 155).
[75] Cass (2024a, p. 157).
[76] Churcher Clarke & Spiliadis (2019); Cohen-Kettenis & Kuiper (1984); Costa et al. (2015); Smith et al. (2001); Spiliadis (2019).
[77] See Chapter 5.

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and noted that "neither systematic review suggested that there is indication of harm from psychotherapy." One of the SRs concluded:

> Most analyses of mental health, psychological and/or psychosocial outcomes showed either benefit or no change, with none indicating any negative/ adverse effects of the interventions offered.[78]

Although there is no reliable evidence to suggest that psychotherapy for GD is harmful, some proponents of PMT have alleged that it is a form of "conversion therapy." This allegation is addressed in the following section; the final section surveys psychotherapeutic approaches to GD.

14.5.2.1 The charge of "conversion therapy"

Although psychotherapy for GD is described by its practitioners as "neutral" and "unbiased,"[79] some advocates for PMT maintain that such "exploratory" approaches are equivalent to conversion practices.[80]

"Conversion therapy"—sometimes called "reparative therapy"—originally referred to efforts to change the sexual orientation of gay and lesbian people. In 1973, homosexuality was officially de-pathologized by the American Psychiatric Association (APA) when it was declassified as a mental disorder (via its removal from the DSM).[81] While proponents of PMT have characterized exploratory psychotherapeutic approaches for GD as a form of "conversion therapy," others have claimed that PMT

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[78] Heathcote et al. (2024, p. s19).
[79] D'Angelo et al. (2021, p. 12).
[80] E.g. Ashley (2022b, 2023); see also the quotation by Colt St. Amand conflating psychological assessments for minors seeking medical or surgical transition with conversion therapy in Bazelon (2022a). Turban, Beckwith et al. (2020), a widely-cited peer-reviewed analysis of data from the 2015 U.S. Transgender Survey (USTS) concluded that individuals who recalled having been exposed to "gender identity conversion efforts" in the past were more likely to have experienced recent psychological distress and lifetime history of suicidal thoughts, but D'Angelo et al. (2021, p. 12) pointed out that this analysis was based on a "simplistic 'affirmation' versus 'conversion' binary … The notion that all therapy interventions for GD can be categorically classified into this simplistic binary betrays a misunderstanding of the complexity of psychotherapy. At best, this blunt classification overlooks a wide range of ethical and essential forms of agenda-free psychotherapy that do not fit into such a binary; at worst, it effectively mis-categorizes ethical psychotherapies that do not fit the "affirmation" descriptor as conversion therapies" (p. 7). For methodological concerns about the USTS itself, see Chapter 4, Note 117.
[81] Drescher (2010, p. 434); McNally (2011, pp. 21-24). The first edition (1952) of the DSM classified same-sex attraction as a type of "sociopathic personality disturbance" (American Psychiatric Association, 1952, pp. 38-39).

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itself deserves that label. This latter group contends that altering a person's body in response to distress rooted in internalized social disapproval is no more appropriate than attempting to change someone's sexual orientation for similar reasons.[82] Public and academic debates over what constitutes "conversion" in the context of youth with GD have been hindered by the politicization of the issue.[83]

Critics of exploratory psychotherapy for GD claim that therapists are trying to "promote gender identities that are aligned with the person's sex assigned at birth."[84,85] A less theoretically-laden description would be that some therapists are trying to help children and adolescents come to terms with their bodies.[86] Discomfort with the sexed body or with societal sex-based expectations is common during puberty and adolescence. For this and other reasons, characterizing as "conversion therapy" any approach focused on reducing a minor's distress about their body or social role is a problematic and potentially harmful rhetorical device.[87] There is evidence that the specter of being

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[82] See Bannerman (2019) and Hamedani (2014). A recent bioethics article argues that "a society that marginalizes youth who do not conform to gender norms must, as a matter of justice, change its ways. The burden of enacting this change is all of ours to bear. It should not be borne by the bodies of our youth" (Gorin, 2024, p. 43).

[83] Defenses of psychotherapy for GD have roundly rejected the label of "conversion therapy": e.g., "Psychotherapy resides outside the affirmation-conversion binary and aims to address the distress of gender-dysphoric youth rather than to correct a sense of misalignment. Psychotherapy does not attempt to force change or impose any predetermined notion … A core ethical principle of psychotherapy is that therapists must respect patient autonomy and self-determination and refrain from any attempt to influence the patient … A genuine psychotherapeutic process starts from a position of not knowing and seeks to open things up. Anything else is a misuse of psychotherapy" (D'Angelo, 2023, p. 3).

[84] The full quotation is: "Trans conversion practices refer to sustained efforts to promote gender identities that are aligned with the person's sex assigned at birth and/or to discourage behaviours associated with a gender other than the person's sex assigned at birth" (Ashley, 2022b, p. 26). This seems to more broadly characterize conversion therapy as an attempt to encourage conformity with sex stereotypes. However, as explained by D'Angelo, "Psychotherapy does not impose restrictive gender stereotypes, as is sometimes claimed, but critically examines them" (D'Angelo, 2023, p. 1). Such examination is necessary, because restrictive stereotypes could plausibly have contributed to the patient's GD.

[85] The 2020 United Nations (UN) Report on Conversion Therapy begins by explaining that "conversion therapy" refers to "interventions of a wide-ranging nature, all of which have in common the belief that a person's sexual orientation or gender identity (SOGI) can and should be changed. Such practices aim (or claim to aim) at changing people from gay, lesbian or bisexual to heterosexual and from trans or gender diverse to cisgender" (United Nations, 2020). See Lawford-Smith (2024) for discussion of recent legislation banning "conversion therapy" as the UN understands it.

[86] Once it is recognized that the operative notion of "gender identity" has not been properly explained (Chapter 2), the charge of "conversion therapy" makes little sense. If gender identity is obscure, the goal of changing the patient's gender identity is equally obscure.

[87] E.g., D'Angelo (2023); D'Angelo et al. (2021); Edwards-Leeper & Anderson (2021); Jenkins & Panozzo (2024); McDeavitt (2025); Sinai & Sim (2024). Also, as noted in the Cass Review, "The role of

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labeled a “conversion therapist”— a damaging accusation given the profession’s history with the mistreatment of gay people—has created a climate of anxiety among mental health professionals. Therapists worry that failing to affirm or recommend medical interventions for youth who meet the World Professional Association for Transgender Health’s (WPATH) eligibility criteria could jeopardize their careers and reputations.[88]

Equating “exploratory therapy” with “conversion therapy” is misguided for two additional key reasons. First, exploratory therapy was a fundamental and mandatory element of the original Dutch Protocol, which serves as the foundation for the current PMT model.[89] Second, quality psychotherapy is exploratory *by definition*: it is “a process of shared decision making in which the therapist … guides the patient in exploration of their material but does not input their own beliefs or ideas.”[90]

The conflation of psychotherapy with conversion therapy has been condemned not only by expert therapists who question the current emphasis on medical transition and surgical transition for youth, but also by practitioners and researchers in the PMT field itself.[91]

14.5.2.2 Psychotherapeutic approaches

The effectiveness of psychotherapy for a wide range of mental health problems, including those that often present with GD, suggests it may also be beneficial for GD specifically. The Cass Review’s emphasis on the de-exceptionalization of youth with GD underscored the observation that clinicians

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psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an unhelpfully polarised debate around conversion practices. Terms such as ‘affirmative’ and ‘exploratory’ approaches have been weaponised to the extent that it is difficult to find any neutral terminology” (Cass, 2024a, p. 150).

[88] Jenkins & Panozzo (2024). As summarized in McDeavitt (2025): “Some therapists who engage in exploratory talk therapy with [transgender and gender diverse] youth have faced licensure complaints related to accusations of “conversion therapy”—complaints made not by patients, but by activists and colleagues. One therapist reported having attended a workshop … in which activists described “hunting” for such therapists with the goal of bringing lawsuits and prompting licensure revocation.”

[89] Weaknesses of the original Dutch research are discussed in Chapter 4.

[90] Sinai & Sim (2024, p. 148); see also Churcher Clarke & Spiliadis (2019).

[91] For example, psychologist Laura Edwards Leeper has stated that “Conflating conversion therapy and identity exploration is perhaps the largest threat to both gender-distressed cisgender youth and transgender youth, alike. The rhetoric being used to conflate the two must stop immediately” (McDeavitt, 2025, p. 1298). See also Edwards-Leeper & Anderson (2021).

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> just need the appropriate training, support and most importantly the confidence to do what [they] have been trained to do and treat this population as [they] would any other young person in distress.[92]

Unfortunately, efforts to research the influence of cultural and social factors, trauma, or co-occurring mental health conditions on GD have been denigrated as "harmful."[93] When combined with the highly charged accusation of "conversion therapy," therapists may be under significant pressure to assume—often without critical evaluation—that mental health issues co-occurring with GD are primarily the result of minority stress.[94] This pressure may cause clinicians to overlook the significant possibility that in some patients, GD has *arisen from* trauma, "primary" mental health concerns, or neurodevelopmental conditions (see Section 14.1 above). Publications by psychotherapists working with this population have noted that patients with GD may seek hormonal or surgical interventions in response to experiences of sexual violence, negative attitudes towards homosexuality, or bullying related to self-expression, interests, or behaviors that deviate from sex stereotypes.[95]

If these possibilities are ignored, medical and surgical interventions may be recommended as the obvious treatment.[96] The mischaracterization of psychotherapy for GD as "conversion therapy" or "doing nothing" may also contribute to a nocebo effect, disincentivizing therapists from providing care and patients from engaging in it.[97] In this way, the denigration of psychotherapy has "a chilling effect on the ethical

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[92] Cass (2024a, p. 15).
[93] E.g. Coalition for the Advancement and Application of Psychological Science (2021).
[94] Application of minority stress theory to mental health disparities in sexual minority adults was originally done in Meyer (2003). As defined in Chelliah et al. (2024), the "minority stress framework…has been used to conceptualize relationships between…mental health disparities and stressors associated with a minority identity or status." This framework, which (like all other conceptual frameworks) has its limitations (Bailey, 2020; Zucker et al., 2016), has over the past 5-10 years been widely-relied upon in the pediatric gender medicine literature (see examples in Chapter 13). Although it is important for therapists to elucidate patient experiences of bullying or hostility, it is not psychotherapeutically sound practice to make reflexive assumptions, especially when these assumptions could lead to inappropriate treatment recommendations.
[95] Churcher Clarke & Spiliadis (2019); D'Angelo et al. (2021); Lemma (2018); Sinai & Sim (2024); Spiliadis (2019).
[96] E.g. Tordoff (2022).
[97] Clayton (2023).

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psychotherapists' willingness to take on complex GD patients, which will make it much harder for GD individuals to access quality mental health care."[98]

The practice of reflexive assumption contravenes fundamental principles of the psychotherapeutic approach, which emphasizes curiosity and consideration of *all* factors that may have contributed to the patient's problems.[99] It is also challenged by research on desistance and detransition.[100]

Stephen Levine, professor of psychiatry at Case Western Reserve University, has explained how the psychotherapeutic approach includes biological, psychological and social factors to formulate GD holistically:

> [If] the evaluator understands the focus of the [mental health assessment] to be on identifying the predisposing, precipitating, and maintaining forces on the patient's identity, a long list of influences will be explored. Problems such as autism, ADHD, difficulty making friends, crises of loneliness, depression, restrictive or excess eating, sexual abuse, and feedback from virtual friends will be investigated. The [therapist] will explore suicidality, self-harm, pre- and post-trans-identity psychiatric problems, and relationships with each parent. The parents will provide a developmental history beginning with pregnancy.[101]

Psychiatrist and psychoanalyst Roberto D'Angelo, a proponent of psychotherapy for GD, describes the role of psychotherapy for minors with GD as follows:

> Psychotherapy does not impose restrictive gender stereotypes, as is sometimes claimed, but critically examines them. It empowers young people to develop creative solutions to their difficulties and promotes agency and autonomy. Importantly, an exploratory psychotherapeutic process can help to clarify whether

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[98] D'Angelo et al. (2021, p. 13).
[99] As the Cass Review noted, "a single focus on gender raises the issue of 'diagnostic overshadowing' … children [may have] more than one presenting issue, but different services … dealing with each issue in isolation, without considering how they might impact on each other" (Cass, 2024a, p. 200). See also discussion of diagnostic overshadowing in Section 13.2.4.
[100] E.g. Littman (2021).
[101] Levine (2024, p. 775).

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gender dysphoria is a carrier for other psychological or social problems that may not be immediately apparent.[102]

Given that this population often presents with complex psychosocial histories and multiple mental health concerns, psychotherapy takes a holistic approach—addressing the full range of issues rather than focusing exclusively on GD. “Transdiagnostic psychotherapy”—that is, therapy that works across or with multiple diagnoses or problems—is already a convention.[103] While there is a clear need to develop and study therapeutic approaches tailored specifically for GD, effective therapy need not always center on a single issue. Psychotherapy for adolescents with GD is a well-suited intervention, as it is intended to help patients develop self-understanding, engage with emotional vulnerability, and build practical strategies for managing distress.

Human psychology is complex and the presence of one psychiatric diagnosis often increases the likelihood of others. A transdiagnostic psychotherapeutic approach—designed to address underlying patterns across multiple conditions—may be particularly effective in reducing distress among youth with GD, as it has been in other complex cases. The goals of psychotherapy remain the same regardless of a young person’s self-identification: to alleviate distress and improve interpersonal and social functioning.

Table 14.1 below presents a brief overview of psychotherapeutic modalities that are relevant for children and adolescents with GD.

[102] D’Angelo (2023, p. 1).
[103] Jeppesen et al. (2021).

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Table 14.1

Type of psychotherapeutic modality	Definition of modality	Application to GD
Manualized approaches[104]	These approaches are performed according to manualized instructions that provide structure and standardization. The most-studied approach is cognitive behavioral therapy (CBT), which helps patients identify thoughts, feelings, and behaviors and the way they impact one another. Manualized therapies focus on development of coping skills and behavioral activation. Dialectical behavioral therapy, commonly used to address self-harm and suicidality, fosters distress-management techniques and interpersonal effectiveness. Manualized approaches typically involve several months of weekly individual or group sessions, and patients complete therapy-related assignments between sessions.	Manualized approaches are an evidence-based treatment for mental health problems that co-occur with GD, such as depression, anxiety, and eating disorders. For GD, manualized approaches can help patients identify thoughts and feelings related to sex-based distress, including cognitive distortions. Therapists can help patients develop healthy coping skills for managing this specific type of distress and can encourage behavioral activation. For example, engaging in physical activity, in-person social socialization, and/or mindfulness practices, can over time, decrease ruminations, including ruminations on sex-related discomfort.

[104] In Austin et al. (2018), mental health outcomes (including depression) improved with CBT in 8 adolescents who identified as transgender (subgroup of study population; unclear if hormonal interventions were used). Hollinsaid et al. (2020) re-analyzed data from four RCTs of standard manualized psychotherapeutic approaches, focusing on the cohort of 64 patients who had expressed desire to be the other sex (it is unclear how many would have met criteria for GD, however; additionally, there was no information about hormonal interventions). These patients' internalizing and externalizing symptoms improved, albeit more slowly than other patients. In Lucassen et al. (2021) the depression outcome measure did not change after online CBT in 14 patients who identified as transgender. In Silveri et al. (2021) mental health outcomes improved in 62 adolescents who self-identified as transgender/gender-expansive after CBT, DBT, and family therapy, integrated into a two-week long residential treatment program for psychiatric problems. In a study reporting longitudinal data on 26 adolescents (Bluth et al., 2023), mental health outcomes (including depression and suicidality) improved after eight sessions of mindfulness-based group therapy in transgender-identified patients who were not taking hormonal interventions.

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Type of psychotherapeutic modality	Definition of modality	Application to GD
Psychodynamic approach[105]	This is a psychoanalytic approach that involves exploration of ego defenses and unconscious motivations. Through exploration of transference, patients come to better understand their interpersonal dynamics. Psychodynamic psychotherapy classically involves biweekly or weekly sessions and is not time-limited.	This approach is evidence-based for mental health conditions that co-occur with GD. Additionally, psychodynamic work around the theme of cross-sex identification or sex-related distress can facilitate exploration of patients' early childhood experiences, family of origin, beliefs/values system, and interpersonal patterns in familial and romantic relationships as well as in school/work environments. This approach can help patients gain deeper understanding of their personal identity, including any external factors that may contribute to their cross-sex identification and desire for medical/surgical interventions. Patients can gain clarity about their own wishes or desires for medical or surgical transition interventions.
Family therapy[106]	This approach identifies problems affecting the patient and the family unit and aims to strengthen familial bonds and improve communication skills, by supporting work around attachment ruptures, communication and understanding different family members' perspectives. It may involve parental education and development of strategies for improved interpersonal effectiveness within the family unit.	A child or adolescent exhibiting GD may occasionally lead to intense conflict and distress within the family unit. In family-based approaches a knowledgeable therapist can provide education about GD to parents and promote well-being of the family by bolstering effective communication and interpersonal skills. Family therapy is an evidence-based approach to treating adolescent eating disorders, where familial distress and embodied distress are heightened, as in GD. Family therapy is either the first-line intervention or the treatment of choice for many diagnoses in adolescence.

14.5.2.3 Evidence for benefit

As discussed earlier, the overview of systematic reviews conducted for this Review found that evidence for the effectiveness of psychotherapy for GD (or for co-occurring mental health problems in patients with GD) is of very low certainty. When direct evidence for the role of psychotherapy in children and adolescents with GD is lacking, the best available evidence can be obtained from the robust evidence supporting

[105] For case reports, vignettes, and case series describing the incorporation of dynamic aspects into exploratory work, see Churcher Clarke & Spiliadis (2019); D'Angelo (2020); Spiliadis (2019). For descriptions of dynamic approaches, see D'Angelo (2023); Sinai & Sim (2024).
[106] For a case report of family therapy for an adolescent with suicidality, see Russon et al. (2022). See also Silveri et al. (2021) and Churcher Clarke & Spiliadis (2019). For example of parent psychoeducation, see Levine (2024).

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treatment effectiveness for children and adolescents with similar types of psychological distress. Psychotherapy is a noninvasive intervention that can be used transdiagnostically. It generally promotes improved mental health and psychosocial functioning and carries little risk.[107] As the Cass Review noted,

> the focus on the use of puberty blockers for managing gender-related distress has overshadowed the possibility that other evidence-based treatments may be more effective.[108]

[107] See also Baron & Dierckxsens (2022); Clayton (2023); Levine et al. (2022b).
[108] Cass, 2024a (p. 31).

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Limitations, Strengths, and Conclusion

Limitations

The present Review has some limitations.[1]

1. This document is not intended to serve as a clinical practice guideline and does not aim to issue treatment recommendations.[2] The Review was shaped by a distinct set of goals: namely, to clarify the evidentiary landscape; identify areas of uncertainty; and support the development of accountable care models. As such, it does not follow formal guideline development procedures, such as the use of GRADE to inform clinical recommendations. The purview of this Review is limited to evidence and best practices for the care of minors.
2. This Review does not make any specific policy recommendations regarding the regulation of medicine. For instance, it does not make policy recommendations about the treatment of children and adolescents who have already begun puberty blockers or cross-sex hormones.

Strengths

This Review also has some strengths.

1. Although not a CPG, this document provides clinicians and other decision makers with essential pieces of knowledge regarding PGM.
    a. *Quality of evidence*: This Review describes the very low-quality evidence underpinning treatment approaches in pediatric gender medicine (Chapter 5).
    b. *Risk profile of hormones and surgeries*: This Review contains an extensive description of potential or plausible harms associated with certain treatment options (namely, hormonal interventions and surgeries), some of which are significant (Chapter 7).

[1] For strengths and limitations specific to the overview of systematic reviews (SRs), see Chapter 5.
[2] This is not technically a limitation (as this Review does not purport to be a CPG), but a clarification.

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c. *Ethics review*: This Review contains an ethical assessment of the use of hormonal interventions and surgeries for treatment of GD in children and adolescents. It concludes that these interventions are inconsistent with widely endorsed principles of medical ethics (Chapter 13).

d. *Consideration of alternative treatments*: The role of psychotherapy, which has been sidelined in discussions of PGM, is one focus of this Review. This Review examines psychotherapy for GD in detail and concludes that its risk/benefit profile is favorable (Chapter 14).

2. The review of guidelines (Chapter 9) demonstrates that CPGs recommending psychotherapy for pediatric GD are higher-quality and are commensurate with evidence from PGM SRs. In contrast, CPGs recommending an approach involving standard-of-care use of PBs, CSH, or surgery are lower-quality, with recommendations that are not commensurate with evidence from SRs. CPGs followed in the U.S., in particular that of WPATH, are of the latter type and are inadequate to inform clinical practice for a vulnerable and distressed population of children and adolescents. High quality CPGs are urgently needed in this field.
3. This Review describes the enforced professional insularity of the field of pediatric gender medicine and the intense and hostile nature of the debates around PGM. Stakeholders should keep these in mind when presented with claims of medical consensus among U.S. medical organizations (Chapter 12).

Conclusion

> The delegation of authority to the medical profession rests on an implicit social contract: Doctors as a profession receive the 'privilege of self-regulation' and financial awards on the expectation that they will serve the health needs of individual patients and society.[3]

A central theme of this Review is that many U.S. medical professionals and associations have fallen short of their duty to prioritize the health interests of young patients. First,

[3] Patashnik et al. (2017, p. 10).

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there was a rapid expansion and implementation of a clinical protocol that lacked sufficient scientific and ethical justification. Second, when confronted with compelling evidence that this protocol did not deliver the health benefits it promised, and that other countries were changing their policies appropriately, U.S. medical professionals and associations failed to reconsider the “gender-affirming” approach. Third, conflicting evidence—evidence that challenged the foundational assumptions of the protocol and the professional standing of its advocates—was mischaracterized or insufficiently acknowledged. Finally, dissenting perspectives were marginalized, and those who voiced them were disparaged.

While no clinician or medical association intends to fail their patients—particularly those who are most vulnerable—the preceding chapters demonstrate that this is precisely what has occurred.

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APPENDICES

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Appendix 1. Abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
APA	American Psychological Association/American Psychiatric Association
ASD	Autism Spectrum Disorder; also ASC (Autism Spectrum Condition)
BDD	Body Dysmorphic Disorder
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and prevention
CMS	Centers for Medicare and Medicaid
COHERE	Council for Choices in Health Care (Finland)
COI	Conflict of Interest
CPG	Clinical Practice Guideline
CPP	Central Precocious Puberty
CSH	Cross-Sex Hormones
DBT	Dialectical Behavioral Therapy
DSD	Disorder (Difference) of Sex Development
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DSM-5-TR	DSM, 5th edition, Text Revision (latest version, 2024)
DSM-5	DSM, 5th edition (2013)
DSM-IV	DSM, 4th edition (1994)
DSM-III	DSM, 3rd edition (1980)
EBM	Evidence-Based Medicine
EPC	Evidence-based Practice Center (at Johns Hopkins)
ES	Endocrine Society
FAERS	FDA's Event Reporting System

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FBT	Family-Based Treatment
FDA	Food and Drug Administration
FM	Female-to-Male
FP	Fertility Preservation
FSH	Follicle-Stimulating Hormone
FT-ED	Family Therapy for Eating Disorders
GD	Gender Dysphoria (DSM-5; formerly Gender Identity Disorder (GID) in the DSM-IV)
GDG	Guideline Development Group
GeMS	Gender Multispeciality Service (at Boston Children's; formerly Gender Management Service)
GICE	Gender Identity Conversion Efforts
GIDS	Gender Identity Development Service (U.K.)
GnRHa	Gonadotropin Releasing Hormone Agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBIGDA	Harry Benjamin International Gender Dysphoria Association
HH	Hypogonadotropic Hypogonadism
HPG	Hypothalamic-Pituitary Gonadal axis
HRC	Human Rights Campaign
ICD-11	WHO's International Classification of Diseases, 11th edition (latest version, 2022)
IQ	Intelligence Quotient
ITJH	*International Journal of Transgender Health*
JAMA	*Journal of the American Medical Association*
JHU	Johns Hopkins University
LH	Luteinizing Hormone
MDC	Medical Decision-making Competence
MDT	MultiDisciplinary Teams
MF	Male-to-Female
MHP	Mental Health Professional
MMHA	Major Medical and mental Health Association

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NAM	National Academy of Medicine
NEJM	*New England Journal of Medicine*
NGCF	Netherlands Gender Care Foundation
NHS	National Health Service (U.K.)
NICE	National Institute for Health and Care Excellence (U.K.)
NIH	National Institutes of Health
NLM	National Library of Medicine
NOS	Newcastle-Ottawa Scale
OCD	Obsessive Compulsive Disorder
PBs	Puberty Blockers
PCOS	Polycystic Ovary Syndrome
PDT	PsychoDynamic Therapy
PGM	Pediatric Gender Medicine
PICO	Population, Intervention, Comparator, Outcome
PMT	Pediatric Medical Transition
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RoB 2	Cochrane Risk-of-Bias tool
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
ROBIS	Risk of Bias In Systematic reviews
ROGD	Rapid-Onset Gender Dysphoria
RSG	Review of Data, Statistics and Research on Sex and Gender (U.K., 2025)
SAMHSA	Substance Abuse and Mental Health Services Administration
SOC-8	*Standards of Care for the Health of Transgender and Gender Diverse People*, Version 8 (latest version, 2022)
SOC-7	*Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, Version 7 (2012)
SOC-6	*Standards of Care for Gender Identity Disorders*, Version 6 (2001)
SR	Systematic Review
SRS	Sex Reassignment Surgery
SSRI	Selective Serotonin Reuptake Inhibitor

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TGD	Transgender and Gender Diverse
UCSF	University of California, San Francisco
USPATH	United States Professional Association for Transgender Health
USTS	US Transgender Survey
WHO	World Health Organization
WPATH	World Professional Association for Transgender Health

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Appendix 2. Diagnostic Criteria

DSM-III (1980)[1]

Diagnostic criteria for Transsexualism

A. Sense of discomfort and inappropriateness about one's anatomic sex.

B. Wish to be rid of one's own genitals and to live as a member of the other sex.

C. The disturbance has been continuous (not limited to periods of stress) for at least two years.

D. Absence of physical intersex or genetic abnormality.

E. Not due to another mental disorder, such as Schizophrenia.

Diagnostic criteria for Gender Identity Disorder of Childhood

For females:

A. Strongly and persistently stated desire to be a boy, or insistence that she is a boy (not merely a desire for any perceived cultural advantages from being a boy).

B. Persistent repudiation of female anatomic structures, as manifested by at least one of the following repeated assertions:

(1) that she will grow up to become a man (not merely in role)

(2) that she is biologically unable to become pregnant

(3) that she will not develop breasts

(4) that she has no vagina

(5) that she has, or will grow, a penis

C. Onset of the disturbance before puberty.

For males:

[1] American Psychiatric Association (1980, pp. 261-266).

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A. Strongly and persistently stated desire to be a girl, or insistence that he is a girl.

B. Either (1) or (2):

(1) persistent repudiation of male anatomic structures, as manifested by at least one of the following repeated assertions:

(a) that he will grow up to become a woman, (not merely in role)

(b) that his penis or testes are disgusting or will disappear

(c) that it would be better not to have a penis or testes

(2) preoccupation with female stereotypical activities as manifested by a preference for either cross-dressing or simulating female attire, or by a compelling desire to participate in the games and pastimes of girls

C. Onset of the disturbance before puberty.

DSM-IV (1994)[2]

Diagnostic criteria for Gender Identity Disorder

A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex). In children, the disturbance is manifested by four (or more) of the following:

(1) repeatedly stated desire to be, or insistence that he or she is, the other sex

(2) in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing

(3) strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex

[2] American Psychiatric Association (1994, pp. 537-538).

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(4) intense desire to participate in the stereotypical games and pastimes of the other sex

(5) strong preference for playmates of the other sex

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.

B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.

In children, the disturbance is manifested by any of the following: in boys, assertion that his penis or testes are disgusting or will disappear or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, or assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.

In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.

C. The disturbance is not concurrent with a physical intersex condition.

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

DSM-5 (2013)[3]

Gender Dysphoria

[3] American Psychiatric Association (2013, pp. 452-453).

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Diagnostic Criteria

Gender Dysphoria in Children

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).

2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire: or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.

3. A strong preference for cross-gender roles in make-believe play or fantasy play.

4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.

5. A strong preference for playmates of the other gender.

6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.

7. A strong dislike of one's sexual anatomy.

8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

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Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).

2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).

3. A strong desire for the primary and/or secondary sex characteristics of the other gender.

4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).

5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).

6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning.

ICD-11 (2022)[4]

Gender incongruence of adolescence or adulthood

[4] World Health Organization (2022b).

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Gender Incongruence of Adolescence and Adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.

Gender incongruence of childhood

Gender incongruence of childhood is characterized by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.

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Appendix 3. Systematic Reviews and Evidence-Based Medicine

Imagine a courtroom where guilt or innocence is decided solely by the police, drawing on their extensive experience of investigating crime. Someone can be convicted of murder, say, on the verdict of these criminal experts, who have seen many murders before, and who have firm opinions about the sort of people most likely to commit them.

Such a courtroom would be better than nothing. The police have relevant knowledge and experience and are not simply guessing. But it would be far inferior to a real courtroom, where police testimony is just part of the evidence brought before judge and jury: the blood-stained knife, fingerprints, cellphone records, eyewitness testimony, and so on, are all included. Moreover, every piece of evidence is critically examined, weighed, and compared. The attitude is more scientific. Not all evidence is equal: eyewitness testimony can be unreliable, whereas properly collected DNA evidence is of high quality. Independent pieces of evidence (DNA, cellphone records) can point to the same conclusion, making the verdict more secure. Of course, the process is imperfect, but it's a vast improvement over simply relying on the opinions of police officers.

Medicine used to be more like the first (hypothetical) courtroom than the second:

> Clinical practice was historically viewed as the "art of medicine." Expert opinion, experience, and authoritarian judgment were the foundation for decision making. The use of scientific methodology, as in biomedical research, and statistical analysis, as in epidemiology, were rare in the world of medicine.[1]

Starting in the 1970s, evidence-based medicine (EBM) has attempted to move medicine from the first courtroom to the second, towards more empirical rigor.

EBM "is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[2] The fundamental EBM principle is that clinical practice and practice guidelines should be based on the totality of evidence,

[1] Sur & Dahm (2011, p. 487).
[2] Sackett et al. (1996, p. 71).

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assessed and synthesized in clear and reproducible ways from the medical literature. EBM contrasts with "eminence-based medicine," in which physicians make clinical decisions based on personal experience and expertise, and treatment guidelines themselves are created using a process humorously described as "GOBSAT" ("good old boys sitting around a table").[3]

It is important to emphasize that EBM does not say that evidence about treatments should be the *only* factor in medical decisions. Quite the opposite. According to the American Medical Association's (AMA) *User's Guides to Medical Literature: Essentials of Evidence-Based Clinical Practice*:

> [E]vidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits and risks, burden, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and values and preferences.[4]

Evidence is never sufficient to make health policy either, although policy makers have different priorities than clinicians. A clinician's primary concern is for the individual patient and their "unique predicament"; policy makers need to set general rules and standards with public health in mind. They may consider the cost-effectiveness of treatment, public values and preferences, the feasibility of widely offering the treatment, how its benefits can be distributed fairly, and so forth.

EBM uses a "hierarchy of evidence," often depicted as pyramid with colored layers, as in Figure A.1. Since the layers represent different types of study, the hierarchy is more strictly a hierarchy of *research methods* than a hierarchy of evidence. The pyramid in Figure A.1 should not be taken too seriously: many pyramids have been proposed, with varying numbers of layers and kinds of labels, not to mention colors.[5] In fact, the AMA's

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[3] Lima, Tangamornsuksan et al. (2023, p. 1).
[4] Guyatt et al. (2015, p. 10, emphasis omitted). "Burden [of treatment]" means "the inconvenience of attending to the treatment's optimal use, of its monitoring, the limitations in lifestyle that it entails, and the possibility of interactions with other treatments" (p. 426). "Values and preferences" refer to "the collection of goals, expectations, predispositions, and beliefs that individuals have for certain decisions and their potential outcomes. The incorporation of patient values and preferences in decision making is central to evidence-based medicine" (p. 490).
[5] Blunt (2022). For another pyramid, see Cass (2024a, p. 55).

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User's Guides to Medical Literature contains no such illustration.[6] But the basic point these pyramids make is sound: some ways of gathering evidence about the effects of a treatment are better than others. Systematic reviews (SRs, to be explained below) and meta-analyses are better than randomized controlled trials (RCTs), which are better than cohort studies and case reports,[7] with expert opinion coming in last. The medical consensus based on expert opinion or experience has been shown to be wrong many times before, after rigorous experimental studies were conducted. (See Section 1.2.2.)

EBM prioritizes findings from population-level research, such as RCTs and observational epidemiological studies. This can have drawbacks, sometimes resulting in insufficient consideration of biochemical or physiological evidence from laboratory, animal, or in vitro studies.[8]

In the last few decades EBM has been refined and improved. This appendix includes a brief introduction to SRs, the methodology to systematically identify, synthesize, and assess the best available evidence, and to Grading of Recommendations Assessment, Development, and Evaluations (GRADE), the methodology to assess the quality of evidence and determine the strength of recommendations.

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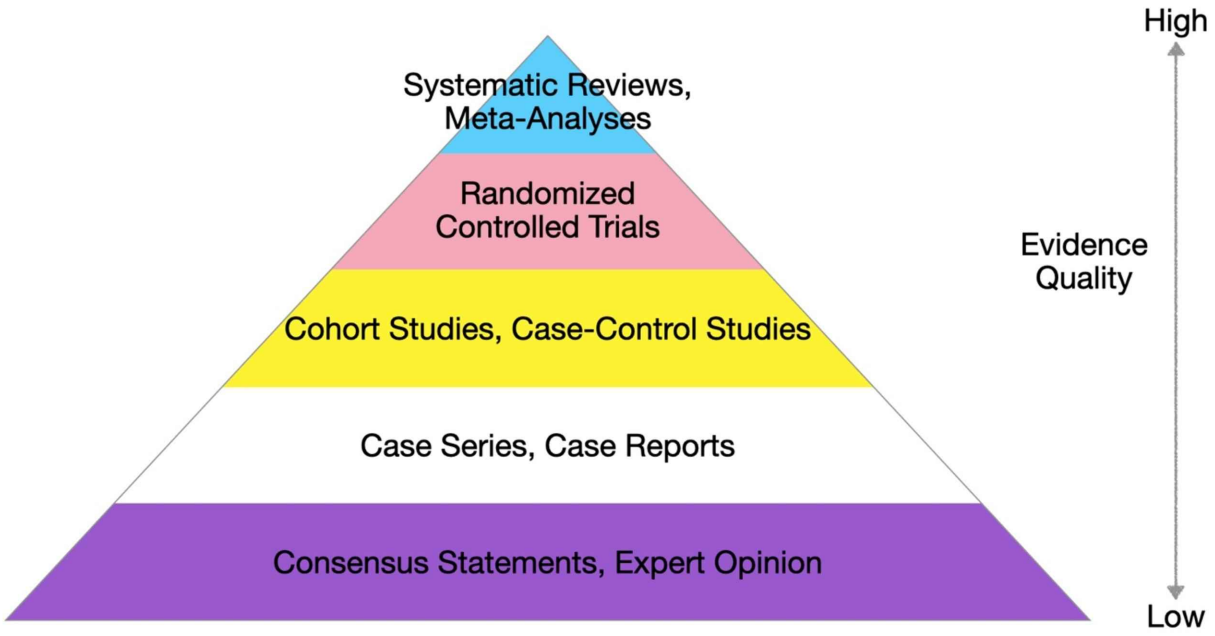
[6] See Guyatt et al. (2015, p. 48, Figure 4-1), which displays a simple three-level hierarchy of evidence in a blue box.

[7] A *meta-analysis* combines data from separate similar studies and statistically analyses the result. Two studies may investigate the same treatment in sufficiently different ways so that a meta-analysis of both is not possible. SRs may involve meta-analyses but need not. A *randomized controlled trial* (RCT) allocates treatment/non-treatment randomly to a group (*cohort*) of patients and follows them over time; the no-treatment group is the *control* group. Control groups may receive another kind of treatment, a *placebo* (an inert pill or procedure that superficially mimics the treatment), or no treatment at all. In a *double-blind* RCT neither the patients nor the attending medical staff know who is in the treatment group and who is in the control group. *Cohort studies* (or *longitudinal* studies) examine groups of patients over time, either *prospectively* (data collected as the study proceeds) or *retrospectively* (the data has already been collected, say in past medical records); there is no randomization to treatment/non-treatment as in an RCT. A *case-control* study starts with two groups, those who have the disease or condition of interest (the *cases*), and those who don't (the *controls*), and examines them retrospectively. The latter two kinds of study are called *observational*, to contrast them with RCTs. A *case report* describes a single patient's treatment and outcome; a *case series* is a collection of similar case reports.

[8] Clarke et al. (2014).

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Figure A1.1 Example EBM Pyramid



1. Systematic reviews

Systematic reviews (SRs) synthesize evidence from multiple studies in the medical literature and assess its quality, using a standard and reproducible methodology. The general steps are outlined below:[9]

Research questions and study eligibility criteria

SRs begin by asking four questions. What is the population being studied? What is the intervention or treatment? What groups are being compared to the group that received the treatment? What results or outcomes are of interest? This is the "PICO" framework: Population, Intervention, Comparator, Outcome. Study eligibility criteria are defined accordingly and documented.

Comprehensive search

Having defined the eligibility criteria for studies, the next step is to locate them. A properly conducted search requires expertise, and includes searching a variety of

[9] What follows is simplified; for more detail see Higgins et al. (2019).

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medical databases, for instance Embase (produced by the publisher Elsevier) and Medline (produced by the U.S. National Library of Medicine (NLM)). The search could also cover registries of clinical trials and so-called grey literature (material outside academic publishing, such as reports and government documents).

Study selection

Reviewers then screen the search results, looking at a study's title and abstract, and then its full text to determine if the study is eligible to be included in the SR. This study selection process follows the pre-defined eligibility criteria. To minimize the risk of bias in the review process, independent duplicate screening may be applied in both the stage of title and abstract screening, and the stage of full text screening.

Data extraction and effect estimate computation

The reviewers extract all relevant data from the studies. The procedure is standardized, and the same kind of data is extracted from all studies. Most of this is in the methods and results sections of the study (and the supplementary material). Depending on the data, there are various ways of measuring the effect of an intervention; the extracted data may need to be converted to a consistent format so the treatment effect estimates reported across eligible studies can be combined as a pooled effect estimate.

Risk of bias assessment

Bias is "systematic error, or deviation from the truth, in results. Biases can lead to under-estimation or over-estimation of the true intervention effect and can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be due entirely to bias)."[10] Two or more independent reviewers assess the risk of bias of each study, using appropriate tools. One major consideration for choosing a risk of bias tool is the type of study design. For example, Version 2 of the Cochrane Risk-of-Bias tool for randomized trials (RoB 2) is the recommended tool to assess the risk of bias in randomized trials included in

[10] Higgins et al. (2019, pp. 177-178). Note that "biased" here does not mean *prejudiced*. Fair and impartial researchers may produce a "biased" study in the sense relevant to this Appendix.

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Cochrane Reviews, while Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) is the recommended tool to assess the risk of bias in non-randomized studies.

Data synthesis and analysis

One key step for SRs is evidence synthesis, which means the results from the different studies are synthesized or combined. Meta-analyses of effect estimates, the quantitative synthesis strategy, may be performed, as well as sensitivity analyses (which examine whether the results would change if different statistical assumptions were made, if outcomes were defined slightly differently, and so on). If a meta-analysis is not feasible, other ways of synthesizing the results are available. A narrative that describes results study by study is not acceptable.[11]

Quality of evidence assessment

The quality of the evidence is now evaluated using, e.g., the methodological framework Grading of Recommendations Assessment, Development, and Evaluations (GRADE) (explained in the following section).

Discussion and conclusion

The discussion section of the SR includes: "Summary of main results (benefits and harms); potential biases in the review process; overall completeness and applicability of evidence; certainty of the evidence; agreements and disagreements with other studies or reviews."[12] The conclusions section considers the implications for clinical practice and for research.

High-quality SRs organize their PICO information, search strategy, methodologies, and findings according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, which facilitates completeness, accuracy, transparency,

[11] McKenzie & Brennan (2024).
[12] Higgins et al. (2019, p. 404, quotation marks and capitalization omitted).

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and replicability.[13] Registering the protocol for a SR in a system such as PROSPERO increases transparency and trustworthiness of an SR.

2. GRADE

Grading of Recommendations Assessment, Development, and Evaluations (GRADE) is a widely adopted framework for assessing the quality (or "certainty") of the evidence and strength of recommendations.[14] GRADE uses four tiers to classify quality:

> *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
>
> *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
>
> *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
>
> *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.[15]

There is frequent confusion about the relationship between GRADE and tools that assess individual studies for risk of bias such as RoB 2 and ROBINS-I. When assessing risk of bias, the reviewers are assessing individual studies. When SR authors assess the quality or certainty of evidence with GRADE, they are assessing the total body of evidence. They ask: How confident should we be in the effect estimate (e.g., the estimate of average mortality, level of depression, degree of disease progression), given the evidence derived from all the included studies? GRADE does consider risk of bias in the individual studies that yielded the estimate, but that is just one of five factors that can downgrade the quality of the evidence. The other four are *inconsistency* (how consistent the results are across all the studies reporting on the same outcome);

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[13] Page et al. (2021). See also Santesso et al. (2020).
[14] However, because GRADE "has become increasingly complex, such that new as well as existing users may find it unwieldy," a simplified and slightly revised version has recently been proposed, "Core GRADE" (Guyatt et al., 2025).
[15] Balshem et al. (2011, Table 2). See also M. Prasad (2024, p. 2).

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indirectness (how applicable the evidence is to the PICO in question); *imprecision* (whether the sample is too small or confidence intervals[16] surrounding the estimates too wide), and *publication bias* (e.g. whether studies with negative results have not been published).[17] Evidence quality can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors would likely reduce the observed effect but did not.

GRADE not only provides guidance on assessing the quality of evidence, but guidance on recommending treatments. Key determinants for the strength of recommendations include the balance between benefits and harms of the alternative treatments, the certainty of evidence, values and preferences, and cost and resource allocation. Values and preferences of patients are a major consideration, especially when the certainty of evidence is low or very low.

In GRADE, there is an "explicit separation of the process for assessing the quality of a body of evidence from the process for making recommendations based in part on those assessments. Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not imply a particular strength of recommendation. Sometimes, low or very low-quality evidence can lead to a strong recommendation."[18] For example, a low-cost safe treatment supported by low-quality evidence could lead to a strong recommendation if the potential benefits are large and there is no alternative. Conversely, a treatment might be supported by high quality evidence and yet not be strongly recommended, because it has side effects that some patients would not be willing to accept.

A treatment might be potentially promising but have harmful side effects with only weak evidence of benefit. In such cases a recommendation for "treatment-only-in-research" may be given under the following conditions:

[16] A confidence interval is a range of effect values and is used to quantify uncertainty about effect estimates.
[17] Higgins et al. (2019, Table 2-1).
[18] Balshem et al. (2011, p. 402).

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> [T]here is insufficient evidence supporting an intervention for a panel to recommend its use; further research has a large potential for reducing uncertainty about the effects of the intervention; and further research is deemed good value for the anticipated costs.[19]

3. Overviews of reviews

Overviews of reviews, or "umbrella reviews," such as the one performed to systematically assess the clinical evidence for this Review, use a similar methodology to SRs to evaluate SRs themselves. Overviews employ explicit and systematic methods to identify and analyze multiple systematic reviews that address related research questions within a common topic area, with the goal of synthesizing results across key outcomes.[20] This approach is particularly useful when multiple systematic reviews exist on overlapping or related research questions within the same topic area, or when stakeholders need a high-level synthesis to inform clinical, policy, or public health decision-making. Like SRs, overviews use GRADE or related tools and standardized reporting practices.

The process of an overview follows these steps:

1. Systematically search for all SRs addressing the relevant PICOs.

2. Identify and include the eligible SRs

3. Extract information about the estimated treatment effects, and assess each SR for risk of bias using the tool such as "Risk of Bias In Systematic reviews" (ROBIS)

4. Collect, analyze, and present the data from included systematic reviews, including characteristics of the SRs and their included primary studies; risk of bias of included primary studies; outcome data; and certainty of evidence for pre-defined, clinically important outcomes. Specifically, for each outcome of interest, reviewers summarize the information about treatment estimates from the SRs.

[19] J. Andrews et al. (2013, p. 724).
[20] Pollock et al. (2024).

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To assess the certainty of evidence, reviewers may opt to summarize and report the original GRADE ratings reported by the SRs in the included systematic reviews. However, reviewers may need to re-analyze outcome data from systematic reviews or conduct GRADE assessments themselves using the information reported in the SRs, for example, when the SRs do not include GRADE assessment, or when there is disagreement across included SRs.

Performing a new SR is preferred when there is a lack of recent SRs or when existing SRs are limited in quality; but if the literature contains several recent high-quality SRs the overview is an approved option.[21]

4. Other types of reviews

Not every medical publication with "review" in its title is an SR or an overview of SRs. Such publications can be useful but are not systematic and reproducible syntheses of evidence. Other types of reviews include:

Narrative reviews

Also called *literature reviews*, a narrative review is "a review article (such as a typical book chapter) that is not conducted using methods to minimize bias (in contrast to a systematic review)."[22] For this reason, narrative reviews must be treated with caution, although they can be helpful as an introduction to a research topic.

Scoping reviews

The purpose of a scoping review is to survey the available research on a specific topic. Scoping reviews are systematic and reproducible like SRs but are usually not as rigorous. The aim of a scoping review is to survey existing research and suggest areas for future study, not to assess the evidence for a particular intervention.[23]

[21] Pollock et al. (2024).
[22] Guyatt et al. (2015, p. 461).
[23] Tricco et al. (2016).

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Appendix 4. Overview of Systematic Reviews: Methodology, Evidence Synthesis, Tables

This Appendix is published separately.

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Overview of Systematic Reviews

Methodology, Evidence Synthesis, Tables

Appendix 4:

Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices

Department of Health and Human Services

May 1, 2025



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Minor corrections made May 15, 2025: see Errata

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1 Methodology

The methodology of this overview followed the recommendations for an overview of systematic reviews (SRs) in the *Cochrane Handbook for Systematic Reviews of Interventions*.[1]

Literature search: Medline, Embase, and the psychological database PsycINFO were searched for potentially eligible records. The search strategy included terms related to SRs ("systematic review," "meta-analysis," etc.) and others related to gender dysphoria ("gender incongruence," "gender-affirming hormones," "puberty blockers," etc.), using Boolean operators AND and OR as appropriate. The search was limited to items from 2015 to Feb 20, 2025. A complementary literature search was conducted in other databases including ACCESSSS (a service providing current evidence for clinical decisions) and Epistemonikos (a database of SRs), and grey literature search was conducted through the systematic review registry PROSPERO and Google Scholar, as well as a manual search of reference lists of eligible SRs. Box 1.1. provides an example of search strategies used in Medline.

Literature screening: After the removal of duplicate records, two reviewers reviewed titles and abstracts and independently determined study eligibility. Once potentially eligible records were identified, a thorough review of full-text articles with a standardized and piloted screening form was performed. Reviewers resolved disagreement by discussion.

A record was included if it met the following criteria:

1. It is an SR.
2. The study population is youth with GD whose age is below 26 years old.[2]

[1] Higgins et al. (2019).
[2] Empirically, SRs in this area are usually provided for patients under 18 or those under 26. This decision of age below 26 years balances the comprehensiveness and the directness (applicability) of the evidence review. Though there is a concern regarding the directness of evidence, the evidence for <18 and for <26 years did not identify any significant differences in outcomes.

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3. The study assesses at least one of the following: social transition, psychotherapy, puberty blockers (PBs), cross-sex hormones (CSH), or surgery.

The exclusion criteria were the following:

1. Comingling of mature adult (≥ 26 years old) and youth, which means systematic reviews with more than 25% of included studies on mature adults were excluded because these reviews were not applicable (too indirect) to inform the outcomes on youths.[3]
2. Overlapping efforts.

Data extraction and appraisal of included reviews: Data extracted included review authors, research team, and research question answered; number and characteristics of included studies; study population; treatment; outcomes of interest; analysis and synthesis strategy; risk of bias assessment used for included studies.

The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) tool[4] was used to assess the risk of bias for included SRs. The data extraction and risk of bias assessment was completed by one reviewer and checked by a second reviewer. ROBIS assesses the quality of the systematic review according to four domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis of findings. Additionally, ROBIS assesses the overall risk of bias in a systematic review process and SRs with concerns identified in the four domains can still be assessed at low risk of bias if the SRs have properly addressed these concerns in the evidence interpretation.

Evidence synthesis and certainty of evidence: The evidence synthesis summarizes the outcome data across SRs that were published in English and classified at low risk of bias.[5] The evidence synthesis was organized by types of treatment, and the outcomes

[3] The SRs including both >26 years old and <26 years old skew toward the >26 population, and so are less directly applicable to this overview than SRs on youth with GD.
[4] Whiting et al. (2016).
[5] One non-English systematic review was considered eligible and included and classified at low risk of bias. This overview did not summarize the results by outcomes from this review. Nevertheless, its conclusions were similar.

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of interest included GD, mental health and well-being, treatment goal (for example, puberty suppression for puberty blockers), need for or progression to further treatment, safety outcomes including side effects and adverse outcomes, and regret. For each outcome, this overview summarized the effect estimates and the certainty of evidence (confidence in the effect estimates, the quality of evidence).

The certainty of evidence was summarized following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[6] In GRADE, certainty of evidence can be downgraded for: risk of bias (study limitations), inconsistency (unexplained variation in results), indirectness (evidence not directly applicable), imprecision (wide confidence intervals or small samples), and publication bias (selective reporting).[7] Evidence can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors expected to reduce the observed effect did not do so.[8] Evidence could be classified into four levels of certainty: high, moderate, low, or very low.[9] This overview summarized the GRADE rating from the original review for the respective outcome wherever it is available. Nevertheless, there were two modifications made:

1. Where a formal GRADE appraisal had not been performed by the systematic review, but expressions such as “we are very uncertain” and “no conclusions could be drawn” were used in SRs’ conclusions, these statements were considered equivalent to a “very low quality” GRADE assessment.[10]

[6] In GRADE, quality of evidence is equivalent to certainty of evidence. “The quality of evidence is very low” is equivalent to “the certainty of evidence is very low.” See Guyatt et al. (2008), Balshem et al. (2011).
[7] Balshem et al. (2011); Guyatt et al. (2008); Guyatt, Oxman, Kunz, Brozek, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al. (2011); Guyatt, Oxman, Montori, et al. (2011); Guyatt, Oxman, Vist, et al. (2011).
[8] Guyatt, Oxman, Sultan, et al. (2011).
[9] According to GRADE, high certainty evidence means that “we are very confident that the true effect lies close to that of the estimate of the effect” and very low certainty evidence indicates that “we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect” (Balshem et al., 2011).
[10] Balshem et al. (2011); Santesso et al. (2020).

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2. If SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale for the assessment.

Box 1.1 Search strategy in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations 1996 to Feb 20, 2025

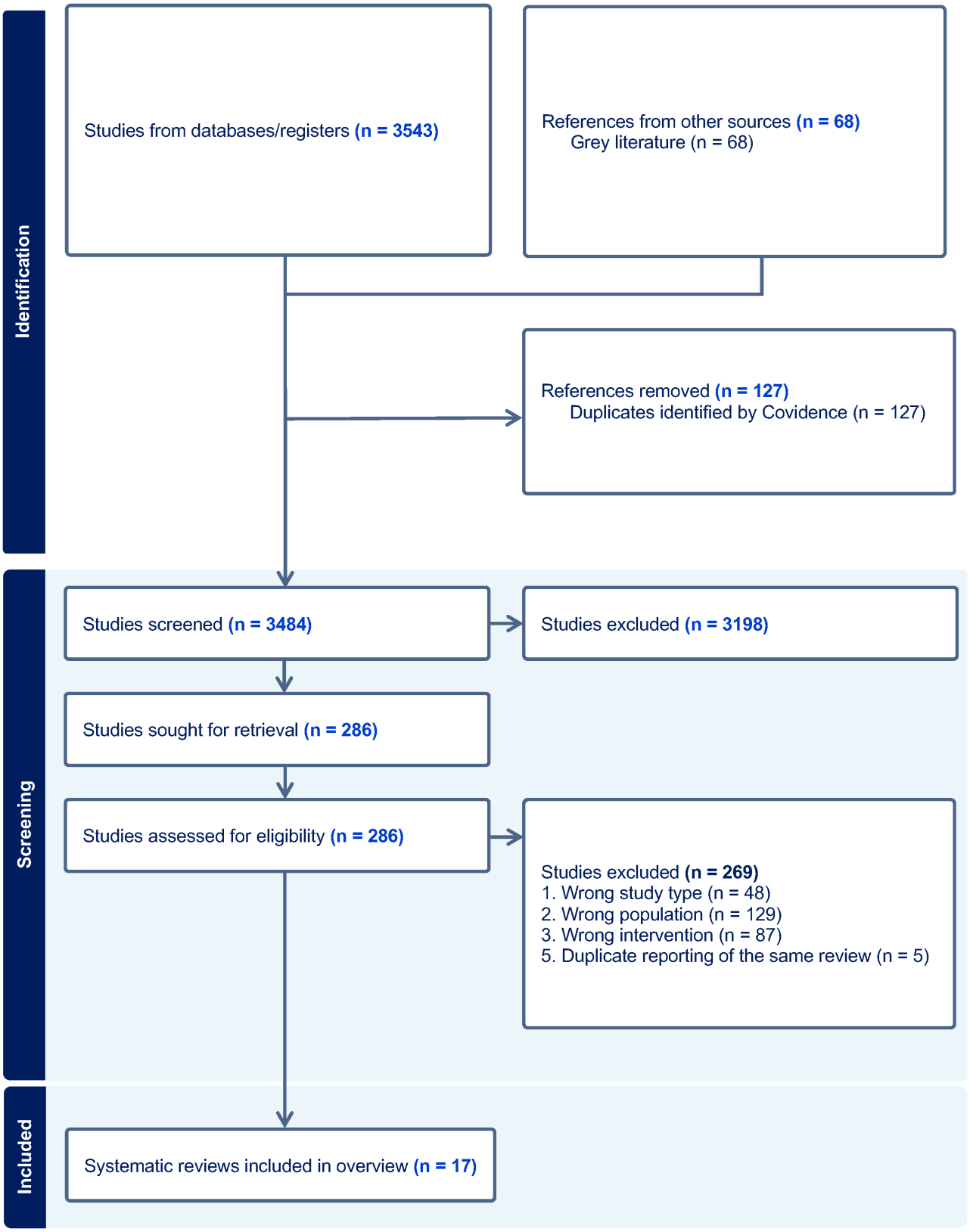
1	exp "Sexual and Gender Minorities"/
2	Gender Dysphoria/
3	Gender Identity/
4	Gender Role/
5	"Sexual and Gender Disorders"/
6	Transsexualism/
7	Transgender Persons/
8	Health Services for Transgender Persons/
9	exp Sex Reassignment Procedures/
10	gender identity disorder.mp.
11	non-binary.mp.
12	transgender.mp.
13	(gender* adj3 (dysphori* or disorder* or distress or nonconform* or non-conform* or atypical or incongru* or identi* or disorder* or confus* or minorit* or queer* or variant or diverse or creative or explor* or question* or expan* or fluid)).tw.
14	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
15	(transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw.
16	(genderfluid or genderqueer or agender).mp.
17	((correct or chosen) adj3 name).mp.
18	(trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
19	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
20	(male-to-female or m2f or female-to-male or f2m).tw.
21	or/1-20
22	exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/
23	Minors/
24	(child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn.
25	(young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn.
26	pediatrics/
27	(pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn.
28	Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/
29	Puberty/
30	(adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn.
31	Schools/ or Schools, Nursery/
32	exp Child Day Care Centers/ or Child Care/

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33	(school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	systematic review/
36	meta-analysis/
37	(meta anal* or meta-anal* or metaanal*).ti,ab.
38	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
39	((pool* or combined) adj2 (data or trials or studies or results)).ab.
40	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41	(search* adj4 literature).ab.
42	or/35-41
43	21 and 34 and 42

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Figure 1.1 Searching, screening, and inclusion process



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2 Literature screening results

Following the removal of duplicates, 3,484 records were screened by title and abstract. Of these, 286 full-text articles were assessed for eligibility. A total of 269 full-text articles were excluded for the following reasons: 48 were not SRs (incorrect study type), 129 did not focus on children or adolescents with GD, 87 did not address the treatment of interest, and 5 were excluded due to duplicate reporting (See Figure 1.1). After screening, 17 SRs met the inclusion criteria, examining the effects of psychotherapy (n = 5),[11] social transition (n = 2),[12] PBs (n = 9),[13] CSH (n = 8),[14] and surgeries (n = 3)[15] among children or adolescents with GD.

2.1 Risk of bias assessment in included SRs

Of the 17 included SRs, ten were rated as having a low risk of bias (see Table 2.1).[16]

The low risk of bias SRs could be organized into five groups:

1. The SRs by scholars from McMaster University in Canada on PBs (Miroshnychenko 2025a[17]), CSH (Miroshnychenko 2025b[18]), and mastectomy (Miroshnychenko 2024[19]).

[11] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[12] Dopp et al. (2024); Hall et al. (2024).
[13] Chew et al. (2018); Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Ramos et al. (2021); Rew et al. (2021); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[14] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[15] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[16] Dopp et al. (2024); Hall et al. (2024); Heathcote et al. (2024); Ludvigsson et al. (2023); Miroshnychenko et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024); Zepf et al. (2024).
[17] Miroshnychenko, Roldan, et al. (2025).
[18] Miroshnychenko, Ibrahim, et al. (2025).
[19] Miroshnychenko et al. (2024).

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2. The SRs conducted by scholars from University of York to inform the Cass Review, comprising the reviews of PBs (Taylor 2024a[20]), CSH (Taylor 2024b[21]), psychotherapy (Heathcote 2024[22]), and social transition (Hall 2024[23]).
3. The systematic review by researchers from Rand Corporation on all treatment strategies (Dopp 2024[24]).
4. The systematic review by Swedish Agency for Health Technology Assessment and Assessment of Social Services on hormone therapies (Ludvigsson 2023[25]).
5. The systematic review by Zepf et al., which was an update and followed the same methodology of the two SRs published in German.

SRs within each group generally followed the same methodological approach. The three SRs by McMaster University scored as having a low risk of bias across all four domains, as well as low risk of bias overall.[26] Other SRs rated at low risk of bias had limitations in one or more domains. For instance, though published in 2024, the literature search for the University of York SRs was conducted in April 2022. Additionally, there were concerns regarding the risk of bias assessment. Though the Newcastle-Ottawa Scale is an appropriate tool for the study types included in the systematic reviews, the high quality studies (for example, high quality cross-sectional or retrospective studies) are not adequate to provide high certainty evidence on the treatment effect.[27] While narrative descriptors such as “very uncertain” and “no conclusions can be drawn” correspond to the rating of “low/very low certainty” using GRADE, no formal GRADE assessment was performed. The Dopp et al. (2024)[28] review had limitations in the domain of study eligibility criteria as it included case reports and qualitative studies for

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[20] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[21] Taylor, Mitchell, Hall, Langton, et al. (2024).
[22] Heathcote et al. (2024).
[23] Hall et al. (2024).
[24] Dopp et al. (2024).
[25] Ludvigsson et al. (2023).
[26] Hall et al. (2024); Heathcote et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).
[27] van der Miesen 2020 was the only high-quality study in the systematic review on PBs, though it is a cross-sectional study and not adequate to assess treatment effect. Jensen 2019 was assessed as the only high-quality study in the systematic review on CSH, and it was a retrospective chart review and only reported side-effects, not treatment effects.
[28] Dopp et al. (2024).

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estimating treatment effects, and in the domain of identification and selection of studies was limited by searching in only one database.

A total of seven SRs[29] were rated at high risk of bias overall, often due to limited or poorly defined research questions and eligibility criteria, lack of risk of bias assessments, and inadequate synthesis of findings. This appendix includes a detailed summary of study characteristics and risk of bias considerations for all included SRs. The variation in methodological rigor highlights the need for cautious interpretation of findings, especially from reviews rated at high risk of bias.

[29] Chew et al. (2018); Expósito-Campos et al. (2023); Karalexi et al. (2020); Malpas et al. (2022); Ramos et al. (2021); Rew et al. (2021); Thompson et al. (2023).

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Table 2.1. Scope of included SRs

Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Chew 2018[30]	Y	Y				High risk of bias	Low risk of bias	High risk of bias	High risk of bias	High risk of bias
Dopp 2024[31]	Y	Y	Y	Y	Y	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Expósito-Campos 2023[32]				Y		High risk of bias	High risk of bias	Low risk of bias	High risk of bias	High risk of bias
Hall 2024[33]					Y	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Heathcote 2024[34]				Y		Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Karalexi 2020[35]		Y				High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Ludvigsson 2023[36]	Y	Y				Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	**Low risk of bias**

[30] Chew et al. (2018).
[31] Dopp et al. (2024).
[32] Expósito-Campos et al. (2023).
[33] Hall et al. (2024).
[34] Heathcote et al. (2024).
[35] Karalexi et al. (2020).
[36] Ludvigsson et al. (2023).

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Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Malpas 2022[37]				Y		High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Miroshnychenko 2025a[38]	Y					Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2025b[39]		Y				Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2024[40]			Y			Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Ramos 2021[41]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Rew 2021[42]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Taylor 2024a[43]	Y					Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**

[37] Malpas et al. (2022).
[38] Miroshnychenko, Roldan, et al. (2025).
[39] Miroshnychenko, Ibrahim, et al. (2025).
[40] Miroshnychenko et al. (2024).
[41] Ramos et al. (2021).
[42] Rew et al. (2021).
[43] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Taylor 2024b[44]		Y				Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Thompson 2023[45]	Y	Y	Y	Y		Low risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Zepf 2024[46]	Y	Y				Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	**Low risk of bias**

[44] Taylor, Mitchell, Hall, Langton, et al. (2024).
[45] Thompson et al. (2023).
[46] Zepf et al. (2024).

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2.2 Excluded SRs

Box 2.1 provides examples of excluded SRs due to focusing on a mixed population, or interventions not relevant to this overview.

Box 2.1 Examples of excluded SRs

SRs that were a mixed population (with more than 25% included studies on mature adults):

Baker 2021

Baker, K. E., Wilson, L. M., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2021). Hormone therapy, mental health, and quality of life among transgender people: A systematic review. Journal of the Endocrine Society, 5(4), 1-16.

Doyle 2023

Doyle, D. M., Lewis, T. O. G., & Barreto, M. (2023). A systematic review of psychosocial functioning changes after gender-affirming hormone therapy among transgender people. Nature Human Behaviour.

Dunford 2021

Dunford, C., Bell, K., & Rashid, T. (2021). Genital reconstructive surgery in male to female transgender patients: A systematic review of primary surgical techniques, complication profiles, and functional outcomes from 1950 to present day. European Urology Focus, 7(2), 464-471.

Haupt 2020

Haupt, C., Henke, M., Kutschmar, A., Hauser, B., Baldinger, S., Saenz, S. R., . . . Schreiber, G. (2020). Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. Cochrane Database of Systematic Reviews(11).

Javier 2022

Javier, C., Crimston, C. R., & Barlow, F. K. (2022). Surgical satisfaction and quality of life outcomes reported by transgender men and women at least one year post

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gender-affirming surgery: A systematic literature review. International Journal of Transgender Health, 23(3), 255-273.

Kloer 2021

Kloer, C., Parker, A., Blasdel, G., Kaplan, S., Zhao, L., & Bluebond-Langner, R. (2021). Sexual health after vaginoplasty: A systematic review. Andrology, andr.13022.

Kotamari 2021

Kotamarti, V. S., Greige, N., Heiman, A. J., Patel, A., & Ricci, J. A. (2021). Risk for venous thromboembolism in transgender patients undergoing cross-sex hormone treatment: A systematic review. The Journal of Sexual Medicine, 18(7), 1280-1291.

Thornton 2024

Thornton, S. M., Edalatpour, A., & Gast, K. M. (2024). A systematic review of patient regret after surgery- a common phenomenon in many specialties but rare within gender-affirmation surgery. The American Journal of Surgery.

van Leerdam 2021

van Leerdam, T. R., Zajac, J. D., & Cheung, A. S. (2021). The effect of gender-affirming hormones on gender dysphoria, quality of life, and psychological functioning in transgender individuals: A systematic review. Transgender Health, trgh.2020.0094.

Wilson 2020

Wilson, L. M., Baker, K. E., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2020). Effects of antiandrogens on prolactin levels among transgender women on estrogen therapy: A systematic review. *International journal of transgender health*, *21*(4), 391–402.

SRs that were not on the interventions of interest:

Diana 2024

Diana, P., Belluzzi, B., Corona, F., Barbi, E., & Tornese, G. (2024). Nonmedical gender-affirming practices in transgender and gender diverse adolescents: A narrative review. Transgender Health.

di Giacomo 2018

di Giacomo, E., Krausz, M., Colmegna, F., Aspesi, F., & Clerici, M. (2018). Estimating the Risk of Attempted Suicide Among Sexual Minority Youths: A Systematic Review and Meta-analysis. *JAMA pediatrics*, *172*(12), 1145–1152.

Notably, this overview excluded two SRs by National Institute for Health and Care Excellence (NICE) in October 2020.[47] This was because these two SRs were commissioned by NHS England to inform Dr Hilary Cass' independent review. In 2024, several SRs funded and commissioned by NHS England to inform the Cass review were published and were more comprehensive and updated than the two NICE SRs.

2.3 Baker et al. 2021

This overview also excluded the SR by Baker and colleagues,[48] which was funded by the World Professional Association for Transgender Health (WPATH), because it predominantly included studies on mature adults and was therefore too indirect to inform the healthcare of children or adolescents with GD. However, since the Baker et al. review supported the recommendations in the Adolescent chapter of WPATH SOC-8 it was subjected to a separate ROBIS analysis and was found to be at "high risk of bias" due to limitations in data collection and risk of bias assessment, and synthesis of results.

Study eligibility criteria: Low risk of bias.

The systematic review authors registered a protocol and had explicit and appropriate eligibility criteria. The systematic review excluded studies with follow up less than 3 months and studies that did not provide sufficient information about regimen of intervention.

Identification and selection of studies: Low risk of bias.

The authors searched in several databases and other resources. The authors also reported duplicate screening process.

[47] National Institute for Health and Care Excellence (2020b, 2020a).
[48] Baker et al. (2021).

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Data collection and study appraisal: High risk of bias.

The authors reported using a standardized form and they performed screening and risk of bias assessment in duplicate, suggesting that data collection was also done in duplicate. The authors described the most important characteristics of the included studies. The results collected, however, are not standardized across studies. For some studies, authors reported magnitudes of effect and confidence intervals, whereas for others they reported only that "no changes were observed."[49] Although the authors aimed to use the correct tools, when assessing risk of bias they did not consider that the design of the studies was not the same for the researchers of the primary studies versus the systematic review's question, leading the authors to assess studies using an inappropriate tool: for example, the systematic review authors assessed a primary study as a trial while it should have been assessed as a case series for the review purposes.

Synthesis and findings: High risk of bias.

Although reported per outcome, Baker et al. describe the results at the study level instead of across studies without justifying why they did not conduct a meta-analysis or reporting whether they planned to do so. Therefore, it is challenging for readers to draw any conclusions at the outcome level. While the review used the AHRQ guidelines for assessing strength of evidence, the authors did not comment on a formal assessment of heterogeneity, regardless of apparent between-study variation. The AHRQ guidelines do not consider publication bias. The authors did comment on risk of bias at the outcome level.

Risk of bias in the review: High risk of bias.

While the authors mention some limitations of the evidence, they did not comment on applicability or address all concerns identified with the evidence.

3 Synopses of SRs assessed at low risk of bias

Dopp et al. 2024:[50] This RAND SR examined evidence on interventions for GD and related health problems in youth with GD. The SR applied a strategy of combining

[49] Baker et al. (2021).
[50] Dopp et al. (2024).

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targeted search from existing clinical guidelines, reviews, and legal proceedings, and a broad search from PubMed. It included 105 studies and organized them into seven categories of interventions: psychosocial interventions, PBs, CSH, surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, and other treatments described as "gender identity and expression change efforts." Although this systematic review is comprehensive (49 studies for PBs, 56 studies for CSH, and 18 studies for surgery), a notable limitation is the inclusion of case reports. Case reports are inherently limited in their ability to establish treatment effects due to the lack of control groups and high risk of bias. The inclusion of case reports inflated the number of included studies but provided no additional benefits in informing about treatment effectiveness, which was reflected by the very low certainty of evidence despite a large number of eligible studies. This SR is limited by having systematically searched PubMed but no other databases. Compared with other low risk of bias SRs on hormonal and surgical treatment (Miroshnychenko 2024, Miroshnychenko 2025a,[51] Miroshnychenko 2025b,[52] Taylor 2024a,[53] Taylor 2024b[54]), the Dopp et al. 2024 review missed more case series and before-after studies while including more case reports. It summarized effect estimates by reviewing all reports of outcomes across studies and applied the GRADE methodology to assess the certainty of evidence. This SR reported that the evidence was limited by lack of long-term outcomes, lack of randomized controlled trials, and inconsistent measurement of outcomes, concluding that the certainty of evidence was frequently low or very low. For interventions including PBs, CSH, and surgeries, the certainty of evidence was very low for GD and mental health outcomes.

Hall et al. 2024:[55] This SR is part of the systematic review effort commissioned by the Cass Review. It assessed the effects of social transition (e.g., name/pronoun use, clothing changes) in patients under 18 with GD/incongruence. The authors included 11

[51] Miroshnychenko, Roldan, et al. (2025).
[52] Miroshnychenko, Ibrahim, et al. (2025).
[53] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[54] Taylor, Mitchell, Hall, Langton, et al. (2024).
[55] Hall et al. (2024).

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KS-AG-26-1037-A-001027

studies, most from the US and of low quality, using cross-sectional and cohort designs. The literature search was conducted in April 2022. The authors used an adapted version of the Newcastle-Ottawa Scale for cohort studies. Notably, the Newcastle-Ottawa Scale is suitable for the study type, but a high-quality study as assessed by this tool may be assessed as having high risk of bias according to other tools such as ROBINS-I, which has been developed to consider both the study design and the appropriateness of a study for answering questions about treatment effects. This SR did not conduct meta-analysis to synthesize evidence quantitatively; instead, it narratively summarized the effect estimates by outcomes. The review authors interpreted the evidence with caution, considering the limitations of the evidence (small sample sizes, lack of longitudinal or controlled designs, and heterogeneous outcomes across included studies), but did not use GRADE methodology to explicitly assess the certainty of evidence. The authors concluded that there is insufficient evidence to determine benefits or harms of social transition.

Heathcote et al. 2024:[56] This SR is part of the systematic review effort commissioned by the Cass Review. It evaluated psychosocial support interventions for children and adolescents experiencing GD. Ten studies with diverse designs (cohort, pre–post, mixed methods) were included. The literature search was conducted in April 2022. This SR used the Mixed Methods Appraisal Tool for quality assessment. Although the review followed systematic methods and focused on interventions beyond medical or surgical treatments, the evidence base was limited by the small number of studies, low quality, lack of comparators, and heterogeneity in interventions and outcomes. According to the authors, conclusions were limited due to poor reporting and inconsistent measurement. The authors called for clarity in intervention description and core outcome sets to enhance future research synthesis.

[56] Heathcote et al. (2024).

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Ludvigsson et al. 2023:[57] This systematic review by the Swedish National Board of Health and Welfare synthesized evidence on hormonal and surgical interventions in adolescents with GD. The review conducted a literature search in 2022 and included 24 studies (eight studies on GnRH alone, 13 studies on GnRH and CSH, and three studies on CSH alone). The review applied the GRADE methodology and downgraded the evidence due to concerns related to risk of bias and imprecise outcome measurement. However, the review authors mistakenly concluded that the certainty of evidence "cannot be assessed." Based on the authors' assessment to downgrade the evidence, the certainty of evidence should be "very low" for all outcomes assessed, including global function, suicidal ideation, GD, depression, anxiety, and quality of life. The SR concluded that evidence for benefits and harms of hormonal and surgical interventions remains insufficient for routine clinical use in adolescents.

Miroshnychenko et al. 2024:[58] This systematic review and meta-analysis examined the psychological and physical effects of mastectomy in birth-registered females under 26 years with GD. The search included databases through June 2023, yielding 39 studies (3 comparative observational, 2 before–after, and 34 case series). Outcomes included mental health measures, GD, body satisfaction, and surgical complications. The review used ROBINS-I for risk of bias assessment, conducted meta-analyses for evidence synthesis, and applied the GRADE methodology for certainty of evidence assessments. Comprehensive and methodologically sound, the SR found the certainty of evidence was limited by a predominance of case series, lack of prospective comparative studies, and other risk of bias concerns in the included studies, as well as small sample sizes. Indirectness was also a concern when participants' age at surgery was above the eligibility threshold. The authors found very low to low certainty evidence regarding mental health outcomes including global functioning, suicide attempt, and non-suicidal self-injuries.

[57] Ludvigsson et al. (2023).
[58] Miroshnychenko et al. (2024).

AMERICAN OVERSIGHT

Miroshnychenko et al. 2025a:[59] This SR evaluated the effects of PBs in individuals under 26 years with GD. The authors searched ten databases up to September 2023 and included studies employing observational and interventional designs. Outcomes assessed included psychological functioning, bone health, growth, and progression to CSH. The methodology of this systematic review was the same as that of another systematic review on mastectomy by the same group of researchers (Miroshnychenko 2024). The SR included 10 studies, including 3 comparative observational studies and 7 before-after studies. The review authors concluded that the certainty of evidence for psychological and physical health is very low. This SR found that 92% of individuals who received PBs progressed to receiving CSH, though the evidence on the impact of PBs on this outcome is very uncertain (very low certainty of evidence).

Miroshnychenko et al. 2025b:[60] This SR and meta-analysis assessed the effects of cross-sex hormone therapy in individuals with GD aged under 26 years. The authors searched ten databases through September 2023 and included 24 studies (9 comparative observational, 13 before–after, and 2 case series). Outcomes assessed included psychological (e.g., depression, global function) and physical effects (e.g., bone mineral density, cardiovascular events). The review followed the same methodology as two other SRs (on PBs and surgery) by the same group of researchers (Miroshnychenko 2024, Miroshnychenko 2025a[61]). The review found very low to low certainty evidence for psychological outcomes, and very low certainty evidence on bone mineral density. This SR found high certainty evidence on the proportion of natal females experiencing cardiovascular events during a 7 to 109 months of follow-up, which was 40 per 1000 following CSH use.

[59] Miroshnychenko, Roldan, et al. (2025).
[60] Miroshnychenko, Ibrahim, et al. (2025).
[61] Miroshnychenko, Roldan, et al. (2025).

AMERICAN OVERSIGHT

Taylor et al. 2024a:[62] This SR is part of the systematic review effort commissioned by the Cass Review. It focused on the outcomes of puberty blocker treatment in adolescents with GD or gender incongruence. The authors searched the literature through April 2022 and narratively synthesized studies on psychological, physical, and developmental effects. The SR followed the same methodology as the other reviews by the same research group (Hall 2024), including using the Newcastle-Ottawa scale to assess the risk of bias for included studies. This SR included 50 studies, including one high quality cross-sectional study and 25 moderate-quality observational studies. Notably, "moderate-quality observational studies" is not equivalent to "moderate-quality evidence." Moderate-quality observational studies or high-quality cross-sectional studies are inherently limited in evaluating treatment effects. Moreover, most included studies were observational with small sample sizes and varying outcome definitions. The review employed a narrative synthesis, including only moderate- and high-quality studies but did not explicitly assess the certainty of evidence using the GRADE methodology. The review findings were inconclusive, with inconsistent evidence on psychological benefits and concerns about effects on bone health and growth.

Taylor et al. 2024b:[63] This SR is part of the systematic review effort commissioned by the Cass Review. It synthesized studies on the outcomes of masculinising and feminising hormone therapy in adolescents with GD. It included 53 studies (12 cohort, 9 cross-sectional, 32 pre–post) identified through a search conducted in April 2022. Of all included studies, there was only one high-quality cohort study, which measured adverse outcomes only. The other included studies were moderate-quality studies. The review employed a narrative synthesis, which was limited by heterogeneity in study designs and outcome measures. Compared with other low risk of bias reviews, not using GRADE methodology to explicitly assess the certainty of evidence is a limitation and creates confusion among users: the review authors discuss "moderate quality" studies, rather than moderate certainty of evidence. The authors found inconsistent or insufficient evidence for the effect of CSH on GD, body satisfaction, psychosocial,

[62] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[63] Taylor, Mitchell, Hall, Langton, et al. (2024).

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cognitive, and physical health outcomes and concluded that robust evidence is lacking. This conclusion is consistent with other SRs of similar scope (Dopp 2024,[64] Miroshnychenko 2025b[65]), which suggested very low certainty of benefits.

[64] Dopp et al. (2024).
[65] Miroshnychenko, Ibrahim, et al. (2025).

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4 Summary of all included SRs

Chew et al. 2018[66]	
Study population description	Young people with gender dysphoria
Intervention	Hormonal treatment including PBs and CSH
Outcomes	Physical effects (including physical sex characteristics, side effects, bone mineral density, etc.), psychological effects, cognitive effects
Included studies	13 studies including 9 on GnRHas, 3 on estrogen, 5 on testosterone, 1 on antiandrogen (cyproterone acetate), and 1 on progestin (lynestrenol). There were no randomized trials included, and only 2 studies included control groups.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol available, though the authors describe the eligibility criteria with details for the population (age and diagnosis) and intervention, which seem appropriate for the question and are clear and unambiguous. Identification and selection of studies: The authors searched in the largest electronic databases, and although they did not use a formal search strategy, their search terms were broad enough to have likely captured all relevant studies. They also searched the reference list of relevant studies. Data collection and study appraisal: Data extraction captured relevant outcomes including mental health and physical parameters. The authors describe the most important characteristics of the included studies. The results collected, however, are not standardized across studies. Although the authors reported that two reviewers performed risk of bias assessments, they used a tool not designed for these types of study. Synthesis and findings: Only narrative synthesis was used. Although reported per outcome, the authors describe the results at the study level. For some outcomes, they provide a summary that focuses on counting the number of studies with statistically significant results. Risk of bias in the review: The authors mentioned some of the limitations of the evidence; however, they ignored these when interpreting the results and made claims about the presence of associations.
Results	Most of the included studies were assessed as studies with high risk of bias. This systematic review did not conduct evidence synthesis and instead relied on narrative description of individual studies. There was no formal assessment of the certainty of evidence. Nevertheless, the review authors concluded that hormonal treatments effectively achieved their intended physical effects, with GnRHas and cyproterone acetate suppressing sex hormones, and estrogen or testosterone promoting the development of feminized or masculinized secondary sex characteristics. GnRHa treatment was associated with improvements in several domains of psychological functioning, though not in gender dysphoria itself.

[66] Chew et al. (2018).

AMERICAN OVERSIGHT

Dopp et al. 2024[67]	
Study population description	Transgender and gender-expansive youth
Intervention	A health intervention related to recipients' transgender and gender-expansive identity (i.e., targeting gender dysphoria, related health problems, or both): psychosocial interventions, puberty-suppressing hormones, CSH, and surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, other treatments described as "gender identity and expression change efforts."
Outcomes	Psychosocial interventions: suicidality, mental health outcomes (including both depression or mood symptoms, and functioning), regret or dissatisfaction, family support. Puberty-suppressing hormones: decrease in pubertal changes targeted for suppression, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. CSH: increase in pubertal changes targeted for initiation, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Surgeries: gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Reproductive health interventions: successful cryopreservation of oocytes and embryos, successful cryopreservation of semen. Treatment of co-occurring mental health or developmental disorders: eating disorder symptoms co-occurring with gender dysphoria, depression and/or anxiety symptom co-occurring with gender dysphoria, gender dysphoria co-occurring with autism spectrum disorder. "Gender identity and expression change efforts": suicidality, mental health symptoms.
Included studies	Psychosocial interventions: 22 studies, including 1 randomized controlled trial (intervention as video narratives of lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities of overcoming coming-out-related difficulties),[68] 2 cohort studies, 6 quasi-experimental studies, 9 cross-sectional studies, 3 case reports, and 1 qualitative study. Puberty-suppressing hormones: 49 studies, including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study. CSH: 56 studies, including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study. Surgeries: 18 studies, including 6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study. Reproductive health interventions: 9 studies, using cross-sectional or case report designs with small samples (one to 20 transgender youth per sample). Treatment of co-occurring mental health or developmental disorders: 7 studies, all studies using case report design. "Gender identity and expression change efforts": 4 studies, including 3 using retrospective survey designs with community samples, and 1 case report.

[67] Dopp et al. (2024).
[68] This randomized controlled trial compared "coping-oriented brief videos" as an intervention for suicidality among sexual or gender minority. It was not a trial comparing psychotherapy with no psychotherapy for youth with gender dysphoria.

AMERICAN OVERSIGHT

Dopp et al. 2024[67]	
Risk of bias assessment consideration	Study eligibility criteria: The review did not include a preregistered protocol. The eligibility criteria focused on youth with gender dysphoria under 26 years old and required post-intervention outcomes. However, case reports and qualitative studies were included, which may be limited in estimating the treatment effects. Identification and selection of studies: There were two phases of literature search, and a comprehensive search was conducted in PubMed. However, other databases were not searched. Data collection and study appraisal: Data collection followed a structured form with critical appraisal procedures. Reviewers conducted risk of bias assessments using the JBI critical appraisal checklist. The tool was appropriate for the study research design. The reviewers discussed disagreements for consensus. Synthesis and findings: The review synthesized all identified studies for each intervention into a summary of effect estimates for each outcome that had been studied. Results for all prespecified outcomes reported and summarized. However, this review only narratively described the results for each outcome, without details on the evidence synthesis strategy or rationale. The interpretation of review findings were based on study quality and the limitations of included studies. Applicability of evidence was discussed, including study demographics, and statistical results were not overemphasized.
Results	Psychosocial interventions: very low certainty evidence for all outcomes. Puberty-suppressing hormones: low certainty evidence for decrease in pubertal changes targeted for suppression, very low certainty evidence for all the other outcomes. CSH: low certainty evidence for increase in pubertal changes targeted for initiation, very low certainty evidence for all the other outcomes. Surgeries: low certainty evidence for decrease in gender dysphoria after mastectomy, very low certainty evidence for decrease in gender dysphoria after other surgeries and other outcomes. Reproductive health interventions: very low certainty evidence for two outcomes. Treatment of co-occurring mental health or developmental disorders: very low certainty for all outcomes. “Gender identity and expression change efforts”: low certainty evidence in increases in suicidality, very low certainty for mental health symptoms.

AMERICAN OVERSIGHT

Expósito-Campos et al. 2023[69]	
Study population description	Transgender and non-binary youth and adults
Intervention	Empirically supported affirmative psychological intervention.
Outcomes	Mental health outcomes including anxiety, depression, trauma, suicidality, substance abuse, etc.
Included studies	22 studies, with 10 studies reporting outcome information for transgender and non-binary people (3 randomized controlled trials and 7 uncontrolled before-after studies), while 12 studies reporting mixed outcome information for transgender and non-binary and non-transgender populations.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were vague, for example, "well-described psychological interventions" introduces subjectivity. It is unclear whether studies following up parallel groups of study participants were considered as "quasi-experimental designs" and included or not. Identification and selection of studies: The search strategy combined five blocks with Boolean logic "AND", including "transgender" "distress" "affirming" "psychotherapy" and "intervention". This strategy was narrow. Data collection and study appraisal: Duplicate efforts and consensus process were reported. Synthesis and findings: The planned meta-analysis was not feasible. However, the narrative synthesis was reported inappropriately. The synthesis was by studies, according to the study population, types of study design, and interventions, while preferably it should be by outcomes and types of interventions. Risk of bias in the review: The interpretation of evidence did not address the concerns in the systematic review process.
Results	This systematic review did not conduct evidence synthesis by outcome, and there was no formal certainty of evidence assessment. The review authors concluded found “improvements in psychological distress, depression, anxiety, suicidality, substance-related risk behaviors, coping skills/emotion regulation, stress appraisal, self-esteem, self-acceptance, social support, minority stress, resilience, hope, positive identity, and identity acceptance” but also noted that conclusions are limited by moderate-to-high risk of bias.

[69] Expósito-Campos et al. (2023).

AMERICAN OVERSIGHT

Hall et al. 2024[70]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Social transition
Outcomes	Mental health outcomes including depression, anxiety, substance use, and suicidality, gender identity outcomes (e.g., persistence of gender dysphoria/incongruence)
Included studies	11 studies including 8 cross-sectional studies, 1 reanalysis of previously published cross-sectional data, 1 prospective longitudinal study, and 1 retrospective cohort study
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in July 2023, and published in April 2024. Databases were searched comprehensively and search dates accurately reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	No prospective longitudinal studies with suitable comparator groups have evaluated the effects of social transition on mental health or gender-related outcomes in children and adolescents. Existing studies consistently found no significant differences in mental health outcomes among children who had socially transitioned. For adolescents, the findings were mixed.

[70] Hall et al. (2024).

AMERICAN OVERSIGHT

Heathcote et al. 2024[71]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Psychosocial support
Outcomes	Mental health outcomes (including depression, anxiety, combined outcome measurement, emotional dysregulation, suicidality), psychological change (including relationship, resilience, self-compassion, self-care, coping, and problem solving, anger, life satisfaction), psychosocial change (including quality of life, well-being).
Included studies	10 studies including 4 cohort studies, 2 pre–post studies, 3 mixed methods, and 1 was a secondary analysis of intervention group data from four randomised controlled trials (these trials were not eligible).
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that the literature search was updated until April 2022, while the review was submitted for publication in September 2023, and published in April 2024. Databases searched comprehensively and search dates were reported. Though one overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool was Mixed Methods Appraisal Tool. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	Research on the outcomes of psychosocial interventions for children and adolescents with gender dysphoria or incongruence is limited. The risk of bias and poor reporting of the 10 included studies limited the conclusions about the effectiveness of psychosocial support.

[71] Heathcote et al. (2024).

AMERICAN OVERSIGHT

Karalexi et al. 2020[72]	
Study population description	Transgender young adults
Intervention	Hormone therapy
Outcomes	Cognitive outcomes including visuospatial ability, verbal memory, verbal reasoning, verbal working memory, computation, motor coordination.
Included studies	10 studies, including 6 cohort studies, 3 cross-sectional studies, and 1 with both longitudinal and cross-sectional analysis.
Risk of bias assessment consideration	Study eligibility criteria: The review included cohorts and cross-sectional studies. It is unclear whether a single group of participants with before-after study design but not labeled as "cohort" would be included or not. Identification and selection of studies: Literature search was conducted only in one database, MEDLINE. The search strategy included terms for "outcome", which may exclude records that are eligible but not indexed by reported outcomes. The number of records was low compared with other reviews. Data collection and study appraisal: Data collection seemed to be appropriate. Risk of bias was assessed using Newcastle-Ottawa Scale; However, the description of how the assessment was done suggested that the assessment may not be properly done. For example, all cohort studies were awarded with two stars in the ''Comparability'' section. Synthesis and findings: Meta-analysis was conducted where appropriate; but the review also conducted narrative synthesis elsewhere. Sources of heterogeneity was assessed using I^2 and this review briefly described the heterogeneity was not evident. No certainty of evidence assessed. Risk of bias in the review: No discussion or interpretation was included considering the risk of bias of included studies, and the limitation of the evidence.
Results	The review included meta-analyses on the cognitive functions, but did not formally assess the certainty of evidence. The systematic review did not identify evidence on adverse impact of hormone therapy on cognitive function.

[72] Karalexi et al. (2020).

AMERICAN OVERSIGHT

Ludvigsson et al. 2023[73]	
Study population description	Children with gender dysphoria
Intervention	Hormone therapy
Outcomes	Psychosocial and mental health outcomes (including gender dysphoria, depression, anxiety), cognitive outcomes, bone health outcomes, body composition and metabolic markers.
Included studies	24 studies, all observational studies, including 8 studies on GnRH alone, 13 studies on GnRH and CSH, and 3 studies on cross-sex hormone alone.
Risk of bias assessment consideration	Study eligibility criteria: This review followed PRISMA and internally register the protocol in the Swedish health technology assessment agency- However, the original protocol was not accessible. Identification and selection of studies: The literature search was comprehensive and reported in detail. However, the search may be outdated when the report was submitted for publication. Data collection and study appraisal: Two independent reviewers extracted data and conducted risk of bias assessment. Synthesis and findings: Narrative synthesis by outcome groups was justified given heterogeneity in studies. Robustness of results was considered through methodological description and bias discussion. Risk of bias in the review: The interpretation of review findings considered study quality and limitations of included studies. Conclusions aligned with evidence and noted significant research gaps. Though the GRADE assessment was labelled as "cannot be assessed", when four or more levels of downgrading happened. It should be very low.
Results	This systematic review did not identify any randomized control trails. The limited number of longitudinal observational studies were constrained by small sample sizes and high dropout rates. The evidence of long-term psychosocial effects of hormone therapy was limited. Treatment with GnRHas was found to delay bone maturation and the accrual of bone mineral density; however, partial recovery was observed during cross-sex hormone therapy when assessed at age 22.

[73] Ludvigsson et al. (2023).

AMERICAN OVERSIGHT

Malpas et al. 2022[74]	
Study population description	Transgender and gender expansive youth
Intervention	Family-based interventions: (1) providing psychoeducation, (2) allowing space for families to express reactions to their child's gender, (3) emphasizing the protective power of family acceptance, (4) utilizing multiple modalities of support, (5) giving families opportunities for allyship and advocacy, (6)connecting families to transgender and gender expansive youth community resources, and (7) centering intersectional approaches and concerns.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol. This review included three review processes, and the inclusion criteria were vague. For example, for Review 1, the inclusion criteria were: "(1) the article was published in English, and (2) the article provided treatment strategies, best practices, clinical recommendations, or outcome data related to family therapy or interventions to increase family engagement with transgender and gender expansive (TGE) youth." Identification and selection of studies: This review included three stages of search. Review 1 was the part that best met the scope of this overview. However, the number of results was low compared with other reviews. Separating Review 1 and Review 2 may have introduced bias in the review process. Though the search was updated until 2018, while the review was published in 2022. Data collection and study appraisal: No details were reported other than only "Relevant information was then coded ...". There was very brief information for included studies. No formal risk of bias assessment was applied. Synthesis and findings: The review did not identify quantitative outcome information; thus, this review narratively describe the qualitative results. The themes identified through this review included "(1) the change of clinical stance on families of youth with gender dysphoria over time, (2) the theoretical models often cited and used, (3) the most frequently recommended best clinical practices when working with youth with gender dysphoria and their families, and (4) the commonalities of these best practices with outcome data on family therapy with lesbian, gay, and bisexual youth." The review results and analyses deviated from the purpose of summarizing the evidence on family-based intervention. Risk of bias in the review: The concerns identified were not addressed in the interpretation of evidence.
Outcomes	No quantitative outcome for effectiveness. This systematic review identified four themes related to family-based intervention.
Included studies	32 studies on clinical practice recommendations for family-based interventions for transgender and gender expansive youth.
Results	This systematic review found that clinical strategies have moved from pathologizing to affirming of transgender and gender expansive youths' gender journey.

[74] Malpas et al. (2022).

AMERICAN OVERSIGHT

Miroshnychenko et al. 2024[75]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	Mastectomy
Outcomes	Mental health measures (including distress, suicide), gender dysphoria, body satisfaction, and surgical complications (including death, necrosis, and scarring).
Included studies	39 studies, including 3 comparative observational studies, 2 before–after, and 34 case series.
Risk of bias assessment consideration	Study eligibility criteria: The protocol was registered, and the eligibility criteria were clear. Identification and selection of studies: The literature search covered multiple databases with support from an information specialist. The authors described their duplicate screening and consensus processes. Data collection and study appraisal: Standardized data extraction form and duplicate extraction efforts were used; and a third reviewer was available for consensus. The risk of bias tool was appropriate for the review purpose. Synthesis and findings: Meta-analyses were conducted. When meta-analyses were not feasible, narrative syntheses were conducted. Certainty of evidence was rated using GRADE and considered the heterogeneity and risk of bias in included studies. Risk of bias in the review: The interpretation of evidence was appropriately cautious given very low to low certainty of much of the evidence.
Results	The authors found low certainty evidence on non-suicidal self-injuries, and very low certainty evidence regarding gender dysphoria and other psychological outcomes such as global functioning and suicide attempt. The review also identified high certainty evidence for outcomes of death, necrosis, and excessive scarring after surgery. The numbers of events after mastectomy were estimated to be 0, 10 to 30, and 50 per 1,000 persons for death, necrosis, and excessive scarring, respectively.

[75] Miroshnychenko et al. (2024).

AMERICAN OVERSIGHT

Miroshnychenko et al. 2025a[76]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	PBs
Outcomes	Gender dysphoria, global function, depression, bone mineral density, progression to CSH.
Included studies	10 studies, 3 comparative observational studies, and 7 before–after design studies.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[77]
Results	The systematic review identified very low certainty of evidence on the outcomes of gender dysphoria, global function, depression, and bone mineral density. There remains considerable uncertainty regarding the effects of PBs in individuals experiencing gender dysphoria.

[76] Miroshnychenko, Roldan, et al. (2025).
[77] Miroshnychenko et al. (2024).

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Miroshnychenko et al. 2025b[78]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	CSH
Outcomes	Gender dysphoria, global function, depression, death by suicide, bone mineral density, sexual dysfunction, cardiovascular events.
Included studies	24 studies, including 9 comparative observational studies, 13 before–after studies, and 2 case series.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[79]
Results	This systematic review found very low to low certainty evidence about depression, very low certainty evidence on gender dysphoria, global function, and bone mineral density. The systematic review found moderate to high certainty evidence on the incidence of cardiovascular events after receiving CSH.

[78] Miroshnychenko, Ibrahim, et al. (2025).
[79] Miroshnychenko et al. (2024).

AMERICAN OVERSIGHT

Ramos et al. 2021[80]	
Study population description	Adolescents with gender incongruity
Intervention	PBs
Outcomes	Gender dysphoria, bone mineral density, side effects.
Included studies	11 studies including 9 observational studies and 2 qualitative studies.
Risk of bias assessment consideration	Study eligibility criteria: The authors used study design as a reason for exclusion (e.g. literature reviews, systematic reviews, reports and case series, guidelines, summaries and comments). "Theme" was described as an exclusion reason at full-text screening, but the associated eligibility criterion was not clear. Identification and selection of studies: Search terms, filters, and strategies were reported. However, search strategy included restrictive terms including "NOT" operators that could be related to outcomes of interest (e.g. depressive disorder), which was probably not appropriate as psychosocial functioning is one of the outcomes summarized. The literature search only identified 108 records, which was low compared to other included reviews. Data collection and study appraisal: The study characteristics were not systematically reported. The authors noted using "Cochrane risk of bias assessment for observational and intervention studies", assessing, "bias of selection, performance, selective reporting, detection, attrition, and other (e.g., inadequate control for key confounders)...", and provided an alphanumeric rating at the study level in Table 1 (e.g. 2B, 2C, 4). There was no legend provided for the meaning of these ratings. It was not clear whether the Cochrane risk of bias tool is referring to ROBINS-I, which does not have these rating categories. At least one of the studies included is a qualitative study, and it was not clear how the risk of bias tool for observational and intervention studies would apply to the qualitative study. There was no mention of whether the assessment was conducted independently, in duplicate. Synthesis and findings: The authors included a narrative synthesis at the study-level highlighting results or conclusions from individual studies. The synthesis was not organized by outcome, and there was high risk of bias for selectively including study results in the narrative synthesis. The authors did not address heterogeneity in the synthesis, rather in the limitations it was noted, "Studies found are heterogeneous (different definitions, population and evaluation techniques) and sometimes based on small sample size, restricting statistical power." Risk of bias in the review: The concerns identified were not addressed.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results by individual studies. There was no certainty of evidence assessment, but according to the review authors, the use of GnRHa seems to be well tolerated by the studied population, prevent the irreversible phenotypic changes, and “contribute to the mental health.”

[80] Ramos et al. (2021).

AMERICAN OVERSIGHT

Rew et al. 2021[81]	
Study population description	Transgender and gender diverse youth
Intervention	PBs
Outcomes	Anthropomorphic measurements, sexual characteristics, mental health functioning, depression, emotional and behaviour problems, suicide, and side effects.
Included studies	9 studies including 6 observational studies, 1 cross-sectional study, and 2 case reports.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criterion for outcomes was vague by being specified as studies needing to "identify risks and/or benefits associated with the use of these medications." Identification and selection of studies: The literature search only identified 151 records after de-duplication, which was low compared to other included reviews. The study selection approach was not described. Screening involved multiple reviewers but there was no detailed reporting of calibration or adjudication. Data collection and study appraisal: A data extraction form was developed, but approach to data extraction was not described. Synthesis and findings: Narrative synthesis was justified due to design heterogeneity. Some of the included studies reported the same outcomes (e.g., body composition), but the synthesis (Table 2) was presented at the study-level instead of at the outcome-level, and the summary in the main text was collated under 'risks/adverse outcomes' and 'positive outcomes'. Risk of bias in the review: The interpretation of findings did not address the concerns identified in the process. While the risk of bias was described for the studies, it was not described in relation to the outcomes and findings.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results. This systematic review listed studies reporting positive outcomes and adverse effects. For example, “positive outcomes were decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life. Adverse factors associated with use were changes in body composition, slow growth, decreased height velocity, decreased bone turnover, cost of drugs, and lack of insurance coverage.” There was no certainty of evidence assessment, and the interpretation did not take into consideration of the strengths and limitations of the evidence.

[81] Rew et al. (2021).

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Taylor et al. 2024a[82]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	PBs
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including puberty progression, hormone levels, menstrual suppression, height/growth, body composition, bone geometry, etc.).
Included studies	50 studies, including 11 cohorts, 8 cross-sectional and 31 before-after studies. The descriptive evidence synthesis included 1 high quality cross-sectional study, and 25 moderate observational studies.
Risk of bias assessment consideration	Study eligibility criteria: There was a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in November 2023, and published in April 2024. Databases searched comprehensively and search dates reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality were discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	This systematic review did not identify high-quality studies with appropriate designs (only 1 “high-quality” cross-sectional study). Of the 11 cohort studies, only five were rated as moderate in quality. The evidence on the effects of PBs in adolescents with gender dysphoria or incongruence regarding its impact on gender dysphoria, mental or psychosocial health, or cognitive development was limited. Evidence also suggests that bone health and height may be adversely affected during treatment. Recently published studies which were not included in this systematic review align with the findings of this systematic review.

[82] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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Taylor et al. 2024b[83]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	CSH
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including induced puberty progression, hormone levels, menstrual suppression, height/growth, body composition/shape, bone geometry, etc.), and fertility.
Included studies	53 studies including 12 cohort, 9 cross-sectional, 32 pre–post studies. This systematic review included 1 high quality cohort study.
Risk of bias assessment consideration	Same as Taylor 2024a.[84]
Results	High-quality research on the outcomes of hormone interventions in adolescents with gender dysphoria or incongruence is lacking, and few studies include long-term follow-up. There is uncertainty regarding their effects on gender-related outcomes, body satisfaction, psychosocial health, cognitive development, or fertility, and the impacts on height, growth, cardiometabolic health, and bone health. The review authors identified "moderate quality" studies[85] mental health may be improved during treatment.

[83] Taylor, Mitchell, Hall, Langton, et al. (2024).
[84] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[85] This review had identified "moderate quality" observational studies. Including "moderate-quality observational studies" is not equivalent to "moderate quality (certainty) evidence." According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).

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Thompson et al. 2023[86]	
Study population description	Adolescents with gender dysphoria
Intervention	Psychosocial only PBs CSH Surgeries
Outcomes	Psychosocial only: mental health. PBs: blood pressure, biochemistry and hematological measurements, anthropometric, bone density and physical changes, mental health. CSH: biochemical and hematological, anthropometric, bone density and physical changes, and mental health. Surgeries: mental health.
Included studies	19 studies, including 13 retrospective studies and no randomized controlled trial.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: There was no literature search for unpublished literature. Reference list of included studies was checked. But the inclusion criteria also excluded the possibility of searching grey literature. Data collection and study appraisal: Data were comprehensive and tabulated; overlapping samples were identified. All outcome domains from included studies were described, but synthesis was limited to narrative integration. Risk of bias was assessed using Crowe Critical Appraisal Tool, this tool may lack specificity. For example, with this tool, many papers scored lower on was the issue of consent— but many studies were retrospective in nature and the consent process was waived. Synthesis and findings: Narrative synthesis was used by outcomes. However, the syntheses for outcomes were conducted combining both puberty blockers and cross-sex hormones, which may not be appropriate. Heterogeneity was discussed narratively but no subgroup or sensitivity analysis was performed. This review described risk of bias, however, did not account for the limitations of studies in the synthesis. Risk of bias in the review: The interpretation of evidence did not address the concerns identified.
Results	No certainty of evidence assessment was conducted. Most changes to health parameters were inconclusive, “except an observed decrease in bone density z-scores with PBs.” “Some improvements were observed in global functioning and depressive symptoms once treatment was started.”

[86] Thompson et al. (2023).

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Zepf et al. 2024[87]	
Study population description	Children/adolescents with gender dysphoria
Intervention	PBs CSH
Outcomes	PBs: gender dysphoria, mental health, quality of life, body image, psychosocial effects, health care utilization, satisfaction with surgery following PBs, and treatment discontinuation. Cross-sex hormone: body image, psychosocial outcomes, treatment discontinuation, and bone metabolism.
Included studies	This systematic review was an update on the systematic review efforts by NICE (National Institute for Health and Care Excellence) – which aimed to "inform Dr Hilary Cass' independent review into gender identity services for children and young people." This updated further included two observational studies on CSH.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: Five databases were searched; strategy was comprehensive. Screening process was not fully described. Data collection and study appraisal: It is unclear if a structured risk of bias tool was applied. Synthesis and findings: The authors synthesize the results from all studies. They do not describe methods for data analysis. The studies seemed heterogeneous enough that summarizing them narratively is appropriate. Limitations were discussed in detail, including inconsistency and weak study designs. Risk of bias in the review: The authors considered the limitations of the evidence when interpreting the results.
Results	This systematic review concluded that the evidence on the effectiveness of PBs and/or CSH in children and adolescents with gender dysphoria remains inadequate.

[87] Zepf et al. (2024).

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5 Evidence synthesis: Puberty Blockers

This overview identified nine SRs on the treatment effects of PBs. Across all primary studies included in these SRs, there were no eligible randomized controlled trials. These SRs frequently used the labels based on study design, such as “cohort,” to describe the study design for included studies. However, these labels may be confusing due to the variations in study design with the same label. To address this concern, the researchers from McMaster University used labels such as “comparative observational studies” and “before-after study.” This overview found that across all primary studies in the nine SRs on PBs, only six were observational studies with parallel control groups comparing PBs with no PBs among children or adolescents with GD.[88] The sample sizes in these studies were small: three studies included fewer than 100 participants, ranging from 60 to 438 across these six comparative observational studies. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of PBs.

5.1 Included SRs on PBs

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria

[88] Becker-Hebly et al. (2021); Costa et al. (2015); Grimstad et al. (2021); Jensen et al. (2019); McGregor et al. (2024); Tordoff et al. (2022).

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and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025a

Miroshnychenko, A., Roldan, Y., Ibrahim, S., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Puberty blockers for gender dysphoria in youth: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327909

Ramos 2021

Ramos, G. G. F., Mengai, A. C. S., Daltro, C. A. T., Cutrim, P. T., Zlotnik, E., & Beck, A. P. A. (2021). Systematic review: Puberty suppression with gnrh analogues in adolescents with gender incongruity. *Journal of endocrinological investigation*, *44*(6), 1151-1158.

Rew 2021

Rew, L., Young, C. C., Monge, M., & Bogucka, R. (2021). Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. *Child and adolescent mental health*, *26*(1), 3-14.

Taylor 2024a

Taylor, J., Mitchell, A., Hall, R., Heathcote, C., Langton, T., Fraser, L., . . . Hewitt, C. E. (2024). Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s33-s47.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

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Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

5.2 Low risk of bias SRs

Four English language SRs were classified at low risk of bias.[89] Only SRs with low risk of bias were summarized to assess outcomes.

Of the four low risk of bias SRs, the eligibility criteria and number of included studies varied. Notably, the systematic review by Taylor and colleagues[90] included most studies: 50 studies including 11 cohorts, 8 cross-sectional, and 31 before-after studies. This SR synthesized only study results from high or moderate quality studies. Dopp 2024[91] included 49 studies including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study (case reports and qualitative studies are inadequate to provide quantitative information on treatment effects). In contrast, Ludvigsson 2023[92] included 21 studies, and Miroshnychenko 2025a[93] included 10 studies (including 3 comparative observational studies and 7 before–after design).

[89] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[90] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[91] Dopp et al. (2024).
[92] Ludvigsson et al. (2023).
[93] Miroshnychenko, Roldan, et al. (2025).

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Only seven studies were included in all four low risk of bias SRs, including two comparative cohorts (one in Germany,[94] one in the UK[95]), as well as the five before-after studies reported in Canada,[96] Netherlands,[97] and UK.[98])

5.3 Outcome 1. Gender dysphoria

A total of four low risk of bias SRs assessed the impact of PBs on GD.[99] Dopp 2024[100] included the most studies, though these included case reports and a qualitative study, which have limited value in estimating treatment effects. This systematic review narratively described that PBs lead to improved GD, without details on its methods for evidence synthesis. In contrast, the other three SRs reported no change in GD associated with PBs.

The interpretation of these results requires caution regarding the certainty of evidence. All three SRs using the GRADE methodology to assess certainty of evidence concluded the certainty of evidence was very low.[101] Taylor 2024a did not formally assess the certainty of evidence but found that "no high-quality studies using an appropriate design were identified, … no conclusions can be drawn," [102] which is equivalent to very low certainty evidence.

In summary, this overview concludes that the certainty of evidence is very low, and no conclusion could be drawn on the impact of PBs on GD.

5.4 Outcome 2. Mental health and wellbeing

A total of four SRs assessed the impact of PBs on mental health, using varying measures of mental health such as global function, suicidality, depression, anxiety, and

[94] Becker-Hebly et al. (2021).
[95] Costa et al. (2015).
[96] Navabi et al. (2021).
[97] Klink et al. (2015); Schagen et al. (2016).
[98] Carmichael et al. (2021); Joseph et al. (2019).
[99] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[100] Dopp et al. (2024).
[101] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025).
[102] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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quality of life.[103] Similar to the reviews on the GD outcome, Dopp 2024[104] included more studies than the three other SRs because it included case reports and a qualitative study. It narratively described that PBs lead to improved mental health, though the certainty of evidence was assessed as very low. The remaining three SRs reported either no change or small changes in mental health associated with PBs. The certainty of evidence was very low or "uncertain."

In summary, this overview concludes that no conclusion could be drawn on the impact of PBs on mental health due to very low certainty evidence.

5.5 Outcome 3. Pubertal development

Two SRs assessed the impact of PBs on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[105] SRs showed that the use of PBs is consistently associated with reductions in pubertal development. This overview assessed the certainty of evidence as high due to the observed very large effects.[106]

In summary, this overview finds high certainty evidence showing PBs lead to expected physiological effects on pubertal development.

5.6 Outcome 4. Need for or progression to further treatment

Only one systematic review assessed the impact of PBs on proceeding with CSH. Miroshnychenko and colleagues[107] included 2 case series and estimated that 92% of children or adolescents with GD proceeded with CSH, suggesting a high proportion of adolescents receiving PBs proceed to CSH. However, due to concerns related to risk of bias, the certainty of evidence regarding the causal role that PBs play in this progression is very low.

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[103] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[104] Dopp et al. (2024).
[105] Dopp et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[106] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to the very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011).
[107] Miroshnychenko, Roldan, et al. (2025).

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5.7 Outcome 5. Safety

A total of four low risk of bias SRs reported the safety outcomes for PBs in children or adolescents with GD.[108] Outcomes included overall risk of adverse events, bone health, fertility, anthropometric measures, body composition, growth, and other measures. Dopp 2024[109] included the largest number of eligible studies. The SRs reported side effects including mild headaches or hot flushes, moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems. The certainty of evidence on the overall risk of adverse events was very low.

The SRs found no evidence on the long-term safety of PBs.

All four SRs assessed bone health, and the evidence was based primarily on before-after studies. The most frequently reported outcome for bone health was bone mineral density decreases relative to reference values (z score). All SRs reported that bone density is compromised during puberty blocker treatment. Specifically, Miroshnycheko and colleagues[110] reported decreases in bone mineral density for hip, lumbar spine, and femoral neck. There was disagreement across SRs on certainty of evidence assessment, which was low according to Ludvigsson 2023[111] (due to risk of bias and imprecision concerns) but very low according to Dopp 2024[112] and Miroshnycheko 2025a.[113] Taylor 2024a[114] did not formally assess the certainty of evidence but concluded that multiple studies found that bone density is compromised. This overview of SRs assessed the certainty of evidence on bone health as low. This was due to the risk of bias in evidence based on observational studies.[115] In summary, this overview concludes there is low certainty evidence that PBs lead to compromised bone density.

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[108] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[109] Dopp et al. (2024).
[110] Miroshnychenko, Roldan, et al. (2025).
[111] Ludvigsson et al. (2023).
[112] Dopp et al. (2024).
[113] Miroshnychenko, Roldan, et al. (2025).
[114] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[115] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty, due to risk of bias concerns arising from unbalanced prognostic factors and uncontrolled confounding (lack of randomization). There is no further downgrade of evidence by this overview. The certainty of evidence is low.

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Only one systematic review reported on fertility outcomes. Based on two case reports of fertility preservation, Dopp et al[116] concluded that there was very low certainty evidence on the risk of infertility after PBs. This overview has not identified empirical evidence on fertility outcomes from included SRs. However, based on high certainty evidence in this overview on PBs' effects on pubertal development and the consideration of fertility preservation in clinical practice, adolescents receiving PBs who then proceed with CSH probably experience infertility, though the impact may depend on natal sex and stage of pubertal development when starting PBs.

Two SRs[117] reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low, or uncertain. This overview concludes that the certainty of evidence for these outcomes is very low.

5.8 Outcome 6. Regret

Only one SR assessed regret after PBs and reported high satisfaction ratings and low rates of regret. The certainty of evidence was very low, and no conclusions can be reached on the regret rate after PBs.

5.9 Evidence gap

Important gaps remain in both the range and quality of outcomes assessed across the existing literature. Many primary studies were not designed to adequately measure or report on outcomes related to puberty blocker use. For example, only a small number of primary studies included in the SRs assessed the impact of PBs on outcomes such as GD or mental health. Although PBs are frequently described as a "pause button," no studies have systematically examined their role in the decision-making process or the outcomes of those who discontinue treatment.

When outcomes were assessed, the primary focus was on short term psychological or physiological changes, or surrogate outcomes—such as suicidal ideation or bone mineral density—rather than clinically important endpoints like suicide or fractures.

[116] Dopp et al. (2024).
[117] Ludvigsson et al. (2023); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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There is particularly limited evidence on long-term outcomes related to fertility, growth, and cognitive development.

While studies suggest that a high proportion of youth proceed to cross-sex hormones after puberty suppression,[118] there is minimal evidence on the impact of this combined pathway compared to CSH alone, on long-term outcomes such as surgical outcomes, or on the need for future surgery. Furthermore, no studies have clearly examined the physical or psychosocial trajectories of those who stop PBs without transitioning to CSH. As a result, there is little data on what happens after treatment ends, and the assumption of reversibility of all puberty blocker effects remains largely untested. A further important limitation is that most primary studies did not consider the effects of PBs on males versus females. Overall, the absence of long-term, high-certainty evidence on these critical outcomes (including suicide, fractures, fertility, growth, and cognitive development) leaves substantial uncertainty about the effects of PBs.

5.10 Summary

In summary, this overview identified nine SRs addressing the effects of PBs on GD, mental health, safety, pubertal development, and further treatment decisions. There is high certainty evidence that PBs exert physiological effects such as puberty suppression, and that they probably lead to infertility when adolescents receiving PBs go on to receive CSH. PBs may compromise bone health. A high proportion of youth proceed to CSH from PBs. The evidence is very uncertain regarding the effect on GD, improvement in mental health, and safety.

[118] Miroshnychenko, Roldan, et al. (2025).

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5.11 Evidence mapping: SRs on PBs

Table 5.1. Evidence mapping of the SRs on PBs and the primary studies that these SRs included

	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Achille 2020		Y		Y			Y		
Akgul 2019		Y					Y		
Arcelus 2016							Y		
Arnoldussen 2022		Y							
Barnard 2019		Y							
Becker-Hebly 2021		Y	Y	Y			Y	Y	
Brik 2020		Y							Y
Burke 2020	Y						Y		
Caanen 2017		Y							
Cantu 2020			Y						
Carmichael 2021		Y[128]	Y	Y			Y		
Chen 2016								Y	
Chiniara 2018							Y		

[119] Chew et al. (2018).
[120] Dopp et al. (2024).
[121] Ludvigsson et al. (2023).
[122] Miroshnychenko, Roldan, et al. (2025).
[123] Ramos et al. (2021).
[124] Rew et al. (2021).
[125] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[126] Thompson et al. (2023).
[127] Zepf et al. (2024).
[128] Another citation, McPherson 2023 was provided for this study. This report was a re-analysis of the data collected by the previous report. However, this citation was not included by any other SRs on PBs or CSH.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Cohen-Kettenis 2011[129]		Y				Y			
Costa 2015	Y	Y	Y	Y	Y		Y	Y	Y
de Nie 2022							Y		
de Vries 2014	Y		Y		Y		Y		
de Vries 2011	Y	Y		Y	Y	Y	Y	Y	Y
Delemarre-van de Waal 2006	Y	Y					Y		
Donaldson 2018		Y							
Ewan 2014		Y							
Fontanari 2020							Y		
Ghelani 2020							Y		
Giovanardi 2019					Y				
Grannis 2021, Grannis 2023, and Olsavsky 2023		Y[130]							
Grimstad 2021a							Y		
Hisle-Gorman 2021		Y	Y				Y		
Jensen 2019								Y	
Joseph 2019		Y	Y	Y			Y	Y	Y
Karakılıç Özturan 2023				Y					
Khatchadourian 2014		Y			Y	Y	Y		Y
Klaver 2020		Y	Y				Y	Y	
Klaver 2018			Y		Y	Y	Y	Y	

[129] Another citation (Cohen-Kettenis, 1998) was provided for this study. However, this citation was not included by any other SRs on PBs or CSH, although it was included by Dopp et al. (2024) for CSH and surgeries.
[130] Dopp et al. (2024) included three citations for one study.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Klink 2015	Y	Y	Y	Y	Y		Y		Y
Klink 2013					Y				
Kuper 2020		Y					Y	Y	
Lavender 2023		Y							
Lee 2020			Y					Y	
Lee 2024		Y							
Littman 2021		Y							
Lopez 2018					Y			Y	
López de Lara 2020		Y							
Lynch 2015							Y		
Martin 2021		Y							
McGregor 2024		Y							
Mejia-Otero 2021							Y		
Moussaoui 2023		Y							
Nahata 2017						Y		Y	
Navabi 2021		Y	Y	Y			Y		
Neyman 2019		Y					Y		
Nokoff 2021			Y				Y		
Olson 2022		Y							
Olson-Kennedy 2021							Y		
Pang 2020		Y							

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Perl 2021[131]		Y					Y		
Perl 2020[132]		Y	Y				Y	Y	
Pine-Twaddell 2023							Y		
Ristori 2019		Y							
Russell 2021							Y	Y	
Schagen 2016	Y	Y	Y		Y	Y	Y		Y
Schagen 2018							Y		
Schagen 2020		Y	Y	Y			Y	Y	
Schneider 2017		Y				Y			
Schulmeister 2022			Y				Y		
Schwartz 2023		Y							
Segev-Becker 2020							Y		
Staphorsius 2015	Y		Y				Y		Y
Stoffers 2019			Y				Y	Y	
Strang 2022							Y		
Tack 2016		Y					Y	Y	
Tack 2018		Y					Y	Y	
Tack 2017		Y					Y	Y	
Tordoff 2022		Y					Y		
Turban 2020		Y				Y	Y		

[131] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024a included the two citations as two moderate quality before-after studies.
[132] See above note.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
van de Grift 2020		Y					Y		
van der Loos 2022		Y							
van der Loos 2023		Y							
van der Loos 2021			Y				Y		
van der Miesen 2020		Y					Y		
Vlot 2017	Y	Y	Y		Y	Y	Y		Y
Vrouenraets 2016		Y			Y				
Waldner 2023							Y		

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5.12 Evidence tables on outcomes for PBs in youth with gender dysphoria

Table 5.2. Summary of evidence on gender dysphoria after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[133]	11 studies	-[134]	PBs lead to improved gender dysphoria. However, reductions in gender dysphoria were measured less consistently than pubertal changes, and almost never in the same study as pubertal changes	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Ludvigsson 2023[135]	2 prospective observational cohort studies	145 participants on hormones, 49 were evaluated	Two of these studies observed no statistically significant change in gender dysphoria	Very low certainty due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[136]	2 before-after studies	59 participants	Standardised mean change: -0.1 (95% confidence interval: -0.4 to 0.19) (higher score indicating greater gender dysphoria)	Very low certainty due to serious inconsistency and very serious imprecision
Taylor 2024a[137]	2 before-after studies[138]	114 participants were treated	Two before-after studies measured gender dysphoria and reported no change before and after receiving treatment	No high-quality studies using an appropriate design were identified, and only four measured gender dysphoria as an outcome. No conclusions can be drawn
Evidence synthesis			No conclusion can be drawn on the impact of PBs on gender dysphoria.	The certainty of evidence is very low.

[133] Dopp et al. (2024).
[134] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[135] Ludvigsson et al. (2023).
[136] Miroshnychenko, Roldan, et al. (2025).
[137] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review only synthesized excluded low quality.
[138] Though four studies reported gender dysphoria, only two moderate quality before-after studies were included in evidence synthesis.

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Table 5.3. Summary of evidence on mental health and well-being after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[139]	21 studies	-[140]	Receipt of PBs was sometimes associated with improvements in mental health symptoms (depression, anxiety, quality of life, general functioning). In samples that started psychosocial supports prior to starting PBs, however, there were generally no changes in mental health outcomes after PBs began. Effects were also found less consistently for decreases in suicidality, potentially due to the outcome being relatively rare (which makes finding effects more difficult), especially in the younger age range seen in many of these studies.	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Ludvigsson 2023[141]	4 observational cohort studies: 1 prospective and 3 retrospective	254 participants on hormones,[142] 113 were evaluated	Improved global function as assessed with the Children's Global Assessment Scale	Very low certainty[143] due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[144]	2 comparative observational studies, and 2 before-after studies	103 participants from 2 comparative observational studies, and 53 participants from 2 before-after studies	Difference in mean change from baseline 7.67 (95% confidence interval: -2 to 17.34) in PBs group compared with no PBs group from comparative observational studies; and Mean change 3.63 (95% confidence interval: 3.17 to 4.09) from before-after studies (higher score indicating greater global function)	Very low certainty due to serious risk of bias, inconsistency and imprecision

[139] Dopp et al. (2024).
[140] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020). One study included by this review, Grannis 2023, was about CSH not PBs.
[141] Ludvigsson et al. (2023).
[142] In two studies, the participants had also received CSH.
[143] Ludvigsson et al. concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[144] Miroshnychenko, Roldan, et al. (2025).

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Taylor 2024a[145]	1 cohort and 2 before-after studies	174 participants were treated	Three before-after studies reported no clinically significant change	No conclusions can be drawn.
Suicidality				
Ludvigsson 2023[146]	1 prospective observational cohort study with mixed treatment (38 subjects with no pharmacological treatment)	42 participants on hormones, 28 were evaluated	No change in suicide ideation	Very low certainty[147] due to very serious risk of bias and very serious imprecision
Taylor 2024a[148]	1 cross-sectional study and 1 before-after study	222 participants were treated	The cross-sectional study reported less self-harm/ suicidality in those treated, although similar to group with no gender dysphoria. The before-after study did not report change over time.	No conclusions can be drawn.
Depression				
Ludvigsson 2023[149]	2 prospective observational cohort studies of which one included mixed treatment	97 participants on hormones, 60 were evaluated	No change in depression	Very low certainty[150] due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[151]	1 comparative observational study, and 1 before-after study	26 participants from 1 comparative observational study, and 41 participants from 2 before-after study	The comparative observational study with 26 participants (88% using PBs) reported that PBs did not result in a statistically significant decrease in scores in female to male participants; but resulted in a statistically significant decrease in score in male to female	Very low certainty due to very serious risk of bias, and serious imprecision

[145] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[146] Ludvigsson et al. (2023).
[147] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[148] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[149] Ludvigsson et al. (2023).
[150] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[151] Miroshnychenko, Roldan, et al. (2025).

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			participants; and Mean change -3.36 (95% confidence interval: -3.69 to -3.03) from 1 before-after study (higher score indicating greater depression)	
Taylor 2024a[152]	1 before-after study	70 participants were treated	Reduction in depressive symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Anxiety				
Ludvigsson 2023[153]	2 prospective observational cohort studies	97 participants on hormones, 60 were evaluated	No change in anxiety	Very low certainty[154] due to very serious risk of bias and very serious imprecision
Taylor 2024a[155]	1 before-after study	70 participants were treated	No change in anxiety symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Quality of life				
Ludvigsson 2023[156]	2 prospective observational cohort studies, including one retrospective	98 participants on hormones, 46 were evaluated	One study reported improvement in quality of life most pronounced in subjects receiving puberty-blocking hormones, followed by CSH treatment. A second study reported some improvement in quality of life.	Very low certainty[157] due to very serious risk of bias and very serious imprecision.
Taylor 2024a[158]	1 before-after study	44 participants were treated	No change in quality of life	A single study, reporting no improvement. No conclusion can be drawn.

[152] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[153] Ludvigsson et al. (2023).
[154] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[155] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[156] Ludvigsson et al. (2023).
[157] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[158] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Internalising problems				
Taylor 2024a[159]	1 cross-sectional study, and 2 before-after studies	292 participants were treated	No change to small decrease in internalising problems	No high certainty evidence was identified. No conclusion can be drawn.
Externalising problems				
Taylor 2024a[160]	1 cross-sectional study, and 2 before-after studies	292 participants were treated	No change to small decrease in externalising problems	No conclusion can be drawn.
Psychological functioning/psychopathology				
Taylor 2024a[161]	2 before-after studies	114 participants were treated	Two before-after studies reported no change to a small change	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of mental health outcomes by PBs.	The certainty of evidence is very low.

[159] See above note,
[160] See above note.
[161] See above note.

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Table 5.4. Summary of evidence on pubertal development after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Pubertal progression				
Dopp 2024[162]	20 studies	-[163]	Receipt of PBs was consistently associated with reductions in pubertal changes (which were targeted for suppression due to being inconsistent with the youth's gender identity), compared to expected pubertal progress and/or developmental control participants. Various physical and hormonal changes were documented over time, including reductions in endogenous sex-linked hormones, decreased progression (and sometimes regression) of physical sex characteristic development, changes in body hair, changes in height/growth and body fat composition congruent with youths' gender identities, grip strength, vocal register, and cessation of menstruation (both from menstrual suppression treatments and other forms of PBs).	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024a[164]	4 studies including 2 cohort studies and 2 before-after studies	385 participants	In one cohort study, clinical pubertal escape was reported in 2/21 participants. Another cohort study reported that Tanner stage 2/3 treatment resulted in smaller breast size in birth registered females and lower average penile length and fewer testes descended in birth registered males, compared with Tanner stage 4/5 or no GnRH-a.	Four studies showed that PBs exert its expected physiological effects
Hormone level				
Taylor 2024a[165]	9 studies including two cohort studies and seven before-after studies	606 participants were treated	Studies reported decreases in luteinising hormone, follicle-stimulating hormone, oestradiol and testosterone after receiving GnRH-a	Multiple mainly before-after studies showed that PBs exerts its expected physiological effects

[162] Dopp et al. (2024).
[163] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[164] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[165] See note above.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Menstrual suppression				
Taylor 2024a[166]	3 studies including 1 cohort study and 2 before-after studies	202 participants	All studies reported menstrual suppression	Three studies showed that exert its expected physiological effects
Evidence synthesis			PBs lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of PBs).[167]

[166] See note above.

[167] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011). These very large effects on pubertal development would otherwise not have been observed without PBs.

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Table 5.5. Summary of evidence on progression to further treatment after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[168]	2 case series	65 participants	Proportion 0.92 (95% confidence interval: 0.53 to 0.99)	Very low certainty due to risk of bias concern (rating down by three levels)
Evidence synthesis			A high proportion of adolescents receiving PBs proceed with cross-sex hormone therapy.	The certainty of evidence is very low.

[168] Miroshnychenko, Roldan, et al. (2025).

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Table 5.6. Summary of evidence on safety outcomes after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Overall risk of adverse events				
Dopp 2024[169]	18 studies	-[170]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication). Over time, few statistically significant changes were observed in a variety of parameters for cardiovascular health (cholesterol, blood pressure, glucose, lipid levels) and liver enzymes; for the parameters that did show some changes (e.g., body mass index, creatinine levels, hemoglobin/hematocrit levels), values typically remained within the expected or healthy range and thus were not clinically significant. Other minor and infrequent side effects or complications included sterile abscess, headaches, mood changes, hot flashes, decreased libido, and breakthrough menstruation.	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024a[171]	3 before-after studies	109 participants	A cohort study of GnRH-a reported side effects including mild headaches or hot flushes (~20%) and moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems (<10%). Two other studies assessed other medications and reported headaches and hot flushes as common and an increase in acne in a sample of birth-registered females receiving lynestrenol, and complaints of fatigue in birth-registered males receiving cyproterone acetate	No conclusions can be drawn.

[169] Dopp et al. (2024).
[170] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis 2011, Ristori 2019).
[171] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of PBs.	The certainty of evidence is very low.
Bone density				
Dopp 2024[172]	10 studies		The primary concern noted during treatment with PBs was decreases in bone health metrics (e.g., bone mineral density, bone growth markers). These metrics tended to remain stable during PBs treatment but showed decreases relative to age-based reference ranges; as growth rates are slowed during PBs treatment, age-based reference ranges become less relevant, and the clinical significance of these effects is unclear. Bone mineral density generally showed improvement after youth started CSH and initiated puberty consistent with their gender identity; however, it is unclear what the long-term effects on bone health and related functional outcomes (e.g., risk of fracture) would be when a patient desires long-term PBs treatment without future interventions that would enable its discontinuation.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[173]				
• **Bone density during PBs treatment (g/cm2, g/cm3)**	5 observational cohort studies (4 retrospective and 1 prospective)	363 participants on hormones, 297 were evaluated	Unchanged bone density (Dual-Energy X-ray Absorptiometry measurement)	Low certainty due to serious risk of bias and serious imprecision
• **Bone density during PBs treatment in relation to reference data in the literature (z-score)**	5 observational cohort studies (4 retrospective and 1 prospective)	408 participants on hormones, 292 were evaluated	Decreased increase in bone density over time	Low certainty due to serious risk of bias and serious imprecision

[172] Dopp et al. (2024).
[173] Ludvigsson et al. (2023); This review also assessed the effect on bone density when treatment with PBs was followed by CSH.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[174]				
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	2 before-after studies	128 participants	Mean change: -0.71 (95% confidence interval: -1.09 to -0.33)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	5 before-after studies	222 participants	Mean change: -0.72 (95% confidence interval: -0.91 to -0.54)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 20–24 months**	1 before-after study	9 participants	Mean change: -1.3 (95% confidence interval: -1.57 to -1.03)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, short term follow-up assessed with: DXA, z scores scale (−3 to 3).**	2 before-after studies	93 participants	Mean change: -0.7 (95% confidence interval: -1.11 to -0.29)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)

[174] Miroshnychenko, Roldan, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Follow-up: 6 months				
Taylor 2024a	5 before-after studies	331 participants	Five studies found decreases in bone mineral apparent density and z-scores before-after treatment; however, absolute measures generally remained stable or increased/decreased slightly	Multiple studies found that bone density is compromised during PBs treatment
Evidence synthesis			PBs may lead to decreases in bone mineral density (BMD)accumulation that normally occurs during puberty, lowering Z-scores.	The certainty of evidence is low due to evidence based on only observational studies (risk of bias).[175]
Fertility				
Dopp 2024[176]	2 studies	12 participants[177]	Case reports documented healthy, viable oocyte cryopreservation after taking PBs and pausing for at least 3 months	Very low certainty due to very serious risk of bias and very serious indirectness
Evidence synthesis			It is uncertain of PBs alone will result in impaired fertility once PBs are discontinued and puberty resumes. PBs probably lead to infertility if followed by CSH.	No empirical evidence. Inferred based on high certainty evidence on PBs effects on puberty progression.
Anthropometric measures				
Ludvigsson 2023[178]	1 retrospective observational cohort	192 participants on hormones, 192 were evaluated	Increased weight and body mass index	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision

[175] This overview re-evaluates the certainty of evidence because there was disagreement across the SRs. This overview concludes that the certainty of evidence is low because only evidence based on observational studies is available. Evidence based on observational studies without additional risk of bias concerns is assessed as low certainty of evidence, if there is no sufficient justification to upgrade the certainty of evidence.
[176] Dopp et al. (2024).
[177] This systematic review by Dopp et al reported fertility preservation based on case reports, not fertility outcomes.
[178] Ludvigsson et al. (2023).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Ludvigsson 2023[179]	2 prospective observational cohort studies and 1 controlled cross-sectional study	325 participants on hormones, 286 were evaluated	Decreased lean body mass	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[180]	2 before-after studies	152 participants	In both sexes, lean body mass percentage or SD score decreased while fat percentage increased	No conclusions can be drawn.
Blood pressure				
Ludvigsson 2023[181]	1 retrospective observational cohort	15 participants on hormones, 15 were evaluated	Change in blood pressure	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[182]	3 before-after studies	96 participants	Three studies reported no change or small, non-clinically significant change in blood pressure	No conclusions can be drawn.
Metabolic measures				
Ludvigsson 2023[183]	1 retrospective observational cohort study and 1 controlled cross-sectional study	209 participants on hormones, 209 were evaluated	No change in serum lipids or blood pressure Increased insulin level in natal males Decreased insulin sensitivity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[184]	3 before-after studies	127 participants	Three studies reported no change or small change in metabolic measures.	No conclusions can be drawn.
Growth (cm/year)				

[179] Ludvigsson et al. (2023).
[180] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[181] Ludvigsson et al. (2023).
[182] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[183] Ludvigsson et al. (2023).
[184] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Ludvigsson 2023[185]	1 prospective multicentre observational study	55 participants on hormones, 55 were evaluated	Reduced growth velocity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[186]	11 studies, including 1 cohort study, and 10 before-after studies	925 participants	The cohort study found a similar height velocity between the GnRH-a group and adolescent controls. Other studies reported no change or small decrease	No high-quality studies using an appropriate design were identified. No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on anthropometric measures, body composition, blood pressure, and growth.	The certainty of evidence is very low for outcomes such as body composition, anthropometric measures, blood pressure, metabolic measures, and growth.
Cognition				
Ludvigsson 2023[187]	1 cross-sectional study	20 participants on hormones, 20 were evaluated	No change in cognition compared with matched controls	Very low certainty due to very serious risk of bias and very serious imprecision
Taylor 2024a[188]	1 cross-sectional study, and 1 before-after study	109 participants	One cross-sectional study measured executive functioning and found no difference between adolescents who were treated for <1 year compared with those not treated, but worse executive functioning in those treated for >1 year compared with those not treated. A before-after study found no differences in features typically associated with autism spectrum condition after treatment	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on cognitive outcomes.	The certainty of evidence is very low.

[185] Ludvigsson et al. (2023).
[186] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[187] Ludvigsson et al. (2023).
[188] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Table 5.7. Summary of evidence on regret after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[189]	14 studies	-[190]	High satisfaction ratings and low rates of regret (3.5% or lower) were documented, and most youth who received that intervention progressed to CSH.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after PBs.	The certainty of evidence is very low.

[189] Dopp et al. (2024).
[190] The number of participants is not calculated because this review included heterogeneous types of studies, including that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis et al. 2011), qualitative studies (e.g., Vrouenraets et al. 2022).

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6 Evidence synthesis: Cross-sex hormones

This overview identified eight SRs on the treatment effects of CSH.[191] Across all primary studies included in the eight SRs, there were no eligible randomized controlled trials. Furthermore, this overview found only eight observational studies with parallel comparison groups comparing CSH to no CSH among children or adolescents GD.[192] Generally, the sample size of these studies was small: five studies included fewer than 100 participants. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of CSH.

6.1 Included SRs on CSH

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Karalexi 2020

Karalexi, M. A., Georgakis, M. K., Dimitriou, N. G., Vichos, T., Katsimpris, A., Petridou, E. T., . . . Papadopoulos, F. C. (2020). Gender-affirming hormone treatment and cognitive function in transgender young adults: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *119*, 104721.

[191] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[192] Becker-Hebly et al. (2021); Filipov et al. (2023); Grannis et al. (2021), (2023); Grimstad et al. (2021); Hisle-Gorman et al. (2021); Jensen et al. (2019); Tordoff et al. (2022).

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Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025b

Miroshnychenko, A., Ibrahim, S., Roldan, Y., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327921

Taylor 2024b

Taylor, J., Mitchell, A., Hall, R., Langton, T., Fraser, L., & Hewitt, C. E. (2024). Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s48-s56.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

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6.2 Low risk of bias systematic reviews

Four English SRs were classified at low risk of bias.[193] Of these reviews, the eligibility criteria and number of included studies varied. Dopp 2024[194] included 56 studies including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study. The SR by Taylor and colleagues[195] included 53 studies including 12 cohort, 9 cross-sectional, 32 pre–post studies. This SR excluded results from low quality studies in the evidence synthesis. Ludvigsson 2023[196] included 16 studies and Miroshnychenko 2025b[197] included 24 studies (including 9 comparative observational studies, 13 before–after design, and 2 case series) on CSH. Only four primary studies were included in all four low risk of bias SRs, including one comparative cohort study in Germany,[198] and three before-after studies reported in the US[199] and Netherlands.[200]

6.3 Outcome 1. Gender dysphoria

A total of three SRs assessed the impact of CSH on GD.[201] Dopp 2024[202] included a greater number of studies than three other SRs, though it included case reports and a qualitative study, which inflated the overall number of studies. This systematic review narratively described that therapy with CSH was associated with improved GD and body satisfaction, despite concluding that the certainty of evidence was very low. The other two SRs, based on evidence from observational studies, concluded that the evidence on the effect of CSH on GD and body satisfaction was very uncertain.

In summary, the certainty of evidence is very low, and no conclusion can be drawn on the impact of CSH on GD.

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[193] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[194] Dopp et al. (2024).
[195] Taylor, Mitchell, Hall, Langton, et al. (2024).
[196] Ludvigsson et al. (2023).
[197] Miroshnychenko, Ibrahim, et al. (2025).
[198] Becker-Hebly et al. (2021).
[199] Cantu et al. (2020).
[200] Schagen et al. (2020); Vlot et al. (2017).
[201] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[202] Dopp et al. (2024).

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6.4 Outcome 2. Mental health and well-being

Three SRs assessed the impact of CSH on mental health, including global function, suicidality, depression, anxiety, and other symptoms.[203] Like the SRs on GD, Dopp 2024[204] included more studies than the other SRs because it included case reports and a qualitative study. This systematic review narratively described that CSH leads to improved mental health, though the certainty of evidence was assessed as very low. Three SRs reported either no change or small changes in mental health associated with CSH. The certainty of evidence was very low or uncertain. In summary, no conclusion could be drawn on the impact of CSH on mental health due to very low certainty evidence.

For suicidality, the risk of death by suicide among hormonally-treated youth was estimated to be 6 per 1,000 according to Miroshnychenko and colleagues,[205] though the certainty of evidence was very low. According to the review by Taylor and colleagues,[206] two before-after studies reported reduced treatment needs or lower levels of suicidality and self-harm. Two other cross-sectional studies reported mixed findings: one found that adolescents receiving hormones were less likely to have seriously considered or attempted suicide compared to those not receiving hormones, while another found no difference between groups among birth-registered females. It is uncertain whether CSH leads to lower risk of suicide.

In summary, this overview finds the certainty of evidence on mental health and well-being is very low, and no conclusions can be drawn.

6.5 Outcome 3. Pubertal development

Two SRs assessed the impact of CSH on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[207] SRs showed that the use of cross-sex hormone is consistently associated with physical changes. This overview

[203] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[204] Dopp et al. (2024).
[205] Miroshnychenko, Ibrahim, et al. (2025).
[206] Taylor, Mitchell, Hall, Langton, et al. (2024).
[207] Dopp et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).

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assessed the certainty of evidence as high due to the observed very large effects.[208] One example of a very large effect pertains to menstrual suppression, which is expected to be rare without CSH. Taylor and colleagues[209] reported that menstrual suppression occurred in most participants on the basis of three before-after studies. In summary, there is high certainty evidence that CSH exerts physiological effects.

6.6 Outcome 4. Safety

Four SRs reported on safety outcomes for CSH in children or adolescents with GD. These included overall risk of adverse events, cardiovascular events, bone health, fertility, sexual dysfunction, body composition, growth, and other measures.[210] Dopp 2024[211] reported that side effects and complications were limited, and these side effects did not have a major impact on treatment. Taylor 2024b[212] listed adverse event types. In birth-registered females, reported adverse events included acne, mood changes, elevated red blood markers, increased appetite, headaches, hot flashes, fatigue, hair loss, and a slight increase in metrorrhagia. In birth-registered males, adverse events included breast tenderness, elevated liver enzymes, mood swings, and increased appetite. The certainty of evidence on the overall risk of adverse events was very low.

There is limited evidence on the long-term safety of CSH among children or adolescents with GD. Based on evidence from retrospective case series, Miroshnychenko 2025b[213] reported that the risk of cardiovascular events after CSH was estimated to be 0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months. The certainty of evidence was estimated to be moderate to high, because the SR authors contemplated that a comparison group was not needed to estimate the risk of cardiovascular events following cross-sex hormone.

All four SRs assessed bone health. The evidence was primarily based on before-after studies. The most frequently reported outcome for bone health was bone mineral

[208] Guyatt, Oxman, Sultan, et al. (2011).
[209] Taylor, Mitchell, Hall, Langton, et al. (2024).
[210] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[211] Dopp et al. (2024).
[212] Taylor, Mitchell, Hall, Langton, et al. (2024).
[213] Miroshnychenko, Ibrahim, et al. (2025).

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density decreases relative to reference values (z score). Dopp 2024[214] and Ludvigsson 2023[215] reported that bone density may recover after discontinuation of PBs and initiation of CSH. Miroshnycheko and colleagues[216] reported no changes in bone mineral density for hip, lumbar spine, and femoral neck. Taylor 2024b[217] reported conflicting results from four before-after studies: two studies reported an increase in absolute bone density measures and standard deviation (SD) scores at follow-up, with one focusing exclusively on birth-registered females. In contrast, two other studies found no change in bone density or bone biomarkers, though these involved small sample sizes. There was disagreement across SRs on certainty of evidence assessment, which was very low according to Dopp 2024[218] and Miroshnycheko 2025b,[219] but low according to Ludvigsson 2023.[220] Taylor 2024b[221] did not formally assess the certainty of evidence but concluded the evidence was very uncertain. This overview assessed the certainty of evidence for bone health as very low, considering serious risk of bias in included studies, inconsistent findings in included primary studies, and imprecision of evidence (it is unclear whether the difference in bone density is clinically meaningful).

Two SRs reported on fertility outcomes. Dopp et al[222] reported cases describing successful cryopreservation of healthy, viable oocytes, embryos, and semen, often after pausing hormone therapy. According to Taylor et al,[223] 1 cohort study reported mature spermatozoa observed in patients starting treatment at Tanner stage 4 or higher, but immature germ cells present in all patients treated earlier in puberty. This overview concludes that the evidence is very low for the impact of CSH on fertility.

[214] Dopp et al. (2024).
[215] Ludvigsson et al. (2023).
[216] Miroshnychenko, Ibrahim, et al. (2025).
[217] Taylor, Mitchell, Hall, Langton, et al. (2024).
[218] Dopp et al. (2024).
[219] Miroshnychenko, Ibrahim, et al. (2025).
[220] Ludvigsson et al. (2023).
[221] Taylor, Mitchell, Hall, Langton, et al. (2024).
[222] Dopp et al. (2024).
[223] Taylor, Mitchell, Hall, Langton, et al. (2024).

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Miroshnychenko 2025b[224] included 1 before-after study, reporting no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at 6 months or 12 months of follow-up. The certainty of evidence on sexual dysfunction was assessed as very low.

Taylor 2024b[225] also reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low or uncertain. Similarly, Ludvigsson et al[226] included three retrospective longitudinal studies assessing CSH in children without prior PBs treatment. Due to small sample sizes and differing outcomes measured (e.g., lipid levels, hemoglobin, blood pressure, metrorrhagia), the studies had low external validity. No overall conclusions could be drawn.

In summary, this overview concludes that the certainty of evidence for these outcomes is very low.

6.7 Outcome 5. Regret

Only one review assessed regret after CSH and reported high satisfaction ratings and low rates of regret.[227] The certainty of evidence was very low. This overview concludes that the evidence is uncertain, and no conclusion can be drawn on regret rate.

6.8 Evidence gap

Important evidence gaps exist for the effects of CSH. Many studies were not specifically designed to capture the full range of long-term outcomes and have largely concentrated on short-term psychological or physiological changes. Key outcomes such as GD, mental health, and quality of life have been inconsistently measured and, when reported, often are derived from small, observational studies with limited follow-up periods. Critically important long-term outcomes remain poorly understood. Sexual dysfunction, despite being highly relevant to long-term well-being, has been infrequently

[224] Miroshnychenko, Ibrahim, et al. (2025).
[225] Taylor, Mitchell, Hall, Langton, et al. (2024).
[226] Ludvigsson et al. (2023).
[227] Dopp et al. (2024).

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assessed. Although a few studies have reported cardiovascular event rates, long-term follow-up is still needed to evaluate cumulative risk.

Evidence on fertility is also sparse, with little data on whether reproductive effects vary by age at treatment initiation and whether these effects are reversible. Furthermore, the compounded effects of sequential treatment with PBs followed by CSH—such as their impact on bone health recovery, final adult height, or likelihood of requiring surgical interventions—have not been investigated adequately. A lack of primary studies that separately evaluate the effects of estrogen in males and testosterone in females is a significant limitation, as hormone-sex interactions may meaningfully influence outcomes.

6.9 Summary

In summary, this overview identified eight SRs addressing the effects of CSH among children or adolescents with GD. There is high certainty evidence that CSH exerts physiological effects. The evidence is very uncertain regarding effects on GD, mental health, or safety (such as impacts on fertility and bone health).

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6.10 Evidence mapping: SRs on CSH

Table 6.1. Evidence mapping of the SRs on CSHs and the primary studies that these SRs included

	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Achille 2020		Y			Y	Y		Y
Aldridge 2021					Y			
Allen 2019		Y				Y		Y
Amir 2020		Y						
Arcelus 2016						Y		
Arnoldussen 2022		Y						
Ascha 2022					Y			
Barnard 2019		Y						
Becker-Hebly 2021		Y		Y	Y	Y	Y	
Beking 2020						Y		
Bodlund 1996		Y						
Burke 2016	Y	Y	Y			Y		
Burke 2020						Y		
Caanen 2017		Y						
Campbell 2023		Y						

[228] Chew et al. (2018).
[229] Dopp et al. (2024).
[230] Ludvigsson et al. (2023)
[231] Miroshnychenko, Ibrahim, et al. (2025).
[232] Taylor, Mitchell, Hall, Langton, et al. (2024).
[233] Thompson et al. (2023).
[234] Zepf et al. (2024).

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Cantu 2020		Y		Y	Y	Y		
Chen 2023		Y			Y			
Chen 2016							Y	
Chiniara 2018						Y		
Cohen-Kettenis 2011[235]		Y						
de Nie 2022		Y				Y		
de Vries 2014	Y	Y		Y		Y		
de Vries 2011							Y	
Delemarre-van de Waal 2006		Y				Y		
Donaldson 2018		Y						
Filipov 2023					Y			
Fontanari 2020					Y	Y		
Foster 2021					Y			
Friedman 2000			Y					
Gale 2021		Y						
Gómez-Gil 2009			Y					
Grannis 2021[236]		Y				Y		Y
Grannis 2023[237]		Y			Y			

[235] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and surgeries.
[236] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 42 for Grannis 2021. The study population may overlap.
[237] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 82 for Grannis 2023. This report was an update to Grannis 2021. The study population may overlap.

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Green 2022		Y			Y	Y		
Grimstad 2021a		Y				Y		
Grimstad 2021b						Y		
Gupta 2023		Y						
Hannema 2017						Y		
Haraldsen 2005			Y		Y			
Hisle-Gorman 2021		Y		Y		Y		
Insogna 2020		Y						
Jarin 2017	Y	Y		Y		Y		
Jensen 2019						Y	Y	
Kaltiala 2020		Y			Y	Y		Y
Khatchadourian 2014		Y				Y		Y
Klaver 2020		Y		Y		Y	Y	Y
Klaver 2018				Y		Y	Y	
Klink 2015	Y	Y		Y		Y		Y
Kuper 2020		Y				Y	Y	Y
Laurenzano 2021		Y				Y		
Lavender 2023		Y						
Lee 2024		Y						
Lierman 2017		Y						
Littman 2021		Y						
López de Lara 2020		Y				Y		Y
Madsen 2021						Y		

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Martin 2021		Y						
Mehringer 2021		Y						
Miles 2006			Y					
Miles 1998			Y					
Millington 2022						Y		
Millington 2021						Y		
Millington 2019						Y		
Morningstar 2023								Y
Mullins 2021		Y		Y		Y		
Nokoff 2020						Y		
Nota 2019					Y			
Olsavsky 2023		Y[238]			Y			
Olson 2014	Y	Y				Y		
Olson 2022		Y						
Olson-Kennedy 2018a		Y				Y		
Perl 2021[239]		Y				Y		
Perl 2020[240]		Y		Y		Y	Y	
Pyra 2020					Y			
Ristori 2019		Y						

[238] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 75 for Olsavsky 2023. This report was a cross-sectional analysis of recruited participants.
[239] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024b included the two citations as two moderate quality before-after studies.
[240] See above note.

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Schagen 2016		Y						
Schagen 2018						Y		
Schagen 2020		Y		Y	Y	Y	Y	
Schöning 2010			Y					
Segev-Becker 2020						Y		
Sequeira 2019						Y		
Slabbekoorn 1999			Y					
Stanley 2018		Y						
Stoffers 2019		Y		Y		Y	Y	Y
Strang 2022						Y		
Tack 2016	Y	Y		Y		Y	Y	
Tack 2017	Y	Y				Y	Y	
Tordoff 2022		Y			Y	Y		
Turan 2018					Y			
Turban 2018		Y						
Turban 2022		Y				Y		
Valentine 2021						Y		
van de Grift 2020						Y		
van der Loos 2022		Y						
van der Loos 2023		Y						
van der Loos 2021				Y		Y		
van Dijk 2019					Y			
van Goozen 2002			Y					

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
van Goozen 1994			Y					
van Kesteren 1996					Y			
Vlot 2017	Y	Y		Y	Y	Y		Y
Wiepjes 2019					Y			
Wiepjes 2017					Y			

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6.11 Evidence tables on outcomes for CSH in youth with gender dysphoria

Table 6.2. Summary of evidence on gender dysphoria after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[241]	8 studies	-[242]	CSH was associated with reduced gender dysphoria and improved body satisfaction in adolescents and young adults with gender dysphoria. Effect sizes for gender dysphoria and body dissatisfaction were the largest observed for any intervention.	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Miroshnychenko 2025b[243]	1 comparative observational study and 1 before-after study	146 participants from 1 comparative study and 36 from 1 before-after study	Mean difference: -0.4 (95% confidence interval: -0.24 to 0.16) from 1 comparative study and Standardised mean change 0.26 lower (1.64 lower to 1.13 higher) from 1 before-after study (higher score indicating higher levels of gender dysphoria)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision
Taylor 2024b[244]	1 before-after study	23 participants from the before-after study	The pre–post study reported a reduction in dysphoria with no participants in clinical range at follow-up.	There was insufficient evidence regarding changes to gender dysphoria
Evidence synthesis			No conclusion can be drawn on the impact of gender dysphoria by CSH.	The certainty of evidence is very low.

[241] Dopp et al. (2024).
[242] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Ristori et al, 2019).
[243] Miroshnychenko, Ibrahim, et al. (2025).
[244] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Table 6.3. Summary of evidence on mental health and well-being after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[245]	21 studies	-[246]	CSH was associated with improved mental health outcomes in adolescents and young adults with gender dysphoria. The majority of reported outcomes showed statistical significance, and nearly all of those indicated clinical significance as well (measured by effect size or compared to norms). Benefits were most consistent for depression and general functioning or well-being, and sometimes also seen for reductions in outcomes like suicidality, anxiety, and substance use (although these less consistently showed statistically significant changes).	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Miroshnychenko 2025b[247]	2 prospective observational cohort studies; 2 before-after studies	125 from 2 prospective observational cohort studies; 73 participants from 2 before-after studies	Standardised mean difference: 0.87 higher (95% confidence interval: 0.25 lower to 2 higher) from 2 prospective observational cohort studies; Standardised mean change 0.25 higher (0.09 higher to 0.4 higher) from 2 before-after studies (higher score indicating better global function)	Very low certainty due to very serious risk of bias, serious imprecision and indirectness

[245] Dopp et al. (2024)

[246] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. For this outcome of mental health, this systematic review included two reports on the same large cross-sectional study (2015 US Transgender Survey, Lee et al. (2024); Turban et al. (2022)). Cross-sectional studies were of limited value in assessing treatment effects, while the reviewers should not include two studies on the same survey.

[247] Miroshnychenko, Ibrahim, et al. (2025)

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2025b[248]	1 case series study	315 participants	6 per 1000 (1 to 18)	Very low certainty due to very serious risk of bias (rating down by three levels)
Self-harm and suicide				
Taylor 2024b[249]	2 before-after, and 2 cross-sectional studies	99 participants from 2 before-after studies, and 293 participants from 2 cross-sectional studies	Two before-after studies found a reduction in treatment needs for (or lower levels of) suicidality/self-harm, while two cross-sectional studies found conflicting results: those receiving hormones were less likely to have seriously considered/attempted suicide compared with adolescents not receiving hormones, and in birth-registered females there was no difference between groups	Hormone treatment may in the short-term improve psychological health.[250]
Depression				
Miroshnychenko 2025b[251]	2 prospective observational cohort studies; 2 before-after studies	154 from 2 prospective observational cohort studies; 389 participants from 2 before-after studies	Standardised mean difference: 0.3 lower (95% confidence interval: 0.85 lower to 0.25 higher) from 2 prospective observational cohort studies; Standardised mean change 0.41 lower (0.65 lower to 0.17 lower) from 2 before-after studies (higher score indicating worse depression)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision

[248] Miroshnychenko, Ibrahim, et al. (2025)
[249] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[250] This systematic review concluded that there is “moderate-quality evidence from mainly pre–post studies that hormone treatment may in the short-term improve psychological health”. This review had identified “moderate quality” observational studies. Including “moderate-quality observational studies” is not equivalent to “moderate quality (certainty) evidence.” According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).
[251] Miroshnychenko, Ibrahim, et al. (2025)

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Taylor 2024b[252]	1 cohort, 1 before-after, and 2 cross-sectional studies	23 participants from 1 cohort, 52 participants from 1 before-after, and 293 participants from 2 cross-sectional studies	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study. A cross-sectional study reported lower levels of depression in adolescents who had received hormones compared with those who had wanted hormones but had not received them.	Hormone treatment may in the short-term improve psychological health.
Anxiety				
Taylor 2024b[253]	1 cohort, 1 before-after, and 1 cross-sectional study	23 participants from 1 cohort, 52 participants from 1 before-after, and 19 participants from 1 cross-sectional study	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study.	Hormone treatment may in the short-term improve psychological health.
Internalising problems				
Taylor 2024b[254]	1 cohort study	23 participants	Emotional symptoms decreased at follow-up and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.

[252] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[253] See above note.
[254] See above note.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Externalising problems				
Taylor 2024b[255]	1 cohort study	23 participants	Conduct problems and hyperactivity decreased and were lower at follow-up compared to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Psychological difficulties				
Taylor 2024b[256]	1 cohort study	23 participants	Difficulties decreased with fewer in borderline/abnormal range at follow-up, and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by CSH.	The certainty of evidence is very low.[257]

[255] See above note.

[256] See above note.

[257] Two systematic reviews assessed reported very low certainty evidence, while another claimed that there was “moderate quality evidence.” This overview assesses the certainty of evidence as very low.

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Table 6.4. Summary of evidence on pubertal development after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Induced physical changes				
Dopp 2024[258]	14 studies	-[259]	CSH was associated with physical changes resulting from increased levels of masculinizing hormones (e.g., deeper voice, increased body hair, changes in muscle mass, menstrual suppression) or feminizing hormones (e.g., decreased body hair, changes in body fat distribution, breast growth), which were targeted for initiation due to being consistent with the gender identity of youth with gender dysphoria.	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024b[260]	4 before-after studies	187 participants were treated	Two observed an increase in breast volume in birth-registered males after hormones, although objectively breast volume was small, and another reported no change in breast volume in birth-registered females. One study of birth-registered females reported an increase in facial, abdominal, chest and extremities hair, and voice deepening in all participants at follow-up. Another reported no change in Tanner genital stage in birth-registered males, and no change in Tanner pubic hair stage for both	Exogenous hormones increase hormone levels and to varying degrees of induced physical changes, with potential differences depending on birth-registered sex and timing of treatment

[258] Dopp et al. (2024).
[259] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[260] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Hormone level				
Taylor 2024b[261]	15 studies including 2 cohort studies, 12 before-after studies, and 1 cross-sectional study	1519 participants were treated	All pre–post studies and a cohort reporting pre–post data found increased/heightened testosterone and oestradiol in birth-registered females and males	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Menstrual suppression				
Taylor 2024b[262]	3 before-after studies	387 participants were treated	Three pre–post studies reported suppression in most participants	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Evidence synthesis			CSH lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of CSH).[263]

[261] See note above.
[262] Taylor, Mitchell, Hall, Langton, et al. (2024).
[263] According to the GRADE methods, evidence based on observational studies can be upgraded. See Guyatt, Oxman, Sultan, et al. (2011); This overview assessed the certainty of evidence as high, upgraded by two levels due to very large effects on physical changes, hormone level, and menstrual suppression that would otherwise not be observed without CSH.

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Table 6.5. Summary of evidence on safety outcomes after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[264]	19 studies	-[265]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication).[266]	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024b[267]	4 studies, including 1 cohort, and 3 before-after studies	17 participants from 1 cohort, and 184 participants from 3 before-after studies	In birth-registered females, three studies noted increased acne; one also reported mood changes, elevated red blood markers, increased appetite, and less commonly, headaches, hot flashes, fatigue, and hair loss. Another study found a slight rise in metrorrhagia after adding testosterone to <6 months of lynestrenol. In birth-registered males, two studies commonly reported breast tenderness. Less common effects included elevated liver enzymes and high oestradiol levels, while mood swings and increased appetite were frequent.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of CSH.	The certainty of evidence is very low.
Cardiovascular events				
Miroshnychenko 2025b[268]	2 case series studies	5768 participants	0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months	Moderate to high certainty

[264] Dopp et al. (2024).
[265] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[266] This systematic review qualitatively described the types of side effects, such as parameters for cardiovascular health, liver enzyme, etc., but did not provide detailed, separate description for these outcomes.
[267] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[268] Miroshnychenko, Ibrahim, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body mass index				
Taylor 2024b[269]	16 studies (1 cohort, 14 before-after studies, and 1 cross-sectional study)	1275 participants	No change overall but some inconsistencies	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			For every 1,000 young people receiving CSH, 40 may experience cardiovascular events in 9 years.	The certainty of evidence is moderate to high.
Bone health				
Dopp 2024[270]	7 studies	-[271]	CSH was associated with improved bone density in adolescents and young adults who experienced decreases in bone density during PBs treatment. Bone density values after CSH returned to pre-treatment levels or fell within the age-based reference range for some participants.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[272]	3 observational cohort studies (2 retrospective and 1 prospective)	268 participants on hormones, 165 were evaluated	Bone density after 1–3 years (up to 22 years of age) of CSH, which had been preceded by puberty-blocking hormonal treatment in relation to reference data in the literature: After group median five years with CSH, bone density recovered in hip but not in lumbar spine compared to data at start of treatment (z-score)	Low certainty due to serious risk of bias and serious imprecision

[269] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[270] Dopp et al. (2024).
[271] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[272] Ludvigsson et al. (2023).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025b[273]				
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12 months**	1 before-after study	199 participants	Mean change: 0 (0.01 lower to 0)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	1 before-after study	199 participants	Mean change: 0.01 higher (0.01 higher to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	2 before-after studies	234 participants	Mean change: 0.01 higher (0 to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
Taylor 2024b[274]	4 before-after studies	244 participants from 4 before-after studies	Two studies reported increased bone density and SD scores at follow-up (one study included birth-registered females only), while two others found no change in bone density or biomarkers, though sample sizes were small.	There is insufficient evidence about the risks of hormone interventions

[273] Miroshnychenko, Ibrahim, et al. (2025).
[274] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the impact of CSH on bone health.	The certainty of evidence is very low.
Fertility				
Dopp 2024[275]	7 studies	-[276]	Studies documented healthy, viable oocyte or embryo cryopreservation after taking CSH and pausing for at least 3 months; a case report documented that a transgender young adult man cryopreserved viable oocytes without pausing CSH, and two other case reports documented viable semen cryopreservation after pausing CSH.	Very low certainty due to very serious risk of bias, serious imprecision, and very serious indirectness
Taylor 2024b[277]	1 cohort study	78 participants	Mature spermatozoa only observed in those starting treatment at Tanner stage 4 or higher. Immature germ cells present in all treated in early puberty.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on fertility.	The certainty of evidence is very low.
Sexual dysfunction[278]				
Miroshnychenko 2025b[279]	1 before-after study	193 participants	A linear regression analysis showed no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at 6 months or 12 months of follow up.	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
Evidence synthesis			No conclusion can be drawn on the impact of CSH on sexual dysfunction.	The certainty of evidence is very low.

[275] Dopp et al. (2024).
[276] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. This review assessed fertility preservation outcomes, not fertility outcome.
[277] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[278] Evidence only on natal females.
[279] Miroshnychenko, Ibrahim, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Cognitive				
Taylor 2024b[280]	4 studies including 2 cohort studies and 2 cross-sectional studies	42 participants from 2 cohort studies and 71 participants from 2 cross-sectional studies	Two cohort studies of birth-registered females explored testosterone's impact on brain activity. One found no performance differences in visuospatial working memory across groups but noted stronger frontal and parietal activation in treated individuals and male controls. The other observed slightly more rightward amygdala lateralisation post-treatment, aligning with patterns in male and female controls. A cross-sectional study also found greater amygdala activation and stronger amygdala–prefrontal connectivity in those on hormones. Another study reported better executive function, cognitive flexibility, and working memory in hormone-treated individuals.	There was insufficient evidence regarding changes to cognitive outcomes
Evidence synthesis			No conclusion can be drawn on the impact of CSH on cognitive outcomes.	The certainty of evidence is very low.
Height/growth				
Taylor 2024b[281]	7 studies including 1 cohort study and 6 before-after studies	43 participants from 1 cohort study and 563 participants from 6 before-after studies	For birth-registered males, two studies reported an increase in height SD score and one no change. Three studies reported an increase in absolute height. For birth-registered females, two studies reported no change in height SD score, and three reported an increase in absolute height. One study reported that birth-registered females who received hormones earlier and for longer, were taller than those who started treatment later.	There is insufficient evidence about the risks of hormone interventions

[280] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[281] See note above.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Taylor 2024b[282]	2 studies including 1 cohort study and 1 cross-sectional study	28 participants from 1 cohort study and 35 participants from 1 cross-sectional study	Birth-registered females on testosterone had lower body fat and higher lean mass than female controls. Birth-registered males had higher body fat and lower lean mass after hormone treatment than male controls. A pre–post study in birth-registered males found no fat mass change at 2 years, but an increase at 3 years. Fat percentage and lean mass percentage remained stable.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on height/growth or body composition.	The certainty of evidence is very low.

[282] See above note.

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Table 6.6. Summary of evidence on regret after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[283]	13 studies	-[284]	Findings suggest high levels of satisfaction and low rates of regret with CSH, and most youth who received that intervention did not discontinue it.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after CSH.	The certainty of evidence is very low.

[283] Dopp et al. (2024).
[284] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

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7 Evidence synthesis: surgeries

This overview identified three SRs on surgeries for children or adolescents with GD[285], with most of the evidence considering mastectomy only. Across all primary studies included in the three SRs, there were no eligible randomized controlled trials. Furthermore, this overview found that only two observational studies with parallel control groups comparing surgery with no surgery among youth with GD.[286] Generally, the sample size of these studies was small: one study included 75 participants and another included 136 participants.

7.1 Included SRs on surgeries

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Miroshnychenko 2024

Miroshnychenko, A., Roldan, Y. M., Ibrahim, S., Kulatunga-Moruzi, C., Dahlin, K., Montante, S., . . . Brignardello-Petersen, R. (2024). "Mastectomy for individuals with gender dysphoria below 26 years of age: A systematic review and meta-analysis". *Plast Reconstr Surg*. https://doi.org/10.1097/prs.0000000000011734

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

[285] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[286] Becker-Hebly et al. (2021); Olson-Kennedy et al. (2018).

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7.2 Low risk of bias systematic reviews

Of the two low risk of bias SRs,[287] Dopp 2024[288] included 18 studies (6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study), and included all types of surgeries, though most of the included studies were on mastectomy. Miroshnychenko 2024[289] included 39 studies (3 comparative observational, 2 before–after, and 34 case series), and only assessed the effects of mastectomy. Three studies were included by both reviews.[290]

7.3 Outcome 1. Gender dysphoria

Two SRs assessed the impact of surgery on GD. Dopp 2024[291] narratively described that according to 10 studies mastectomy was associated with reduced GD. The certainty of evidence was low. Miroshnychenko and colleagues included 1 comparative observational study with 136 participants and 1 before-after study with 35 participants and concluded that the certainty of evidence was very low. The authors concluded that no conclusion could be drawn on the effect of surgery in improving GD.

In conclusion, this overview finds that the certainty of evidence is very low.

7.4 Outcome 2. Mental health and well-being

The SRs assessed the impact of surgery on mental health, including global functioning, suicidality, non-suicidal self-harm, depression, and quality of life.[292] Dopp 2024[293] reported that adolescents and young adults generally showed improved mental health after surgery, with about half the outcomes showing clinically significant gains (e.g., self-perception, distress, functioning, quality of life). This systematic review acknowledged that most patients had prior interventions or were already high functioning, making it hard to isolate the effects of surgery. The other systematic review[294] reported a lower level of distress measured by Kessler Psychological Distress from one comparative

[287] Dopp et al. (2024); Miroshnychenko et al. (2024).
[288] Dopp et al. (2024).
[289] Miroshnychenko et al. (2024).
[290] Ascha et al. (2022); Marinkovic & Newfield (2017); Tang et al. (2022).
[291] Dopp et al. (2024).
[292] Dopp et al. (2024); Miroshnychenko et al. (2024).
[293] Dopp et al. (2024).
[294] Miroshnychenko et al. (2024).

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observational study. However, both SRs assessed the certainty of evidence as very low. In summary, no conclusion could be drawn on the impact of surgery on global function due to very low certainty evidence.

Miroshnychenko et al[295] reported very low certainty evidence for the effect of mastectomy on outcomes such as quality of life, depression, suicide attempts and death by suicide compared with no mastectomy. Low certainty evidence suggested that mastectomy may be associated with a lower risk of non-suicidal self-injury.

In summary, this overview suggests that it is unclear whether mastectomy leads to benefits in mental health due to very low certainty evidence.

7.5 Outcome 3. Safety

Dopp 2024[296] concluded that side effects after surgeries, such as scarring or issues with function/appearance, were generally limited. Most complications (e.g., fluid buildup, pain, bruising, infection) were minor and resolved naturally or with simple follow-up care. Miroshnychenko and colleagues[297] found high certainty evidence showing no increased risk of death following the surgery as well as high-certainty evidence for necrosis and excessive scarring after surgery.

7.6 Outcome 4. Regret

Both SRs reported a low level of regret,[298] albeit both reviews found the certainty of evidence was very low. The current evidence basis is not sufficient to reach a conclusion on the regret rate after surgery.

7.7 Evidence gap

There are substantial gaps in the evidence on surgeries for adolescents with GD. Most existing studies are case series or small observational designs, with limited or no comparator groups, and thus are unable to isolate the effects of surgery from prior

[295] Miroshnychenko et al. (2024).
[296] Dopp et al. (2024).
[297] Miroshnychenko et al. (2024).
[298] Dopp et al. (2024); Miroshnychenko et al. (2024).

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medical or psychosocial interventions. Outcomes such as GD, mental health, and quality of life are inconsistently reported and often lack validated measures.

Long-term outcomes, including the durability of psychological benefits, sexual function, need for revision surgeries, and satisfaction and well-being into adulthood, remain poorly characterized. Furthermore, while regret is a frequent topic of public discussion, existing studies do not provide robust data on the factors influencing regret. There are also knowledge gaps for other types of surgeries, including genital surgeries

7.8 Summary

In summary, this overview identified three systematic reviews addressing the effects of surgeries among children or adolescents with GD. There is high certainty evidence that mastectomy is associated with predictable surgical complications such as necrosis and scarring. The evidence is very uncertain regarding the effect of surgery on GD, improvement in mental health including suicidality, depression, and long-term outcomes such as sexual function, quality of life, and regret.

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7.9 Evidence mapping: SRs on surgeries

Table 7.1. Evidence mapping of the SRs on surgeries and the primary studies that these SRs included

	Dopp 2024[299]	Miroshnychenko 2024[300]	Thompson 2023[301]
Arnoldussen 2022	Y		
Ascha 2022	Y	Y	
Ayyala 2020		Y	
Becker-Hebly 2021	Y		Y
Berry 2012		Y	
Bodlund 1996	Y		
Boskey 2023	Y		
Bungener 2020	Y		
Bustos 2020		Y	
Caro 2024		Y	
Cohen-Kettenis 2011[302]	Y		
Cohen-Kettenis 1997[303]	Y		
Cuccolo 2019		Y	
de Vries 2014	Y		
Donaldson 2018	Y		
Donato 2017		Y	
Ederer 2023		Y	
Elfering 2020		Y	
Frederick 2017		Y	
Gold 2021		Y	
Jolly 2023		Y	
Junn 2021		Y	
Kääriäinen 2017		Y	

[299] Dopp et al. (2024).
[300] Miroshnychenko et al. (2024).
[301] Thompson et al. (2023).
[302] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and CSH.
[303] Two other citations were included for this study, Smith 2021 and Smith 2022. Neither citation was included by other reviews on PBs, CSH, or surgeries.

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	Dopp 2024[299]	Miroshnychenko 2024[300]	Thompson 2023[301]
Kamali 2021		Y	
Kaur 2023		Y	
Kelly-Schuette 2022		Y	
Kuper 2020	Y		Y
Lane 2023		Y	
Lang 2021		Y	
Lee 2024	Y		
Littman 2021	Y		
Marinkovic 2017	Y	Y	
McEvenue 2017		Y	
Mehringer 2021	Y		
Naides 2021		Y	
Namba 2009		Y	
Olson-Kennedy 2018a	Y		
Olson-Kennedy 2018b		Y	
Perez-Alvarez 2021		Y	
Robinson 2023		Y	
Rothenberg 2021		Y	
Rothenberg 2018		Y	
Sır 2022		Y	
Skorochod 2023	Y		
Stein 2021		Y	
Stojanovic 2017		Y	
Tan 2023		Y	
Tang 2022	Y	Y	
Top 2017		Y	
van de Grift 2017		Y	
van de Grift 2018		Y	
van de Grift 2016		Y	
Wolf 2021		Y	
Wolter 2018		Y	

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7.10 Evidence tables on outcomes for surgeries in youth with gender dysphoria

Table 7.2. Summary of evidence on gender dysphoria after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Mastectomy				
Dopp 2024[304]	10 studies	-[305]	Mastectomy was associated with reduced gender dysphoria (including specifically chest dysphoria), and related improvements with body satisfaction for primary and sometimes secondary sex characteristics, in natal female adolescents and young adults with gender.	Low certainty due to serious risk of bias and serious indirectness
Miroshnychenko 2024[306]	1 comparative observational study and 1 before-after study	136 participants from 1 comparative observational study and 35 participants from 1 before-after study	Mean difference 26.3 lower (28.84 lower to 23.76 lower) from the comparative observational study; mean change 28 lower (28.33 lower to 27.67 lower) for gender dysphoria related to chest, and mean change 9.1 higher (8.74 higher to 9.46 higher) according to participant reported transgender congruence scale from the before-after study (higher score indicating greater gender dysphoria)	Very low certainty due to serious risk of bias, imprecision, and indirectness
Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty				
Dopp 2024[307]	4 studies	-[308]	Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal female young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness

[304] Dopp et al. (2024).
[305] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[306] Miroshnychenko et al. (2024).
[307] Dopp et al. (2024).
[308] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Vaginoplasty and/or mammaplasty				
Dopp 2024[309]	5 studies	-[310]	Vaginoplasty "bottom surgery" and/or mammaplasty "top surgery" was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal male adolescents and young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of surgeries on gender dysphoria.	The certainty of evidence is very low.

[309] Dopp et al. (2024).
[310] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

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Table 7.3. Summary of evidence on mental health and well-being after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[311]	10 studies	-[312]	Across surgeries, adolescents and young adults with gender dysphoria generally showed improvement in mental health outcomes, with clinically significant effect sizes for about half of reported outcomes; examples of outcomes measured include self-perception, psychological distress, mental health symptoms, global functioning, and quality of life. In cases where improvement was not found, average scores on outcomes were maintained at the same level as pre-surgery. No evidence of mental health harms was found. In most studies, patients had received numerous interventions and/or been required to demonstrate high levels of functioning prior to receiving surgery, which made it difficult to assess mental health outcomes of surgery, and they are considered secondary intervention benefits.	Very low certainty due to very serious risk of bias, very serious imprecision, serious inconsistency and indirectness
Miroshnychenko 2024[313]	1 comparative observational study	299	16.39% participants had mastectomy. A multivariate analysis showed that those who received mastectomy (chest reconstruction surgery) scored an average of -7.13 (CI= -10.25 to -4.02) points lower on the Kessler Psychological Distress.	Very low certainty due to very serious risk of bias and serious indirectness

[311] Dopp et al. (2024).
[312] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), or cross-sectional study (Lee 2024).
[313] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Depression				
Miroshnychenko 2024[314]	1 before-after study[315]	68	mean change 3.16 lower (3.35 lower to 2.97 lower) (higher score indicating greater depression)	Very low certainty due to very serious risk of bias and serious indirectness and imprecision
Suicide attempts				
Miroshnychenko 2024[316]	1 comparative observational study	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.39 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.39 [95% confidence interval 0.11 to 1.45]).	Very low certainty due to very serious risk of bias and serious imprecision
Non-suicidal Self-harm				
Miroshnychenko 2024[317]	1 comparative observational study[318]	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.47 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.47 [95% confidence interval 0.22 to 0.97])	Low certainty due to very serious risk of bias
Quality of life				
Miroshnychenko 2024[319]	1 before-after study and 1 case series	80 participants from the before-after study and 34 participants from the case series	mean change 5.74 higher (5.29 higher to 6.19 higher lower) (higher score indicating better quality of life)	Very low certainty due to serious risk of bias, indirectness, and imprecision

[314] Miroshnychenko et al. (2024).
[315] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[316] Miroshnychenko et al. (2024).
[317] Miroshnychenko et al. (2024).
[318] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[319] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2024[320]	1 case series	464 participants from the case series	10 per 1,000 (0 to 20)	Very low certainty due to serious very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by surgeries.	The certainty of evidence is very low.

[320] Miroshnychenko et al. (2024).

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Table 7.4. Summary of evidence on safety after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[321]	10 studies	-[322]	Across types of surgery, side effects (e.g., scarring, issues with functioning and/or appearance) were limited and primarily would be resolved through improved surgical techniques; concerns about sexual functioning were often noted, but overall sexual functioning tended to improve from pre-surgery. Complications were also generally minor (e.g., blood fluid collection, pain, bruising, infection) and resolved through natural healing or non-invasive follow-up procedures.	Very low certainty due to very serious risk of bias and serious indirectness
Death as a postoperative complication of mastectomy				
Miroshnychenko 2024[323]	5 case series studies	3673	0 per 1,000 (0 to 0)	High certainty evidence
Necrosis (complete and partial nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[324]	8 case series studies	1998	30 per 1,000 (10 to 70)	High certainty evidence
Necrosis (complete nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[325]	13 case series studies	2236	20 per 1,000 (10 to 30)	High certainty evidence

[321] Dopp et al. (2024).
[322] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that are not typically included a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[323] Miroshnychenko et al. (2024).
[324] Miroshnychenko et al. (2024).
[325] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Excessive Scarring				
Miroshnychenko 2024[326]	12 case series studies	2405	50 per 1,000 (30 to 80)	High certainty evidence
Evidence synthesis			Surgery is generally safe and the risk of dying from surgery is low. There are risks of complications such as necrosis, scarring, sexual function impairment, and other functional impairment.	The evidence for mastectomy is high certainty. The evidence for other surgeries is very low certainty.

[326] Miroshnychenko et al. (2024).

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Table 7.5. Summary of evidence on regret after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[327]	9 studies	-[328]	Across types of surgeries, high satisfaction ratings and low rates of regret (<2%) were documented. Comparisons between adolescents and young adults with gender dysphoria suggested rates of regret and satisfaction that were equal or better in youth younger than 18.	Very low certainty due to very serious risk of bias and serious indirectness
Miroshnychenko 2024[329]	4 case series studies	775	10 per 1,000 (0 to 20)	Very low certainty due to very serious risk of bias (rating down for three levels) and serious indirectness
Evidence synthesis			There are cases of regret after surgeries. No conclusion can be drawn on the regret rate after surgery.	The certainty of evidence on regret rate is very low.

[327] Dopp et al. (2024).
[328] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), and qualitative studies (Mehringer 2021).
[329] Miroshnychenko et al. (2024).

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8 Evidence synthesis: psychotherapy

There are five SRs assessing psychotherapy among children or adolescents with GD.[330] Only two were assessed at low risk of bias in the systematic review process.[331]

8.1 Included SRs on psychotherapy

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Expósito-Campos 2023

Expósito-Campos, P., Pérez-Fernández, J. I., & Salaberria, K. (2023). Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: A systematic review. *Clinical Psychology Review*, *100*, 102229.

Heathcote 2024

Heathcote, C., Taylor, J., Hall, R., Jarvis, S. W., Langton, T., Hewitt, C. E., . . . Fraser, L. (2024). Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s19-s32.

Malpas 2022 – family-based intervention (social and psychological)

Malpas, J., Pellicane, M. J., & Glaeser, E. (2022). Family-based interventions with transgender and gender expansive youth: Systematic review and best practice recommendations. *Transgend Health*, *7*(1), 7-29.

[330] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[331] Dopp et al. (2024); Heathcote et al. (2024).

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Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

8.2 Low risk of bias systematic reviews

Evidence on the effects of psychotherapy is limited. Dopp 2024[332] included one randomized controlled trial evaluating the effects of "coping-oriented brief videos" on suicidality. There are no other randomized controlled trials. Both SRs found that psychotherapy interventions were delivered through a range of formats, highlighting considerable heterogeneity in delivery. Most were conducted face-to-face or online. Formats for both face-to-face and online interventions varied widely, including individual, group, family-based, and combined approaches. Face-to-face interventions took place in diverse settings, such as specialist gender services, community programs, community mental health clinics, a weekend retreat, and an acute residential treatment program. These heterogeneities limit the generalizability of evidence.

8.3 Outcome 1. Gender dysphoria

There was no evidence on the impact of psychotherapy on GD.

8.4 Outcome 2. Mental health and well-being

Dopp and colleagues[333] reported that peer group interventions were associated with improvements in general mental health functioning, but professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning. The certainty of evidence was very low. Heathcote and colleagues included 10 studies and found that research on psychosocial interventions for children and adolescents with GD is limited. The 10 included studies were generally low in quality and poorly reported. Most lacked clear participant selection criteria, used varied interventions, applied inconsistent outcome measures, and did not include appropriate comparators. This

[332] Dopp et al. (2024).
[333] Dopp et al. (2024).

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systematic review by Heathcote and colleagues[334] underscored a lack of robust research and the use of inadequate methodologies. In summary, the certainty of evidence for benefits of psychotherapy is very low.

8.5 Outcome 3. Safety

Neither systematic review found any indication of harm from psychotherapy.

8.6 Evidence gap

The evidence base for psychotherapy in children and adolescents with GD is marked by substantial gaps. This may be due to the inappropriate conflation of psychotherapy with "conversion therapy." As noted by the Cass Review, "[the] role of psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an unhelpfully polarised debate around conversion practices."[35] There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with GD,[36] including depression, anxiety, eating disorders, self-harm, and suicidality. Studies often did not isolate the effects of psychotherapy from those of other concurrent interventions such as social transition, PBs, or CSH, making it difficult to attribute observed outcomes to psychotherapy alone. There is little understanding of which therapeutic approaches may be more effective for specific subgroups. The lack of robust research was acknowledged by the Cass Review, which noted that "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[37]

8.7 Summary

In summary, this overview identified five systematic reviews assessing the effects of psychotherapy among children or adolescents with GD. Only two reviews were rated at low risk of bias. The available evidence on psychotherapy is limited and highly heterogeneous in terms of intervention format, delivery setting, and target population. This overview finds no evidence on the impact of psychotherapy on GD from the SRs.

[334] Heathcote et al. (2024).

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For mental health outcomes, the certainty of evidence is very low. No harms were reported.

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8.8 Evidence tables on outcomes for psychotherapy in youth with gender dysphoria

Table 8.1. Summary of evidence on mental health and well-being after psychotherapy

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Peer group intervention				
Dopp 2024[335]	4 studies	-[336]	Peer group interventions were associated with improvements in general mental health functioning in adolescents and young adults with gender dysphoria; examples of outcomes studied include mental health symptoms, well-being / quality of life, and self-esteem. All studies showed benefits on some reported outcomes, but about half of the reported outcomes did not show significant changes, and in one case the effect was not clinically significant (Austin, Craig, and D'Souza, 2018). Furthermore, a group intervention for youth with autism spectrum disorder and gender dysphoria (Brandsma et al., 2022) was associated with increases in gender dysphoria and showed benefits on only one-third of reported outcomes.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness and inconsistency

[335] Dopp et al. (2024).
[336] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Professional psychological support as a precondition for additional interventions for gender dysphoria				
Dopp 2024[337]	2 studies	135 participants	Professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning in adolescents with gender dysphoria who have started puberty. Youth remained in the clinical range on mental health symptom measures post-intervention (compared to norms) and did not show statistically or clinically significant changes over time.	Very low certainty due to very serious risk of bias, and serious indirectness
Depression				
Heathcote 2024[338]	6 studies	n = 226	Four studies found significant reductions in depression levels post-intervention and/or at a later timepoint. Two studies found non-significant differences in depression levels during mid-treatment and/or post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[337] Dopp et al. (2024).
[338] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Anxiety				
Heathcote 2024[339]	3 studies	n = 218	All three studies found significant reductions in anxiety levels post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Depression and anxiety combined				
Heathcote 2024[340]	1 study	n = 17	no significant, although marginal, difference from baseline to 6 months	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[339] Heathcote et al. (2024).
[340] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Internalising and externalising symptoms				
Heathcote 2024[341]	1 study	n = 64	Improvement in internalising and externalising symptoms	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Emotional dysregulation				
Heathcote 2024[342]	1 study	n = 35	significant reductions post-intervention and at a later timepoint (1 month)	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[341] Heathcote et al. (2024).
[342] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Suicidality				
Dopp 2024[343]	1 randomized controlled trial	483 LGBTQ+ youth (“lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities”)	A randomized controlled trial found that coping-oriented brief videos ("It Gets Better" project) led to short-term decreases in suicidality and increases in help-seeking intentions with personal contacts in young adults with gender dysphoria, but these benefits were not maintained at 4 weeks post-intervention and were not large enough to represent clinically significant effects.	Very low certainty due to serious risk of bias and indirectness
Heathcote 2024[344]	3 studies	n = 193	Two studies found significant decreases in suicidality scores from baseline to mid-treatment and/or post-intervention, and/or at a later timepoint. One study found no difference in the proportion of patients at high suicide risk before and after the intervention.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[343] Dopp et al. (2024).
[344] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Family support				
Dopp 2024[345]	2 studies	-[346]	Professional psychosocial support in the form of family and/or caregiver therapy was associated with increased family support for youth with gender dysphoria, with small but clinically significant effect sizes; similar effects were also described in one case report.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness
Psychological change				
Heathcote 2024[347]	5 studies	n = 219	For resilience, self-compassion and self-acceptance, there were significant increases in scores between baseline and post-intervention, and between baseline and 3 months for self-compassion and 6 months for self-acceptance, but the difference was no longer observed for resilience at 3-month follow-up. Participants reported more positive coping and problem-solving and increased confidence. Participants also talked about being more comfortable and accepting of their identity, having a better sense of self and self-worth, and reduced feelings of isolation and distrust towards others.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[345] Dopp et al. (2024).
[346] The sample size was not calculated because one study was an individual case report, and another was a report on parental rating.
[347] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychosocial change				
Heathcote 2024[348]	5 studies	n = 412	Three studies found significant improvements in quality of life/global functioning/well-being post-intervention and/or at later timepoints. Participants reported having better peer relationships and increased acceptance and/or support from peers (from meeting and forging relationships with others in the same situation).	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by psychotherapy.	The certainty of evidence is very low.

[348] Heathcote et al. (2024).

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9 Evidence synthesis: social transition

Two SRs assessed the impact of social transition. Both are assessed at low risk of bias.[349]

9.1 Included SRs on social transition

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Hall 2024

Hall, R., Taylor, J., Hewitt, C. E., Heathcote, C., Jarvis, S. W., Langton, T., . . . Fraser, L. (2024). Impact of social transition in relation to gender for children and adolescents: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s12-s18.

9.2 Outcome 1. Gender dysphoria

Hall 2024[350] reported the impact of social transition on GD based on two observational studies. One study found that children who had socially transitioned were more likely to experience persistence of GD into adolescence compared to those who had not. Another study reported that 92.7% of children who socially transitioned between ages 3 and 12 continued to experience GD an average of 5.4 years later. The systematic review authors did not assess the certainty of evidence, though reported a "lack of robust evidence."

This overview finds the certainty of evidence for effects of social transition on GD is very low.

[349] Dopp et al. (2024); Hall et al. (2024).
[350] Hall et al. (2024).

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9.3 Outcome 2. Mental health and wellbeing

As for mental health outcomes, Dopp 2024[351] reported that social transition among children or adolescents with GD was associated with reduced suicidality and mixed outcomes for depression or mood symptoms. However, associations with other mental health symptoms (e.g., anxiety, substance use, or overall functioning) were inconsistent. The certainty of evidence was very low. The systematic review by Hall 2024[352] highlighted that the evidence on the impact of social transition for children and adolescents with GD is limited and low in quality. Most studies are cross-sectional, US-based, use non-representative samples, and lack appropriate comparator groups. No prospective studies with suitable comparators exist. Furthermore, findings are inconsistent and should be interpreted with caution. For example, some studies suggest benefits from using a chosen name in adolescence, while another found higher rates of suicide attempts and ideation among those who socially transitioned during adolescence compared to those who socially transitioned in adulthood.

In summary, this overview concludes that the certainty of evidence for effects of social transition on mental health and well-being is very low.

9.4 Outcome 3. Regret

There was no evidence on side effects, and Dopp 2024[353] was the only review reporting the regret outcome. Though this systematic review found a low level of regret, the certainty of evidence was assessed as very low.

In conclusion, the evidence is uncertain to determine the regret rate associated with social transition.

9.5 Evidence gap

The impact of social transition on long-term GD, psychological outcomes and well-being, and future treatment decisions such as CSH or surgeries remains poorly understood. Evidence on regret is extremely limited.

[351] Dopp et al. (2024).
[352] Hall et al. (2024).
[353] Dopp et al. (2024).

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Significant evidence gaps remain in the evaluation of social transition as an intervention for children and adolescents with GD. Most available studies are cross-sectional and there are no prospective longitudinal studies with appropriate comparison groups, making it unclear whether observed associations reflect the effects of social transition or other underlying factors. Additionally, studies often did not disentangle the effects of social transition from concurrent interventions such as psychotherapy or medical treatments, further complicating interpretation.

9.6 Summary

In summary, this overview identified two systematic reviews addressing the effects of social transition among children or adolescents with GD. Both reviews were assessed at low risk of bias. The studies reviewed were largely cross-sectional and no high-quality prospective studies with appropriate comparators were identified. This overview finds that the overall certainty of evidence for effects of social transition on children and adolescents with GD is very low, and no reliable conclusions could be drawn regarding the benefits or risks of this intervention.

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9.7 Evidence tables on outcomes for social transition in youth with gender dysphoria

Table 9.1. Summary of evidence on gender dysphoria after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Hall 2024[354]				
Children	2 studies	n = 444	One study found a higher odd of persistence of gender dysphoria/incongruence in adolescence for children who had socially transitioned compared with those who had not socially transitioned. Another study found that 92.7% of those who socially transitioned between ages 3 and 12 continued to experience gender dysphoria/incongruence at the end of the study (on average, 5.4 years after socially transitioning).	There is little evidence of the benefits or harms of social transition in children and adolescents.
Adolescents	1 study	350 participants	Adolescents who preferred to be called by another name compared with no preferred name use reported higher levels of gender distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Evidence synthesis			No conclusion can be drawn on the impact of social transition on gender dysphoria.	The certainty of evidence is very low.[355]

[354] Hall et al. (2024).
[355] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

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Table 9.2. Summary of evidence on mental health and well-being after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Suicidality		
Dopp 2024[356]	5 studies	-[357]	Social transition was associated with decreased suicidality in children, adolescents, and young adults with gender dysphoria. The extent to which youth in a sample or subsample were in supportive environments moderated suicidality outcomes in several studies (Campbell, Mann, Rodgers, and Tran, 2023; Turban et al., 2021), such that social transition was associated with greater decreases in suicidality in less supportive environments. An effect size metric was available for about half of reported outcomes, all of which were clinically significant except for the impacts on suicidality in adulthood (Turban et al., 2021) which were statistically but not clinically significant.	Very low certainty due to serious risk of bias, inconsistency, and indirectness
Hall 2024[358]	2 studies	n = 9,840	A cross-sectional study reported that using a chosen name in more contexts was associated with lower suicidal thoughts and behaviors. However, another cross-sectional study[359] found that social transition during adolescence was tied to higher odds of past-year suicidal ideation and lifetime suicide attempts compared to adulthood.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[356] Dopp et al. (2024).
[357] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional studies.
[358] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with those who have not.
[359] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological functioning				
Hall 2024[360]	3 studies	n = 10,077[361]	The studies comparing children experiencing gender dysphoria/incongruence who have socially transitioned with who have not socially transitioned found that the social transition status was not associated with psychological functioning or self-perception.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Non-clinical depression or mood symptoms				
Dopp 2024[362]	6 studies	-[363]	Social transition was associated with a mix of depression or mood symptom outcomes that showed clinically significant decreases and/or showed a lack of statistically significant effects in children, adolescents, and young adults with gender dysphoria. An effect size metric was available for the majority of reported outcomes, all of which were clinically significant or in the nonclinical range (compared to norms or matched samples of cisgender youth) post-intervention.	Very low certainty due to very serious risk of bias and serious indirectness
Depressive and anxiety symptoms				
Hall 2024[364]	2 studies	n = 479	A cross-sectional study reported that adolescents using a preferred name reported fewer depressive symptoms, with no significant difference in anxiety. Another cross-sectional study found that using a chosen name in more social settings was linked to lower depression levels.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[360] Hall et al. (2024); Evidence comparing children with gender dysphoria who have socially-transitioned with those who have not.
[361] One study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 165 socially-transitioned as children.
[362] Dopp et al. (2024).
[363] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[364] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with who have not

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological distress				
Hall 2024[365]	1 study	n = 9,711[366]	A cross-sectional study found no significant link between social transition timing (adolescence vs. adulthood) and severe psychological distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Other mental health outcomes				
Dopp 2024[367]	7 studies	-[368]	Social transition did not show consistent associations with other mental health symptoms (beyond depression or mood)—such as anxiety, substance use, or broad measures of mental health symptoms or functioning—in children, adolescents, and young adults with gender dysphoria. Some measures showed a lack of statistically significant change or scores that remained elevated (compared to norms or matched samples of cisgender youth) post-intervention, and/or clinically significant improvements or scores in the nonclinical range. The high level of inconsistency suggests that these outcomes are not a core benefit of social transition. No evidence of mental health harms (e.g., increased symptoms) was found.	Very low certainty due to very serious risk of bias, and serious inconsistency and indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by social transition.	The certainty of evidence is very low. [369]

[365] See above note.
[366] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.
[367] Dopp et al. (2024).
[368] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[369] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

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Table 9.3. Summary of evidence on regret after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[370]	3 studies	-[371] ,	Social transition was found to have a very low rate of detransition to a cisgender identity (3.5%) in children with gender dysphoria, suggesting low rates of regret; data were not available for detransition rates in adolescents or young adults, but rates were lower in older children (Olson et al., 2022). Perspectives among youth who detransitioned were variable, and they did not necessarily regret the transition or reverse all social transition steps (Littman, 2021; Turban, Carswell, and Keuroghlian, 2018).	Very low certainty due to very serious risk of bias, and serious indirectness
Evidence synthesis			There are cases of regret. No conclusion can be drawn on the regret rate after social transition.	The certainty of evidence on regret rate is very low.

[370] Dopp et al. (2024).
[371] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case report.

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10 Citations for the primary studies included in the SRs on PBs, CSH, and surgeries

Achille 2020

Achille, C., Taggart, T., Eaton, N. R., Osipoff, J., Tafuri, K., Lane, A., . . . Wilson, T. A. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology, 2020(1), 8. https://doi.org/10.1186/s13633-020-00078-2

Akgul 2019

Akgul, S., Bonny, A. E., Ford, N., Holland-Hall, C., & Chelvakumar, G. (2019). Experiences of gender minority youth with the intrauterine system. J Adolesc Health, 65(1), 32-38. https://doi.org/10.1016/j.jadohealth.2018.11.010

Aldridge 2021

Aldridge, Z., Patel, S., Guo, B., Nixon, E., Pierre Bouman, W., Witcomb, G. L., . . . Arcelus, J. (2021). Long-term effect of gender-affirming hormone treatment on depression and anxiety symptoms in transgender people: A prospective cohort study. Andrology, 9(6), 1808-1816. https://doi.org/https://doi.org/10.1111/andr.12884

Allen 2019

Allen, L. R., Waston, L. B., Egan, A. M., & Moser, C. N. (2019). Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology, 7(3), 302-311. https://doi.org/https://doi.org/10.1037/cpp0000288

Amir 2020

Amir, H., Yaish, I., Samara, N., Hasson, J., Groutz, A., & Azem, F. (2020). Ovarian stimulation outcomes among transgender men compared with fertile cisgender women. J Assist Reprod Genet, 37(10), 2463-2472. https://doi.org/10.1007/s10815-020-01902-7

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KS-AG-26-1037-A-001140

Arcelus 2016

Arcelus, J., Claes, L., Witcomb, G. L., Marshall, E., & Bouman, W. P. (2016). Risk factors for non-suicidal self-injury among trans youth. J Sex Med, 13(3), 402-412. https://doi.org/10.1016/j.jsxm.2016.01.003

Arnoldussen 2022

Arnoldussen, M., van der Miesen, A. I. R., Elzinga, W. S., Alberse, A. E., Popma, A., Steensma, T. D., . . . de Vries, A. L. C. (2022). Self-perception of transgender adolescents after gender-affirming treatment: A follow-up study into young adulthood. LGBT Health, 9(4), 238-246. https://doi.org/10.1089/lgbt.2020.0494

Ascha 2022

Ascha, M., Sasson, D. C., Sood, R., Cornelius, J. W., Schauer, J. M., Runge, A., . . . Jordan, S. W. (2022). Top surgery and chest dysphoria among transmasculine and nonbinary adolescents and young adults. JAMA Pediatr, 176(11), 1115-1122. https://doi.org/10.1001/jamapediatrics.2022.3424

Ayyala 2020

Ayyala, H. S., Mukherjee, T. J., Le, T. M., Cohen, W. A., Luthringer, M., & Keith, J. D. (2020). A three-step technique for optimal nipple position in transgender chest masculinization. Aesthet Surg J, 40(11), Np619-np625. https://doi.org/10.1093/asj/sjaa150

Barnard 2019

Barnard, E. P., Dhar, C. P., Rothenberg, S. S., Menke, M. N., Witchel, S. F., Montano, G. T., . . . Valli-Pulaski, H. (2019). Fertility preservation outcomes in adolescent and young adult feminizing transgender patients. Pediatrics, 144(3). https://doi.org/10.1542/peds.2018-3943

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Becker-Hebly 2021

Becker-Hebly, I., Fahrenkrug, S., Campion, F., Richter-Appelt, H., Schulte-Markwort, M., & Barkmann, C. (2021). Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: A descriptive study from the hamburg gender identity service. Eur Child Adolesc Psychiatry, 30(11), 1755-1767. https://doi.org/10.1007/s00787-020-01640-2

Beking 2020

Beking, T., Burke, S. M., Geuze, R. H., Staphorsius, A. S., Bakker, J., Groothuis, A. G. G., . . . Kreukels, B. P. C. (2020). Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. Psychoneuroendocrinology, 111, 104461. https://doi.org/https://doi.org/10.1016/j.psyneuen.2019.104461

Berry 2012

Berry, M. G., Curtis, R., & Davies, D. (2012). Female-to-male transgender chest reconstruction: A large consecutive, single-surgeon experience. J Plast Reconstr Aesthet Surg, 65(6), 711-719. https://doi.org/10.1016/j.bjps.2011.11.053

Bodlund 1996

Bodlund, O., & Kullgren, G. (1996). Transsexualism--general outcome and prognostic factors: A five-year follow-up study of nineteen transsexuals in the process of changing sex. Arch Sex Behav, 25(3), 303-316. https://doi.org/10.1007/bf02438167

Boskey 2023

Boskey, E. R., Jolly, D., Kant, J. D., & Ganor, O. (2023). Prospective evaluation of psychosocial changes after chest reconstruction in transmasculine and non-binary youth. J Adolesc Health, 73(3), 503-509. https://doi.org/10.1016/j.jadohealth.2023.04.029

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Errata to *Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices*

Numerous minor editorial corrections have been made to the originally published version on May 1, 2025 to improve clarity, consistency, and formatting. These include typographical fixes, minor grammatical adjustments, missing bibliography items, and refinements to citations.

The following errata list notes the substantive corrections—that is, changes involving factual clarification, citation accuracy, or correction of misleading or incorrect statements. Page and footnote numbers refer to the current Review document and Appendix 4.

- Appendix 4, Section 1, Figure 1.1 (p. 8): The number of excluded studies was corrected from 3,200 to 3,198. This correction was also made in Section 5.1, Figure 5.1., of the main document.
- Section 4.2.1 (p. 63): The phrase: “recommended that PBs be offered only within a research context until further data are available” was replaced with: “recommended that PBs be offered only as part of a clinical trial until further data are available, and that all potential interventions should be tested within a research context.”
- Section 5.3 (p. 86): The term “irreversible” was corrected to “reversible.”
- Section 6.2.2 (p. 99): “Tordoff et al., 2023” in the section heading was corrected to 2022.
- Section 7.3.5, Footnote 47 (p. 114): The incorrect citation to Shrier (2020) was corrected to Shrier (2021b).
- Section 10.5, Footnote 133 (p. 177): The incorrect amicus curiae brief citation was corrected to Clinical Practice Guideline Experts (2024).
- Section 11.4, Footnote 58 (p. 193): The quotation was previously attributed in part to another source; attribution was corrected to show the entire quotation is from McNamara (2024).

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KS-AG-26-1037-A-001183

- Section 12.1 (p. 203): A sentence was corrected to indicate that *Gender-Affirming Psychiatric Care* is a textbook published by the American Psychiatric Association, not a clinical practice guideline.
- Section 12.1 (p. 203): The sentence “Instead, the APA reaffirmed its commitment to existing recommendations without addressing the critiques” and its associated footnote were deleted. The originally-referenced policy was issued by the American Psychological Association, not the American Psychiatric Association.
- Section 14.4, Footnotes 51 and 52 (p. 247): The national origin of treatment recommendations was corrected; the U.K.’s recommendations had been mislabeled as Finland’s, and vice versa.

May 15, 2025

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From: Stevens, Lee (OS/IEA)
To: Stevens, Lee (OS/IEA)
Subject: Letter to Health Care Providers on HHS Gender Dysphoria Report
Date: Wednesday, May 28, 2025 9:47:25 AM
Attachments: 5.28.25 Letter to Health Providers re Literature Review FINAL.pdf
Treatment for Pediatric Gender Dysphoria Review of Evidence and Best Practices.pdf

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Dear State Partners,

Attached please find a letter from Secretary Robert F. Kennedy, Jr. and literature review of evidence and best practices associated with Treatment for Pediatric Gender Dysphoria. The Review documents the weak evidence and growing international retreat from the use of puberty blockers, cross-sex hormones, and surgeries to treat gender dysphoria in minors.

We appreciate your attention to this important information. Please do not hesitate to contact the Office of Intergovernmental and External Affairs if you have questions.

Darcie Johnston, Director
Office of Intergovernmental and External Affairs
US Department of Health and Human Services
Washington, D.C.

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STATE OF KANSAS
OFFICE OF THE ATTORNEY GENERAL

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July 31, 2025

The Honorable Robert F. Kennedy, Jr.
Secretary of Health and Human Services
U.S. Department of Health and Human Services
200 Independence Avenue, N.W.
Washington, D.C. 20201

The Honorable Dr. Martin A. Makary, M.D., M.P.H.
Commissioner of Food and Drugs
United States Food and Drug Administration
FDA White Oak Campus
10903 New Hampshire Avenue
Silver Spring, MD 20993

RE: Review of Mifepristone

Dear Secretary Kennedy and Commissioner Makary:

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The FDA's removal of these crucial safety protocols in 2016 (and in 2023) that only five years before the FDA considered necessary begs the question of whether the removal was motivated by considerations other than the safety of patients. Now, the EPPC Study reports that in the years since the safeguards have been removed, the risk to women is far higher than was

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[16] https://www.supremecourt.gov/DocketPDF/23/23-235/298587/20240123210020119_FDA%20v.%20Alliance%20-%20Joint%20Appendix%20Volume%202%20-%20Final.pdf at J.A. 227.
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Respectfully,

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Treg Taylor
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Cc:	Kobach, Kris; Dalton, Charles; Herbert, Danedri; Powell, Anthony J.; Deckard, Connie
Subject:	Reevaluation of Mifepristone
Date:	Thursday, July 31, 2025 2:47:57 PM
Attachments:	Mifepristone letter to Sec Kennedy Final with Signatures.docx

To Whom it May Concern:

Please find attached a letter from over 20 state attorneys general, led by Kansas Attorney General Kris Kobach, requesting that HHS and the FDA conduct a reevaluation of the drug mifepristone.

Please feel free to reach out if you have any questions, concerns, or if I have sent the letter to the wrong persons.

Thank you for your kind attention.

Anthony J. Powell | Solicitor General
Office of Kansas Attorney General Kris W. Kobach
120 SW 10th Avenue, 2nd Floor | Topeka, Kansas 66612
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July 31, 2025

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Utah Attorney General



Keith Kautz
Wyoming Attorney General

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Treatment for Pediatric Gender Dysphoria

Review of Evidence and Best Practices



Department of Health and Human Services

May 1, 2025

KS-AG-26-1037-A-001200

Minor corrections made May 15, 2025: see Errata

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KS-AG-26-1037-A-001201

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Foreword

Over the past decade, the number of children and adolescents who question their sex and identify as transgender or nonbinary has grown significantly. Many have been diagnosed with a condition known as “gender dysphoria” and offered a treatment approach known as “gender-affirming care.” This approach emphasizes social affirmation of a child’s self-reported identity; puberty suppressing drugs to prevent the onset of puberty; cross-sex hormones to spur the secondary sex characteristics of the opposite sex; and surgeries including mastectomy and (in rare cases) vaginoplasty. Thousands of American children and adolescents have received these interventions.

While sex-role nonconformity itself is not pathological and does not require treatment, the use of pharmacological and surgical interventions as treatments for pediatric gender dysphoria has been called “medically necessary” and even “lifesaving.” Motivated by a desire to ensure their children’s health and well-being, parents of transgender-identified children and adolescents often struggle with how best to support them. Many of these children and adolescents have co-occurring psychiatric or neurodevelopmental conditions, rendering them especially vulnerable. When they seek professional help, they and their families should receive compassionate, evidence-based care tailored to their specific needs.

Society has a special responsibility to safeguard the well-being of children. Given that the challenges faced by these patients intersect with deeply contested issues of moral and social significance—including social identity, sex and reproduction, bodily integrity, and sex-based norms of expression and behavior—the medical practices that have recently emerged to address their needs have become a focus of significant controversy.

This Review is published against the backdrop of growing international concern about pediatric medical transition. Having recognized the experimental nature of these medical interventions and their potential for harm, health authorities in a number of countries have imposed restrictions. For example, the U.K. has banned the routine use of puberty blockers as an intervention for pediatric gender dysphoria.

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Health authorities have also recognized the exceptional nature of this area of medicine. That exceptionalism is due to a convergence of factors. One is that the diagnosis of gender dysphoria is based entirely on subjective self-reports and behavioral observations, without any objective physical, imaging, or laboratory markers. The diagnosis centers on attitudes, feelings, and behaviors that are known to fluctuate during adolescence.

Additionally, the natural history of pediatric gender dysphoria is poorly understood, though existing research suggests it will remit without intervention in most cases. Medical professionals have no way to know which patients may continue to experience gender dysphoria and which will come to terms with their bodies.

Nevertheless, the "gender-affirming" model of care includes irreversible endocrine and surgical interventions on minors with no physical pathology. These interventions carry risk of significant harms including infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret. Meanwhile, systematic reviews of the evidence have revealed deep uncertainty about the purported benefits of these interventions.

The controversies surrounding the medical transition of minors extend beyond scientific debate; they are deeply cultural and political. Public discourse is dominated by intensely polarizing narratives. Some view the medical transition of minors as a pressing civil rights issue, while others regard it as a profound medical failure and a sobering reminder that even modern medicine is vulnerable to serious error. In the midst of this highly charged debate, children and adolescents, and their families—who seek only to support their flourishing—have found themselves caught between competing perspectives. They require, and are entitled to, accurate, evidence-based information to guide their decisions.

This Review of evidence and best practices was commissioned pursuant to Executive Order 14187, signed on January 28, 2025. It is not a clinical practice guideline, and it does not issue legislative or policy recommendations. Rather, it seeks to provide the most accurate and current information available regarding the evidence base for the

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treatment of gender dysphoria in this population, the state of the relevant medical field in the United States, and the ethical considerations associated with the treatments offered.

The Review is intended for policymakers, clinicians, therapists, medical organizations and, importantly, patients and their families. It summarizes, synthesizes, and critically evaluates the existing literature on best practices for promoting the health and well-being of children and adolescents with distress related to their sex or to social expectations associated with their sex. Treatment of adults constitutes a separate topic and is not addressed in this Review. A summary of the Review's main findings is presented below.

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Executive Summary

Part I: Background

- Gender dysphoria is a condition that involves distress regarding one's sexed body and/or associated social expectations. Increasing numbers of children and adolescents in the U.S. and other countries are diagnosed with gender dysphoria. Internationally, there is intense disagreement about how best to help them.
- The term "rapid onset gender dysphoria" (ROGD) has been suggested to describe a new clinical presentation of gender dysphoria. Despite sharp disagreement about the concept's validity, symptoms consistent with ROGD have been recorded in clinics in the U.S. and other countries.
- In the U.S., the current approach to treating pediatric gender dysphoria aligns with the "gender-affirming" model of care recommended by the World Professional Association for Transgender Health (WPATH). This model emphasizes the use of puberty blockers and cross-sex hormones, as well as surgeries, and casts suspicion on psychotherapeutic approaches for management of gender dysphoria.
- The understandable desire to avoid language that may cause discomfort to patients has, in some cases, given rise to modes of communication that lack scientific grounding, that presuppose answers to unresolved ethical controversies, and that risk misleading patients and families. This Review uses scientifically accurate and neutral terminology throughout.
- In many areas of medicine, treatments are first established as safe and effective in adults before being extended to pediatric populations. In this case, however, the opposite occurred: clinician-researchers developed the pediatric medical transition protocol in response to disappointing psychosocial outcomes in adults who underwent medical transition.
- The protocols were adopted internationally before the publication of the first outcome studies. In recent years, in response to dramatic shifts in the number

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and clinical profiles of minor patients, as well as to multiple systematic reviews of evidence, health authorities in an increasing number of countries have restricted access to puberty blockers and cross-sex hormones, and, in the rare cases where they were offered, surgeries for minors. These authorities now recommend psychosocial approaches, rather than hormonal or surgical interventions, as the primary treatment.

- There is currently no international consensus about best practices for the care of children and adolescents with gender dysphoria.

Part II: Evidence Review

- Evidence-based medicine is widely recognized by health authorities worldwide as the foundation of high-quality care. Consistent with its principles, this Review undertook a methodologically rigorous assessment of the evidence underpinning pediatric gender medicine.
- Specifically, this Review conducted an overview of systematic reviews—also known as an "umbrella review"—to evaluate the direct evidence regarding the benefits and harms of treatment for children and adolescents with gender dysphoria. Existing systematic reviews of evidence, including several that have informed health authorities in Europe, were assessed for methodological quality. The umbrella review found that the overall quality of evidence concerning the effects of any intervention on psychological outcomes, quality of life, regret, or long-term health, is very low. This indicates that the beneficial effects reported in the literature are likely to differ substantially from the true effects of the interventions.
- Evidence for harms associated with pediatric medical transition in systematic reviews is also sparse, but this finding should be interpreted with caution. Inadequate harm detection in pediatric gender medicine may reflect the relatively short period of time since the widespread adoption of the medical/surgical treatment model; the failure of existing studies to systematically track and report harms; and publication bias. Despite the lack of robust evidence from population level studies, important insights can be drawn from established knowledge about

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human physiology and the effects and mechanisms of the pharmacological agents used.

- The risks of pediatric medical transition include infertility/sterility, sexual dysfunction, impaired bone density accrual, adverse cognitive impacts, cardiovascular disease and metabolic disorders, psychiatric disorders, surgical complications, and regret.

Part III: Clinical Realities

- In the U.S., the most influential clinical guidelines for the treatment of pediatric gender dysphoria are published by WPATH and the Endocrine Society. A recent systematic review of international guideline quality did not recommend either guideline for clinical use after determining they "lack developmental rigour and transparency."[1]
- Problems with the development of WPATH's *Standards of Care*, Version 8 (SOC-8) extend beyond those identified in the systematic review of international guidelines. In the process of developing SOC-8, WPATH suppressed systematic reviews its leaders believed would undermine its favored treatment approach. SOC-8 developers also violated conflict of interest management requirements and eliminated nearly all recommended age minimums for medical and surgical interventions in response to political pressures.
- Although SOC-8 relaxed the eligibility criteria for access to puberty blockers, cross-sex hormones, and surgeries, there is compelling evidence that U.S. gender clinics are not adhering even to those more permissive criteria.
- The "gender-affirming" model of care, as practiced in U.S. clinics, is characterized by a child-led process in which comprehensive mental health assessments are often minimized or omitted, and the patient's "embodiment goals" serve as the primary guide for treatment decisions. In some of the nation's

[1] Taylor, Hall, Heathcote et al. (2024a, p. 7).

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leading pediatric gender clinics, assessments are conducted in a single session lasting two hours.

- The voices of whistleblowers and detransitioners have played a critical role in drawing public attention to the risks and harms associated with pediatric medical transition. Their concerns have been discounted, dismissed, or ignored by prominent advocates and practitioners of pediatric medical transition.
- U.S. medical associations played a key role in creating a perception that there is professional consensus in support of pediatric medical transition. This apparent consensus, however, is driven primarily by a small number of specialized committees, influenced by WPATH. It is not clear that the official views of these associations are shared by the wider medical community, or even by most of their members. There is evidence that some medical and mental health associations have suppressed dissent and stifled debate about this issue among their members.

Part IV: Ethical Considerations

- The principle of autonomy in medicine establishes a moral and legal right of competent patients to refuse any medical intervention. However, there is no corollary right to receive interventions that are not beneficial. Respect for patient autonomy does not negate clinicians' professional and ethical obligation to protect and promote their patients' health.
- The evidence for benefit of pediatric medical transition is very uncertain, while the evidence for harm is less uncertain. When medical interventions pose unnecessary, disproportionate risks of harm, healthcare providers should refuse to offer them even when they are preferred, requested, or demanded by patients. Failure to do so increases the risk of iatrogenic harm and reduces medicine to consumerism, threatening the integrity of the profession and undermining trust in medical authority.
- Proponents of pediatric medical transition claim that regret is vanishingly rare, while critics assert that regret is increasingly common. The true rate of regret is

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not known and better data collection is needed. That some patients report profound regret after undergoing invasive, life-changing medical interventions is clearly of importance. However, regret alone (just like satisfaction alone) is not a valid indicator of whether an intervention is medically justified. Patients may regret medically justified treatments or feel satisfied with unjustified ones.

- A natural response to the absence of credible evidence is to call for more and better research. Even if high quality research such as randomized controlled trials on pubertal suppression or hormone therapy were feasible, however, conducting it may conflict with well-established ethical standards for human subjects research.

Part V: Psychotherapy

- The rise in youth gender dysphoria and the corresponding demand for medical interventions have occurred against the backdrop of a broader mental health crisis affecting adolescents. The relationship between these two phenomena remains a subject of scientific controversy.
- Suicidal ideation and behavior are independently associated with comorbidities common among children and adolescents diagnosed with gender dysphoria. Suicidal ideation and behavior have known psychotherapeutic management strategies. No independent association between gender dysphoria and suicidality has been found, and there is no evidence that pediatric medical transition reduces the incidence of suicide, which remains, fortunately, very low.
- There is a dearth of research on psychotherapeutic approaches to managing gender dysphoria in children and adolescents. This is due in part to the mischaracterization of such approaches as “conversion therapy.” A more robust evidence base supports psychotherapeutic approaches to managing common comorbid mental health conditions. Psychotherapy is a noninvasive alternative to endocrine and surgical interventions for the treatment of pediatric gender dysphoria. Systematic reviews of evidence have found no evidence of adverse effects of psychotherapy in this context.

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PART 1

BACKGROUND

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Chapter 1 Introduction

Currently, an estimated 3.3% of adolescents in the United States identify as transgender, and an additional 2.2% question whether they might be.[1] Many have received hormonal or surgical treatment for accompanying distress. A 2023 study published in the *Journal of the American Medical Association* found that between 2016 and 2020, 3,215 patients between the ages of 12 and 18 received surgical "breast or chest procedures" relating to their transgender identity.[2] A more recent study reported that approximately 0.1% of American 17-year-olds, or one in 1,000, was receiving cross-sex hormones between 2018 and 2022.[3] A national estimate of clinics offering pediatric medical transition interventions found at least 271 such institutions in the U.S. as of March 2023.[4]

This Review assesses the existing literature on best practices for promoting the health of children and adolescents with gender dysphoria (GD; serious distress at one's sexed body and associated social expectations[5]) or milder forms of such distress. Treatment of GD in adults is a separate topic and is not covered here.

In the United States, a number of institutions follow the guidelines of the World Professional Association for Transgender Health (WPATH) and the Endocrine Society (ES) for treating gender-dysphoric children and adolescents. This approach is usually called "gender-affirming care." Diane Ehrensaft, Director of Mental Health at UCSF's Child & Adolescent Gender Center, is a leading proponent. As Ehrensaft explains,

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[1] Suarez et al. (2024, Table 2).
[2] Wright et al. (2023).
[3] Hughes et al. (2025).
[4] Borah et al. (2023, p. 375-376). Some of these clinics were closed due to state age restriction laws.
[5] As an American Psychological Association report put it, quoting the American Psychiatric Association, gender dysphoria is an "aversion to some or all of those physical characteristics or social roles that connote one's own biological sex" (Schneider et al., 2009, p. 28). As explained in Zucker et al. (2016), "gender dysphoria" is a "technical term" that refers to symptoms of distress, but is also, as of the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (2013), a "diagnostic term" (p. 218). Gender Dysphoria is a formal diagnosis in the current (text revision) version of the DSM-5, the DSM-5-TR (American Psychiatric Association, 2022). For the relevant diagnostic criteria for children, adolescents, and adults in the DSM-III, IV, and 5, and in the current *International Classification of Diseases* (ICD-11), see Appendix 2 of this Review. The term "gender dysphoria" is used throughout this Review to refer to sex-related distress or discomfort, unless the context makes clear that the formal diagnosis is the topic.

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> [gender-affirming care] is defined as a method of therapeutic care that includes allowing children to speak for themselves about their self-experienced gender identity and expressions and providing support for them to evolve into their authentic gender selves, no matter at what age. Interventions include social transition from one gender to another and/or evolving gender nonconforming expressions and presentations, as well as later gender-affirming medical interventions (puberty blockers, cross-sex hormones, surgeries).[6]

This Review is needed because—as later chapters will detail—the emphasis on medicalization makes the field of pediatric gender medicine (PGM) highly controversial. WPATH and ES guidelines recommend commencement of puberty blockers (drugs that halt pubertal development) at the earliest signs of puberty (i.e. Tanner Stage 2), which may begin as early as age 8 in girls and 9 in boys. According to these guidelines,[7] cross-sex hormones (CSH; estrogen for boys and testosterone for girls) are started sometime thereafter; surgeries (e.g., breast removal for girls) are also recommended for some adolescents.[8] All these interventions are associated with significant risks, and most cause irreversible physical or physiological effects.[9]

Do PBs, CSH, and surgeries constitute best practice for this population? Guidelines and policies promulgated by professional medical societies in the U.S. differ from some European guidelines that recommend psychotherapy, *not* hormones or surgeries, for children and adolescents with GD. This Review, then, is written against a backdrop of intense disagreement in the international medical community. The number of young people with GD has surged, and many are suffering, as are their families. The question of how to best help these patients hinges on a comprehensive assessment of the evidence base for different treatment approaches, together with ethical considerations. Bringing ethical principles to bear on the evidence is one goal of this Review. While the need for respect and compassion resonates with all reasonable Americans, an invasive

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[6] Ehrensaft (2017a, p. 62). The gender-affirming approach can be applied to adults too; this Review is entirely focused on the pediatric variety.
[7] Coleman et al. (2022); Hembree et al. (2017).
[8] The latest version of WPATH's clinical practice guideline has no recommended age limits for surgical procedures, with the exception of 18 years old for phalloplasty (the construction of a neophallus in females with skin taken from the patient's arm or leg).
[9] See Chapter 7.

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treatment with lifelong ramifications deserves the highest level of dispassionate scrutiny.[10]

The diagnostic description of GD has changed since the condition appeared in the third edition (1980) of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM), as has the terminology used to name it. But one thing has not changed. The DSM-III was clear that "Gender Identity Disorder of Childhood" was "not merely the rejection of stereotypical sex role behavior as, for example, in 'tomboyishness' in girls or 'sissyish' behavior in boys"[11]; the current DSM has a similar emphasis: "The diagnosis is not meant to merely describe nonconformity to stereotypical gender role behavior (e.g., "tomboyism" in girls, "girly-boy" behavior in boys, occasional cross-dressing in adult men)."[12] Non-conformity to sex-role stereotypes is as old as history, and present to some degree in every known culture.[13] This feature of the human experience is not pathological and needs no treatment. What may require treatment is the suffering experienced by those alienated from their sexed bodies.

PGM is a complex topic. This Review, therefore, will cover the field's history and evolution in some detail, from the inception of the medicalized approach in the Netherlands (Chapter 3)[14] to current treatment practices in the U.S. and other countries (Chapter 4, Chapter 9). The Review describes an international trend of retreat from the present "gender affirming" approach and reviews the reasons underlying it.

This Review finds that clinical practice in this field of medicine is exceptional and concerning (Chapter 11). The influential PGM guidelines followed in the U.S. are especially problematic. They were developed in ways that contravene best practices for

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[10] The U.K.'s Cass Review pointed out that although some conceptualize controversies about pediatric gender medicine primarily from political/social standpoints, healthcare guidance should "[work] in an evidence-based way" (Cass, 2024a, p. 20).
[11] American Psychiatric Association (1980, p. 264).
[12] American Psychiatric Association (2013, p. 458).
[13] See Chapter 3, Note 1.
[14] The general treatment paradigm of puberty blockers, cross-sex hormones, and surgeries originated in the Netherlands in the 1990s as an experimental research protocol, and, based on one small study that claimed to demonstrate significant benefits to mental health, was rapidly incorporated internationally into standard practice. As described in the Cass Review's interim report, the "affirmative model" is a "model of gender healthcare that originated in the USA which affirms a young person's subjective gender experience while remaining open to fluidity … This approach is used in some key child and adolescent clinics across the Western world" (Cass, 2022a, p. 78).

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guideline development (Chapter 9, Chapter 10). This Review also finds evidence of extreme toxicity and polarization surrounding this field of medicine. ("There are few other areas of healthcare where professionals are so afraid to openly discuss their views … where name-calling echoes the worst bullying behaviour."[15]) Additionally, this Review describes the inadequate response of professional medical and mental health associations to new evidence and controversies (Chapter 12).

Section 1.1 of this opening chapter emphasizes the exceptional nature of PGM. Section 1.2 outlines the role that evidence-based medicine (EBM) plays in the Review; Section 1.3 does the same for medical ethics.

1.1 Exceptionalism

The field of PGM is exceptional due to the convergence of several distinct features.

First, the *diagnostic criteria* for GD are based solely on subjective reports and behavioral observations in patients with no objective physical pathology; there are no verifiable physiological or biochemical markers–such as abnormal imaging, lab, or clinical findings–to confirm the GD diagnosis.[16]

Second, the condition's *natural course* (also known as "natural history")—i.e., what happens when the condition remains untreated—appears to tend toward resolution absent medical and/or social transition interventions for a significant number of affected youths (see Chapter 4). While the condition will persist in some affected adolescents into adulthood, the Cass Review, commissioned by England's National Health Service (NHS), found that while "a diagnosis of gender dysphoria has been the basis for initiating medical treatment … this is not predictive that the individual will go on to have longstanding trans identity."[17]

Third, the treatments recommended by the medicalized approach are invasive, usually irreversible, and their purported benefits are based on poor quality evidence. In addition

[15] Cass (2024a, p. 13).
[16] Laidlaw et al. (2019). The same goes for the ICD's diagnosis of "gender incongruence": for discussion, see Section 13.4.
[17] Cass (2024a, p. 146).

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to infertility and impairment of sexual function, the anticipated harms include adverse effects on bone health, cardiovascular function, and possible negative impacts on brain development (see Chapter 7).

When taken separately, *none* of these features is unique in medicine. Nearly all mental health and some physical health diagnoses are made on the basis of self-reports and behavioral observations. Also, there are other pediatric conditions such as mild ear infections and strep throat that are self-limiting but still treated to reduce discomfort, promote faster recovery, or prevent complications. Lastly, there are instances in which patients are offered treatments even if the benefits of those treatments are profoundly uncertain and harms are expected. For example, craniotomies are performed to remove certain malignant brain tumors, even though these interventions carry a high risk of permanent adverse effects and the overall prognosis remains poor even with treatment. (In such cases, however, the alternative to intervention is a significantly shorter life expectancy.) What makes PGM exceptional is not any one of these features, but their combination.

Is the fundamental goal of treatment to manage gender dysphoria, a condition recognized in the DSM's catalogue of mental disorders? Or is it to manage common comorbidities such as depression, anxiety, and suicidal ideation? Or, alternatively, is it to help individuals realize their "embodiment goals" (i.e., cosmetic desires)? The stated rationales for these interventions have shifted over time, following decades of research that failed to provide credible evidence of benefit (see Chapter 5). This unclarity surrounding the treatments' fundamental aims is yet another way in which PGM is exceptional. In contrast, there is broad consensus about the purpose of medical intervention for conditions like appendicitis, diabetes, or severe depression.

1.2 Evidence

When assessing a medical intervention, one of the most important questions is: Is it safe and effective? Does drug X reduce all-cause mortality for cancer patients? Does talk therapy alleviate depression? Does knee surgery relieve arthritis pain with few postoperative complications? Even if the treatment is effective, it may not be safe, and there may be better alternatives.

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In the case of invasive treatments for GD, medical authorities in the United States have issued statements indicating that the matter is settled. According to the American Medical Association (AMA):

> Improving access to gender-affirming care is an important means of improving health outcomes for the transgender population. Receipt of gender-affirming care has been linked to dramatically reduced rates of suicide attempts, decreased rates of depression and anxiety, decreased substance use, improved HIV medication adherence and reduced rates of harmful self-prescribed hormone use.[18]

In 2022, the then Assistant Secretary for Health at the U.S. Department of Health and Human Services, Admiral Rachel Levine, gave an even more unqualified endorsement:

> Gender-affirming care is medical care. It is mental health care. It is suicide prevention care. It improves quality of life, and it saves lives. It is based on decades of study. It is a well-established medical practice.[19]

However, according to the U.K.'s April 2024 Cass Review, the most comprehensive assessment of PGM to date:

> This is an area of remarkably weak evidence, and yet results of studies are exaggerated or misrepresented by people on all sides of the debate to support their viewpoint. The reality is that we have no good evidence on the long-term outcomes of interventions to manage gender-related distress.[20]

Whether the approach endorsed by the AMA is based on adequate evidence is the subject of intense controversy. What is considerably less controversial is the best framework for assessing the efficacy of treatments. That framework is EBM, adopted by this Review.

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[18] American Medical Association (2022).
[19] Levine (2022).
[20] Cass (2024a, p. 13).

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1.2.1 Evidence-based medicine

The physician and researcher Gordon Guyatt—who coined the term "evidence-based medicine" in 1991—describes EBM as follows:

> Evidence-based medicine de-emphasizes intuition, unsystematic clinical experience, and pathophysiologic rationale as sufficient grounds for clinical decision making and stresses the examination of evidence from clinical research. Evidence-based medicine requires new skills of the physician, including efficient literature searching and the application of formal rules of evidence evaluating the clinical literature.[21]

EBM sees carefully controlled clinical trials as especially important, along with "systematic reviews" (SRs), methodical syntheses and evaluations of all relevant available evidence. Various "hierarchies of evidence" have been proposed, with SRs at the top and the opinions of individual clinicians, which, although usually valuable, are subject to a variety of biases, at the bottom. EBM has been widely accepted by health authorities around the world.[22]

In keeping with EBM principles, this Review is informed by a methodologically rigorous assessment of the evidence underpinning PGM. An overview of SRs was conducted, and its findings are presented in Chapter 5 and in Appendix 4. In brief, the overview independently confirms Cass's observation that "this is an area of remarkably weak evidence."

Given its emphasis on clinical trials, EBM is less sensitive to evidence about known mechanisms of drug action or relevant biology more broadly. This limits the ability of SRs to uncover potential causal pathways or to understand observed associations or their absence (Chapter 6). Accordingly, Chapter 7 supplements the overview of SRs with evidence from basic science, including physiology. As detailed in that chapter, the risk of harm from the medicalized approach to treating pediatric GD is serious.

[21] Guyatt et al. (1992, p. 2420). See also Akobeng (2005).
[22] E.g. Darzi (2008); Margolis (2018); Carande-Kulis (2022).

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It is important to recognize that evaluating the evidence for a treatment's efficacy does not, on its own, determine whether the treatment ought to be offered. SRs or other sources of high-quality evidence are not rigid formulas for making medical decisions; rather, they are essential components of the decision-making process. The principle is explicitly acknowledged in EBM. Medical evidence is not sufficient to justify clinical recommendations or decisions; other considerations—such as patient values and preferences—also play a critical role.[23] However, as emphasized below, these preferences do not override physicians' ethical and professional duties.

1.2.2 History lessons

An unreasonable skepticism toward medical expertise can lead to patient harm and even death.[24] On the other hand, while physicians are often capable of remarkable healing, they are not immune to human error or bias. However well-intentioned, doctors are not infallible. Even the consensus of professional medical associations can, at times, be mistaken.

Peanut allergies are a recent example. In 2000, the American Academy of Pediatrics (AAP) advised that infants deemed "high risk" should avoid peanuts—and that breastfeeding mothers do the same. In practice, this guidance was widely interpreted as a recommendation for all infants to avoid peanuts as a precaution. Peanut allergies increased dramatically, and in 2017 the AAP reversed course, recommending early *introduction* of peanuts for the highest-risk infants.[25]

This is just one of many examples.[26] Medical error is more prevalent than many Americans realize. Consensus does not guarantee correctness—in fact, it can sometimes entrench error. Nor should it be assumed that all treatment recommendations are motivated by altruism, as the opioid overprescription crisis has starkly demonstrated. This is not to suggest that medical consensus is inherently untrustworthy, but rather that it should be approached with critical scrutiny, not

[23] Djulbegovic & Guyatt (2017, p. 416); see also Guyatt et al. (2000).
[24] Centers for Disease Control (2025).
[25] Makary (2024, Chapter 1).
[26] Apart from Makary (cited above), see Prasad & Cifu (2019, Chapters 1, 2) and Patashnik et al. (2017, Chapter 2).

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unquestioning acceptance. The physicians and researchers Vinay Prasad and Adam Cifu succinctly make this point:

> We expect that medical therapy will change and evolve with time. Good treatments will replace bad ones, and then better ones will replace those. Antibiotics have replaced arsenic, and anesthesia has replaced a bullet held bracingly between the teeth. Recently, however, change has occurred in surprising ways. If you have followed the news about prostate cancer screening, mammography for women in their forties, hormone replacement, cholesterol-lowering medications, and stents for coronary-artery disease, you might think doctors cannot get anything straight. These common practices were not replaced by better therapies; they were found to be ineffective. In some cases, they did more harm than good. You might be worried that some medical practices are nothing more than fads. In some cases, you would be right.[27]

1.3 Ethics

Finding safe and effective treatments is only part of medicine's mission. Questions of ethics–and the complex theoretical issues they raise–emerge immediately alongside clinical decision-making. What if a treatment is effective but the patient doesn't want it? When is informed consent needed before starting treatment? Should doctors ever lie to their patients? What is the difference between cosmetic procedures and those that alleviate a medical problem? What should we do when clinicians disagree with pediatric patients or their parents about the best medical course of action? These and numerous similar questions are the topic of the academic field known as *medical ethics*.[28]

EBM is only decades old, but medical ethics is as old as medicine itself. The Hippocratic Oath, originating in the fourth century BCE, and attributed to the ancient Greek physician Hippocrates, is a pledge to uphold ethical principles in medicine. The Hippocratic writings include: "I will use treatment to help the sick according to my ability

[27] Prasad & Cifu (2019, p. 11).
[28] An alternative name is *biomedical ethics*. *Bioethics* is a broader field encompassing ethical issues in the life sciences beyond healthcare. Although medical ethics is an academic discipline, medical ethicists often work in clinics and hospitals, supporting patients and their families, and assisting clinicians in developing policies.

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and judgment, but I will never use it to injure or wrong them."[29] This commitment laid the foundation for the medical maxim *Primum non nocere*: First, do no harm.[30] Together with the duty of non-maleficence (avoiding harm), the duty of beneficence (promoting the patient's well-being) "undergirds all medical and health care professions and their institutional settings."[31] These duties have been continually affirmed by professional medical societies. For example, the World Medical Association's Declaration of Geneva, first published in 1948 and last revised in 2017, requires physicians to respect the "autonomy and dignity" of patients but recognizes the primacy of non-maleficence and beneficence: "The health and well-being of my patient will be my first consideration."[32]

Importantly, the physician's duties of non-maleficence and beneficence are not overridden by the patient's desire for a particular course of treatment. In 2002, the American Board of Internal Medicine Foundation, the American College of Physicians Foundation, and the European Federation of Internal Medicine articulated this point in a "Physician Charter." Among the three "fundamental principles" of the charter is the "Principle of patient autonomy," defined as follows:

> Physicians must have respect for patient autonomy. Physicians must be honest with their patients and empower them to make informed decisions about their treatment. Patients' decisions about their care must be paramount, *as long as those decisions are in keeping with ethical practice and do not lead to demands for inappropriate care*.[33]

One central question this Review attempts to answer is whether pediatric medical transition—and in particular the provision of hormonal or surgical interventions to children and adolescents—is consistent with widely-accepted principles of medical ethics. This is examined in Chapter 13. Another treatment approach—psychotherapy (talk therapy)—is examined in Chapter 14.

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[29] Beauchamp & Childress (2019, p. 155). Graduating medical students today recite a variety of oaths, sometimes composing them themselves (Weiner, 2018).
[30] The Latin phrase does not trace back to ancient times: it may have been devised by the seventeenth century English physician Thomas Sydenham (1624-1689), the "English Hippocrates" (Smith, 2005).
[31] Beauchamp & Childress (2019, p. 155).
[32] Parsa-Parsi (2017, p. 1971).
[33] American Board of Internal Medicine Foundation (2002, emphasis added).

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The innovation and responsiveness of the U.S. medical system has made it the envy of the world. However, errors are unavoidable in healthcare. The test of a medical system is not its ability to avoid mistakes, but rather how it responds once mistakes become apparent.

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Chapter 2 Terminology in Pediatric Gender Medicine

The choice of words can affect medical decision-making. Medical providers have a professional duty to apprise their patients of their conditions and the treatment options in language that is accurate, ethically neutral, and in no way misleading.[1] In the case of pediatric gender medicine (PGM), language has distorted the clinical picture, obscuring important distinctions. This chapter addresses that issue. Section 2.1 examines commonly used terminology, while Section 2.2 clarifies the specific terms adopted in this Review.

2.1 Terminology in pediatric gender medicine

Concerns about proper terminology and disclosure of all relevant information are common in medicine generally, particularly in the context of physician-patient interactions.[2] PGM, however, presents unique challenges. In this context, the understandable desire to avoid exclusionary or pathologizing language—combined with beliefs firmly embedded in the field—has led to a vocabulary and a mode of communicating that is scientifically ungrounded, that presupposes answers to ethical controversies, and that is in other ways misleading.[3]

Nearly all the core terms used in PGM exhibit these kinds of issues. As mentioned in Chapter 1, the preferred label for the treatment approach endorsed by the World Professional Association for Transgender Health (WPATH), the Endocrine Society (ES), the American Academy of Pediatrics (AAP) and the American Medical Association (AMA) is "gender-affirming care." The surgical removal of breasts (mastectomy) in physically healthy females is called "gender-affirming chest surgery" or "top surgery."[4] "Affirming" has a positive connotation, and someone who objects to "gender-affirming

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[1] Importantly, accuracy and neutrality are not enough. "80% of patients given drug A recovered" is ethically bland; suppose it is also true. Absent further context that statement is misleading if 80% of patients *not* given drug A also recovered. Another example: if a physician truthfully tells a patient, "You either have cancer or a harmless cyst," knowing that the patient has cancer, the patient has been misled.
[2] Shaw et al. (2022).
[3] For related examples in the field of women's health, see Gribble (2025). See also Bartick et al. (2025); the authors make the point that "transgender and gender-diverse people need clear and unambiguous health communications, including those related to sex-based needs, conditions, and symptoms, as much as any other group" (p. 5).
[4] E.g. Coleman et al. (2022, p. S130).

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surgery" sounds lacking in compassion. The euphemisms "chest surgery" and "top surgery" gloss over the relevant fact that breasts are removed.

Word choices can obscure patients' young ages. Terms such as "people" or "folks" are sometimes used by proponents of medicalized interventions instead of "children" or "adolescents." It is frequently emphasized that prepubertal children are not prescribed hormones or surgeries. That is true. However, clinical guidelines recommend initiating puberty blockers (PBs) at pubertal onset, which can occur at 8 or 9 years old—meaning that such interventions may be started during childhood. In discussions of this recommendation, "young people" or "adolescents" are sometimes substituted for "children."[5] Again, this helps camouflage the fact that sometimes serious medical interventions are performed on children's healthy bodies.[6]

Some adolescents transition and later detransition, reverting to living as their sex, changing their name back and making other necessary social adjustments. If the adolescent has undergone some degree of medical transition, the process of detransitioning can present significant challenges.[7] These difficulties are sometimes downplayed through the use of "retransitioning"[8] instead of "detransitioning," or writing

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[5] E.g., from a National Association of Social Workers fact sheet: "MYTH: Gender-affirming hormones, or hormone replacement therapy (HRT), are given to *children*," and: "During and after puberty, some medical treatments may be available [for] the *youth*" (National Association of Social Workers, n.d., emphasis added). According to the AAP, childhood spans ages 2-12 (Hardin et al., 2017).

"Adolescent" is often used for children in the early stages of puberty, when a layperson would use "child." As a member of WPATH put it in an email: "I would avoid children and hormones, and stick to medical definitions: when a young person reaches … puberty, [they are] therefore classed as adolescents (whether they are 9 or 12)," quoted in Boe v. Marshall, No. 2:22-cv-00184: 557-9/700-2 (2024, p. 16). See also Ryan (2025): "Dr. Olson-Kennedy generally avoids using the words 'child,' 'children' or 'kids'"; and Levine et al. (2022b, p. 117). The Endocrine Society made a simple factual error when it stated that "medical intervention is reserved for older adolescents and adults" (Endocrine Society, 2023).

[6] Another phrase is "wrong puberty": e.g., "pubertal blockers … block the progression of puberty so the young person doesn't go through the wrong puberty" (Jacoby, 2022). Apart from presupposing the correct treatment, it is misleading to suggest that the "right puberty" induced by estrogen in males or testosterone in females amounts to a cross-sex version of puberty, because puberty centrally and definitionally involves maturation of the capacity for reproduction. The Endocrine Society guideline adopts this language, writing of the "induction of female puberty" in males (Hembree et al., 2017, Table 8); see also Section 7.4.1.

[7] MacKinnon, Expósito-Campos et al. (2023).

[8] Olson et al. (2022). "Retransitioning" does have a legitimate use, to describe the process of transitioning again, going from detransitioning to living as the other sex (MacKinnon, Expósito-Campos et al., 2023, p. 1).

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of “dynamic desires for gender-affirming medical interventions.”[9] This conceptualizes an experience that can be profoundly distressing for the patient as simply another stop along their “gender journey.”[10]

The lead author of the AAP’s 2018 policy statement (reaffirmed in 2023), “Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents,” has even described detransition as part of the “gender affirming” approach itself, thus making treatment failure impossible to conceive.[11]

The problems go deeper. The terminology of “sex,” “male,” and “female” is indispensable if the medical and ethical issues are to be discussed responsibly. And yet proponents of medicalization go to extraordinary lengths to avoid the plain use of these words, and related words such as “boy” and “girl.” When “sex” is defined, the definition is rarely correct,[12] and in any case the preferred phrase is “sex assigned at birth.” According to the ES’s “Clinical Practice Guideline for the treatment of Gender-Dysphoric/Gender-Incongruent Persons,” “the terms biological sex and biological male or female are imprecise and should be avoided.”[13] Pediatric female patients are not “girls” or “young women,” but rather “AFAB individuals” (people “assigned female at

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[9] Turban, Brady et al. (2022).

[10] Jorgensen (2023b): “we should be cautious about adopting euphemisms that might mask iatrogenic harm” (p. 2180).

[11] “Rafferty [the lead author of the AAP 2018 policy statement] told me patients who live with harms or regrets do not signal a failure of the affirmative care model. If a child or patient doesn’t like the effects of an intervention, or begins to feel different in their identity, then the provider continues to affirm by discontinuing treatment. ‘They’re not treatment failures if that’s what’s affirming’ he said” (Block, 2023d).

[12] E.g. the entry for “sex” in Hembree et al. (2017, Table 1) conflates sex with characteristics highly correlated with sex in humans (“sex chromosomes,” “sex hormones,” etc.); the entry in Rafferty et al. (2018, Table 2) erroneously says that sex is “an assignment that is made at birth.” For the orthodox conception of sex in biology, see, e.g., Dawkins (1976, pp. 183-184); Parker (2011); Futuyama & Kirkpatrick (2017, p. 249). The orthodox conception is in an Endocrine Society “Scientific Statement” (Bhargava et al., 2021), and in a Health and Human Services document (Health and Human Services, 2025).

[13] Hembree et al. (2017, Table 1). Hembree et al. don’t take their own recommendation completely to heart, writing at one point that “in females [i.e. “biological females”] … the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain” (p. 3880). This ES guideline is an update of “Endocrine treatment of transsexual persons: An Endocrine Society clinical practice guideline,” published in 2009. In that earlier guideline the conventional meaning of sex is used, and the authors use the allegedly imprecise phrase “biological females” (Hembree et al., 2009, p. 3139). The AMA also claims that “sex assigned at birth” is “more precise” than “sex” (American Medical Association, 2021, p. 14).

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birth"). Some authorities in PGM say that the patients wanting mastectomies are in fact "young men."[14]

"Assigned sex at birth" is not a harmless euphemism. It suggests an arbitrary decision—not unlike "assigned seating"—rather than the observation of a characteristic present long before birth, namely the child's sex. Moreover, if the phrase "assigned sex" were intended merely as a gentler way of referring to sex in conversations with patients and families, one would expect more direct language to be used in the specialty medical literature. In professional contexts, where clarity is paramount, euphemisms are generally avoided. Yet "assigned sex" is ubiquitous in clinical and academic publications. Not only that: use of such terminology is now *mandated* by certain medical journals.[15] The American Psychological Association (APA) style guide, for example, classifies "birth sex" and "natal sex" as "disparaging terms" which problematically "imply that sex is an immutable characteristic."[16] As law professor Jessica Clarke observes, "'Sex assigned at birth' is not a euphemism for 'biological sex' but a critique of the very concept."[17]

The term "gender identity" is an especially important example of how words can sow confusion. When first introduced in the 1960s, it meant "the sense of knowing to which sex one belongs, that is, the awareness 'I am a male' or 'I am a female'."[18] Almost

[14] "I don't advocate removal [of] breast tissue from young women. I advocate for chest reconstruction in young men" (Olson-Kennedy, 2019, p. 38); this use of language has the effect of making mastectomies for adolescent girls sound unalarming. See also Ehrensaft (2017b, p. 7): "transgender boys are boys and transgender girls are girls."
[15] *The Lancet*'s "Information for Authors" mandates the use of "sex assigned at birth," instead of "biological sex," "birth sex," or "natal sex" because "it is more accurate and inclusive." The same document also incorrectly states that sex is not "binary," that it exists "along a spectrum," and that a person's sex can change (The Lancet, 2025).
[16] American Psychological Association (2024a).
[17] Clarke (2022, p. 1828). The language of "assigned sex" was used in the 1950s for exceedingly rare cases of disorders of sex development (DSDs), where a baby with ambiguous genitalia could be raised as either a boy or a girl (Money, 1955).
[18] Stoller (1964, p. 220); see also Greenson (1964, p. 217). For discussion see Byrne (2023b, 2023a); Haig (2023); D. F. Janssen (2023).

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everyone has a gender identity in this sense, and moreover one that is congruent with their sex: males know that they are male, and females know that they are female.[19]

However, today the phrase "gender identity" is used in a significantly different way. For example, WPATH defines "gender identity" in the glossary to their current clinical practice guideline (SOC-8) as:

> A person's deeply felt, internal, intrinsic sense of their own gender.[20]

This new definition is unclear. For instance, what does "gender" mean in this context? The glossary in SOC-8 offers little clarification—though it does correctly acknowledge that the word is highly ambiguous. One meaning of "gender" given in the glossary is "gender identity." But "gender" in the definition above cannot mean "gender identity," otherwise the definition would be circular. Another meaning provided is "gender expression," but this too leads to circularity, because "gender expression" is itself defined in the same glossary in terms of "gender."[21]

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[19] Some children distressed about their sexed bodies are mistaken about whether they are male or female, but some are not. Accordingly, being mistaken about one's sex is not required for a diagnosis of Gender Dysphoria in Childhood in the *Diagnostic and Statistical Manual of Mental Disorders* (DSM): "A strong *desire* to be of the other gender" is enough. Although the diagnostic criteria for children also mention "an insistence that one *is* the other gender," this is not a necessary criterion, and is altogether absent from the DSM criteria for Gender Dysphoria in Adolescents and Adults (American Psychiatric Association, 2022, pp. 512-513, emphasis added).

[20] Coleman et al. (2022, p. S252). Along the same lines: "On one level, gender identity is something deeply felt and can be difficult to put into words. I often refer to this as one's *transcendent* sense of gender. You simply *feel* a certain gender" (Turban, 2024, p. 38); "Gender identity is a person's inner sense of belonging to a particular gender, such as male or female" (Ehrensaft, 2017b, p. 7). This latter definition would sound strange if "particular gender" was replaced by "particular sex": the implication would then be that there are more sexes beyond male and female.

[21] Another definition of "gender" given in SOC-8 is "social gender role, including understandings and expectations culturally tied to people who were assigned male or female at birth" (Coleman et al., 2022, p. S252). Consider the suggestion that this is the intended sense of "gender" in WPATH's definition of "gender identity." That is, "gender identity" is defined as: "a person's deeply felt, internal, intrinsic sense of their own social gender role." Now it is true that a person might have a sense of their "social gender role." A woman, say, might be aware that in her culture certain expectations apply to women. However, here the language of "deeply felt/internal/intrinsic" is quite inappropriate, which is one piece of evidence that the present suggestion is wrong. More importantly, there is no room for any "mismatch" between a person's sex and their social gender role. A woman may (perhaps rightly) disapprove of the expectations that her culture imposes on females; that is, she may disapprove of her social gender role. Since she has this gender role because she was "assigned female" at birth, her "gender" in this sense will *always* match her sex. But evidently WPATH wishes to define "gender identity" in such a way as to allow for *mismatches* with a person's sex. Hence, the "gender role" sense of "gender" is of no help in defining "gender identity" either. [Note continued on next page.]

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In short, “gender identity” as it appears in SOC-8 and related literature is ill-defined.[22] It may be true that a person’s gender identity is subjective, or undetectable by blood tests or neuroimaging,[23] or otherwise beyond the reach of science, but the more critical point is that no tolerably clear definition of “gender identity” has been offered in the first place.[24] This is a serious problem, because the term figures centrally in the justification for medical intervention.

The term “transgender” is typically explained in terms of gender identity. Transgender people are those whose gender identities do not “align with” or “match” their sex (or “sex assigned at birth”).[25] Since “each of us has a gender identity, though many of us never give it much thought,”[26] the rest of humanity have gender identities that match their sex; these people are said to be “cisgender.” It is important to realize that “transgender” is not a clinical term and does not correspond to a medical diagnosis.[27] Indeed,

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Another way of explaining “gender” is to give a list of representative “genders” with the expectation or hope that the reader will see the pattern. In principle, this sort of explanation can be satisfactory. However, WPATH’s previous guideline offered the following examples: “male (a boy or a man), female (a girl or woman) … boygirl, girlboy, transgender, genderqueer, eunuch” (Coleman et al., 2012, p. 221). Notice that the list includes the category *transgender*, which is itself explained in terms of gender identity and hence gender, introducing a circularity. Another point is that if *eunuch* is a (contemporary) gender, then “gender” as it figures in WPATH’s definition of “gender identity” cannot possibly be explained in terms of “social gender role” (see the first paragraph of this note). Eunuchs had a special social role in Imperial China; they have no such role today. WPATH’s current guideline has an entire chapter on eunuchs, so clearly WPATH thinks the gender *eunuch* is not an anachronism.

[22] Here is another example. The AAP’s 2018 policy statement defines gender identity as “[a] person’s deep internal sense of being female, male, a combination of both, somewhere in between, or neither” (Rafferty et al., 2018, Table 1). The policy statement also says that a “transgender” person is someone “whose gender identity does not match their assigned sex.” Clearly “gender identity” as the AAP defines it cannot mean what it originally did, because a transgender man, for instance, might not be mistaken about being female. How to interpret “female” and “male” in the AAP’s definition is far from clear.

[23] See, e.g. Baldinger-Melich et al. (2020); Levin et al. (2023); Bakker (2024).

[24] The original 1960s explanation of gender identity (see above) was perfectly clear, but that is not the contemporary conception in gender medicine.

[25] Boe v. Marshall, No. 2:22-cv-00184: 558-16 (2024); Ehrensaft (2017b); Olson-Kennedy (2022). According to the previous WPATH guideline (SOC-7): “The gender identity of transgender people differs to varying degrees from the sex they were assigned at birth” (Coleman et al., 2012, p. 221). Remarkably, sometimes “transgender” is defined to include commonplace gender non-conformity, *regardless* of any “mismatched” gender identity. For instance, according to SOC-8, if a person’s “gender expressions are not what is typically expected for the sex to which they were assigned at birth,” they are transgender (Coleman et al., 2022, p. S252).

[26] Forcier et al. (2020, p. 2). Similarly: “Gender identity … is a core and *universal* component of human identity” (Boe v. Marshall, No. 2:22-cv-00184: 592-12, 2024, p. 6, emphasis added).

[27] Thus a recent article on assessing “transgender and gender diverse adolescents” for puberty suppression recommends reassuring patients that the goal is not to determine whether they “are actually transgender” (Turban et al., 2025, p. 14). But see Section 13.3.

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proponents of the medicalized approach emphasize that some transgender people neither desire nor need medical or surgical interventions of any sort.

It is often claimed that gender identity is "innate or fixed at a young age," and so "cannot be changed."[28,29] Putting that idea together with the definition of "transgender," the result is that being transgender is a close-to-immutable trait. (The same goes for being cisgender.) A "transgender child," in this framework, is a child whose unalterable gender identity does not align with their sex, while cisgender children are the other kind.[30] Once this binary paradigm of "trans kids" and "cis kids" is accepted, therapeutic exploration of the underlying causes of a child's discomfort with his or her sexed body is readily dismissed as "conversion therapy," an unethical attempt to interfere with the development of the child's authentic self.[31,32]

According to many authorities in PGM, there is a test to determine whether a child is transgender or cisgender. This is because children "know who they are." Specifically, they know their "gender."[33] If a child's "gender" matches their "assigned sex," they are cisgender; if not, they are transgender. So, to determine whether a child is transgender or cisgender, one only need ask.

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[28] Adkins (2016, p. 4); Ehrensaft (2017b, p. 7); Olson-Kennedy (2022, p. 9). However, an earlier paper on the PMT approach, which has Ehrensaft and Olson-Kennedy as co-authors, states that it is a "myth" that gender identity is "immutable" (Hidalgo et al., 2013, p. 288), indicating at least some confusion about key terms.

[29] In his expert witness report for *Boe v. Marshall*, Aron Janssen, a gender clinician and vice chair of clinical affairs at Lurie's Pritzker Department of Child and Adolescent Psychiatry, wrote that gender identity, "a person's innate sense of their gender," "cannot be altered through medical or psychological interventions" (Boe v. Marshall*,* No. 2:22-cv-00184: 592-12, 2024, p. 6).

[30] Some PMT authorities would dispute this characterization and claim that a transgender child's gender identity *does* match their sex—what it *doesn't* match is their "birth-assigned sex" (Ehrensaft, 2017b, p. 9).

[31] "Psychotherapy may be beneficial but should not be a requirement for gender-affirming treatment, and conversion treatment should not be offered" Coleman et al. (2022, p. S10). On "conversion therapy," see Section 14.5.2.1.

[32] Two books that discuss the "transgender child" are Gill-Peterson (2018) and Meadow (2018). On Gill-Peterson, see Byrne (2024b, pp. 243-244). For an early expression of skepticism, see Brunskell-Evans & Moore (2018).

[33] [R]esearch substantiates that children who are prepubertal and assert an identity of TGD [transgender and gender-diverse] *know their gender* as clearly and as consistently as their developmentally equivalent peers who identify as cisgender and benefit from the same level of social acceptance" (Rafferty et al., 2018, emphasis added). Also: "Individuals whose sex assigned at birth is opposite to the gender they *know themselves to be* are often referred to as *transgender*" (Turban & Ehrensaft, 2018, p. 1, first emphasis added); "studies show that trans children and adolescents know themselves and their gender" (Ashley, 2022b, p. 15).

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An immediate problem is posed by the undeniable phenomenon of temporary youthful transgender identification. (See Section 4.3.1.4.) Attempting to address this difficulty, Aron Janssen, vice chair of clinical affairs at the Pritzker Department of Child and Adolescent Psychiatry at Lurie Children's Hospital in Chicago, and chair of the American Academy of Child and Adolescent Psychiatry's Sexual Orientation and Gender Identity Issues Committee, stated in a deposition that although gender identity is "static" and "fixed," "one's understanding of it can evolve over time."[34]

Dysphoric children and socially transitioned children are routinely referred to as "transgender children." In some cases, this is for convenience or as a gesture of respect.[35] However, its use may subtly influence clinical reasoning. The label "transgender" implies a mismatch between gender identity and the person's sexed body, and that mismatch can supposedly cause gender dysphoria.[36] Since an adolescent's gender identity cannot be changed, the obvious solution to relieve the distress is to change their body.[37]

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[34] Boe v. Marshall, No. 2:22-cv-00184: 558-16 (2024, pp. 104-110). Some PMT clinicians maintain that such change in understanding is not likely: "there is [a] small but non-zero possibility of one's understanding of their gender identity evolving over time" (Turban et al., 2025, p. 2). According to UCSF's Diane Ehrensaft, "My own clinical experience told me that you could discern one group of children from the other prior to adolescence, not with 100% accuracy, but not far from it" (Ehrensaft, 2014, p. 578). As Ehrensaft puts it in her book *The Gender Creative Child*, "we can tell the apples (the transgender children) from the oranges (the gender-nonconforming but not trans kids), sometimes as early as when they are three years old. So, why hold the apples back if they already know who they are?" (Ehrensaft, 2016, p. 55). Put without the framing of "trans kids," the clinical issue is whether one can discriminate between gender dysphoric children whose dysphoria will resolve without any medical intervention, and those whose dysphoria will persist into adulthood (see Section 4.3.2).

[35] E.g. Olson et al. (2022).

[36] According to WPATH, gender dysphoria is "distress that is *caused by* a discrepancy between a person's gender identity and that person's sex assigned at birth" Coleman et al. (2012, p. 221, emphasis added). The quotation continues, "(and the associated gender role and/or primary and secondary sex characteristics)"; so at least in theory, one way of relieving gender dysphoria would be to change the "associated gender role."

[37] The AAP policy statement includes more young people as candidates for medicalization that just those with mismatched or incongruent gender identities. The title of the policy statement is "Ensuring Comprehensive Care and Support for Transgender *and Gender-Diverse* Children and Adolescents" (Rafferty et al., 2018, emphasis added). Transgender youth, the policy statement says, are "a subset of gender-diverse youth." The policy statement explicitly equates "gender diverse" with "gender nonconforming" (the latter term being deprecated only because of its allegedly pejorative connotation). Thus, gender-nonconforming youth *in general* are singled out as potential recipients of sex-related hormone therapy and surgery. The same points apply to WPATH's SOC-8, *Standards of Care for the Health of Transgender and* Gender Diverse *People*, which also deprecates the use of "gender-nonconforming" (Coleman et al., 2022, p. S11, emphasis added); SOC-7 (Coleman et al., 2012) has "gender-nonconforming" in its title.

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2.2 Terminology in this Review

While communication with patients and families must always be sensitive and compassionate, describing sex as a matter of "assignment" is, at best, confusing and accordingly not truly respectful. Patients and their legal caregivers are entitled to the facts regarding their medical situation; this is essential for informed participation in the medical decision-making process. Just as importantly, evidence assessments must use accurate and precise language when referring to sex, in order to maintain scientific integrity and support sound clinical judgment.

Treatment of children and adolescents with GD presents an especially complex case of doctor-patient communication because doctors understandably do not want to alienate their patients; trust is the bedrock of shared decision-making.

There is growing international awareness of the importance of using accurate sex-based language. As the recent U.K.'s *Review of Data, Statistics and Research on Sex and Gender* (RSG) asserts:

> Analysts must be able to use clear and familiar language in reporting findings on sex. Terms such as women, men, boys and girls are synonymous with (respectively) adult human females and males and children of each sex. Similar considerations apply to terms such as mothers and fathers, sons and daughters.[38]

The RSG also recommends against using the phrase "sex assigned at birth," remarking that it is "misleading."[39]

The RSG notes that the word "gender" has "multiple distinct meanings, including: a synonym for sex; social structures and stereotypes associated with sex; and gender identity."[40] For this reason, the RSG cautions against using the word when misunderstandings could arise. A prime example is WPATH's definition of "gender identity" discussed above, which uses the word "gender" without an adequate

[38] Sullivan (2025, p. 11). The Review was commissioned by the previous Conservative government and welcomed by the present Labour Secretary of State for Health and Social Care (Scott, 2025).
[39] Sullivan (2025, p. 7).
[40] Sullivan (2025, p. 5).

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explanation. Because of its unclarity and ambiguity, “gender” will generally be avoided in this Review. “Gender identity” inherits the obscurity of “gender” and will not be used either.[41] As discussed, the term “transgender child” suggests that medical intervention is the default or primary course of action. For this reason, it will be avoided.[42]

The Review will use “social transition” for the process of changing one’s sex-associated name, presenting oneself as a member of the other sex, being referred to with third-person pronouns for the other sex,[43] and so on.

“Gender dysphoria” (GD) is in the DSM and at present has no accepted alternative; therefore, it will be used despite problems with the word “gender.” “Gender nonconformity” is a familiar and well-understood phrase, so it will also be used (although some may prefer “sex-stereotype nonconformity”). As already indicated, “pediatric gender medicine” (PGM) will be used for the clinical field that treats children and adolescents with GD, sometimes with medical interventions. Instead of the term “gender-affirming care” this Review will use “PMT” (pediatric medical transition), as in phrases such as “the PMT approach.” This is more accurate and carries no positive or negative connotation. The PMT approach does not always involve hormones or surgeries, but some of its proponents do tend to view even social transition as an initial step toward medical transition. The older term “cross-sex hormones” (CSH)[44] is more neutral and informative than “gender-affirming hormone therapy.” Surgeries to alter sex characteristics[45] for adolescents will be given medically standard, clinical, neutral descriptions—e.g. “mastectomy.” Finally, the older term “sex reassignment surgery” (SRS) will be used rather than the more recent “gender confirmation surgery.”

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[41] Also relevant from the RSG: “Questions on gender identity should recognize that the concept of gender identity as such will be unfamiliar, unclear or irrelevant to some respondents, and that many respondents may not perceive themselves as having a gender identity. Questions should not assume that respondents will agree that they have a gender identity” (Sullivan, 2025, p. 9). The RSG illustrates how “gender identity” is now firmly embedded, not just in gender medicine, but also in social statistics (and, it could be added, pedagogy). For an illuminating discussion of the history, see Brubaker (2025).

[42] Needless to say, terminology that makes other treatment pathways prominent is equally undesirable.

[43] Or *they* or neo-pronouns (*xe*/*xem* and the like).

[44] Even this terminology is not perfect: estrogens are normally present in males, although at lower levels than in females; vice versa for androgens (including testosterone).

[45] Sex characteristics are either *primary* (the external and internal reproductive organs), or *secondary* (characteristics that emerge at puberty, such as breasts in females and facial hair in males).

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Chapter 3 History and Evolution of Adult and Pediatric Gender Medicine

Medical transition for gender dysphoric youth is a comparatively recent practice and grew out of the clinical experience of transitioning mature adults. It is common in medicine to extend medical treatments to children once they have been proven safe and effective in adults. In this case, however, the opposite occurred. The rationale for transitioning adolescents emerged from the observation that medical transition in adults often failed to produce the desired positive outcomes. This chapter explains how this came about and provides additional historical context.

Sections 3.1, 3.2, and 3.3 briefly review the history of medicalized transitions, which are barely a century old. Sections 3.4 and 3.5 explain how the observed failure of medical transition to produce positive psychosocial outcomes for adults led clinicians in the Netherlands to propose an early intervention model, resulting in the "Dutch Protocol." The final section describes how the Dutch Protocol evolved into the "gender affirming care" approach to pediatric medical transition (PMT), a shift that was accompanied by significant changes in the pediatric patient population presenting with GD—both in terms of size and demographic composition.

3.1 *The Transsexual Phenomenon*

Extremely gender-nonconforming people, including those who live their lives either as members of the other sex, or as a so-called "third gender," have been documented throughout human history.[1] One famous example is the French diplomat and spy Chevalière d'Eon (1728-1810), who dressed and "passed" as a woman during the final 32 years of his life. Everyone was convinced, including the last king of France, Louis XVI.[2] In the early 20th century, the English physician and sexologist Henry Havelock Ellis coined *eonism*, after the Chevalière, for "people who took pleasure in behaving and

[1] See, e.g., Bullough et al. (1997); R. Green (1966); Herdt (1996); Peled (2016); Vasey & VanderLaan (2014). Many earlier cultures and some contemporary ones have "third genders": some people of one sex (typically feminine same-sex attracted males) occupy social roles (somewhat) similar to those of the other sex. It is a mistake to take this phenomenon to be akin to the contemporary Western "transgender moment"—see Vasey (2022).
[2] Kates (2001, p. 218).

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dressing like the opposite sex and yet were not sexually inverted; that is, their sexual feelings were not directed towards persons of their own sex."[3] "Eonism" later came to label a broader category, including individuals with strong cross-sex wishes who were same-sex attracted.[4] In 1949, an American physician, David Cauldwell, used the term "transexual" to label "individuals who are physically of one sex and apparently psychologically of the opposite sex."[5]

"Transsexualism" was popularized by Harry Benjamin, a German-American endocrinologist and the father of transgender medicine. Benjamin's 1966 book, *The Transsexual Phenomenon*, was the first comprehensive English-language discussion of medicalized treatment for people who "want to undergo corrective surgery … so that their bodies would at least resemble those of the sex to which they feel they belong and to which they ardently want to belong."[6] Cross-sex hormones (CSH) followed by surgery, Benjamin thought, could "change a miserable and maladjusted person of one sex into a happier and more adequate, although by no means neurosis-free, personality of the opposite sex."[7]

In the first half of the 20th century, there were few recorded instances of transsexuals. One of the first people to undergo sex-reassignment surgery (SRS) was Einar Wegener, a Danish artist who modeled while cross-dressed for his wife Gerda Gottlieb, a talented painter. In pursuit of the body modifications he so desperately desired, Wegener sought help from the sexologist Magnus Hirschfeld, a long-time friend of Harry Benjamin's and founder of the Institute for Sexual Science in Berlin.[8] Castration, penectomy, and ovarian implantation were performed on Wegener in Berlin and Dresden in 1930, with

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[3] Havelock Ellis (1937, p. 1, Part Two); quoted in Byrne (2024b, pp. 113-114). According to d'Eon's biographer, the historian Gary Kates, "d'Eon was neither a transvestite nor a transsexual … there is simply no indication that d'Eon hated his own body or that he wanted, or even imagined he would be better off with, the body of a woman" (Kates, 2001, p. xxii); quoted in Byrne (2024b, p. 229).
[4] See, e.g., Hamburger et al. (1953) (a report on Christine Jorgensen's case; see the following section). See also Benjamin (1967b, p. 107) and Blanchard (1989, p. 240).
[5] Quoted in Meyerowitz (2009, p. 44). This quotation is from Cauldwell's 1950 *Questions and Answers on the Sex Life and Sexual Problems of Trans-Sexuals*, which hyphenates "transsexual." Cauldwell used "psychopathic transexual" (one "s") in 1949 (Cauldwell, 2006, p. 41).
[6] Benjamin (1966, p. 14)
[7] Benjamin (1966, p. 164).
[8] Li (2023).

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additional procedures the following year. These were unsuccessful. Einar Wegener, transformed into Lili Elbe, died in September 1931, after an "abyss of suffering."[9]

3.2 From George to Christine

Transsexualism was not then a phenomenon. That changed in 1952, when the news broke that George Jorgensen, a 24-year-old American of Danish descent had undergone sex reassignment surgery (SRS) in Denmark:

> [H]er celebrity began December 1, 1952, when a banner headline screaming "EX-GI BECOMES BLONDE BEAUTY: OPERATIONS TRANSFORM BRONX YOUTH" greeted readers of the *New York Daily News*. Hearst Publications' popular Sunday newspaper supplement, *American Weekly*, subsequently paid twenty thousand dollars for an exclusive interview with Jorgensen that brought her story to millions of American homes, and whetted the appetite of the world press. When she returned to the United States in 1953, an unprecedented three hundred reporters were on hand to meet her plane at New York International Airport … Her "sex-change" was viewed by many as a miracle of God in which not Christ, but Christine—Man reborn as Woman—heralded a new dispensation of human history.[10]

Jorgensen met Harry Benjamin in New York that year, and they enjoyed a long friendship. In a 1965 letter, just before the publication of *The Transsexual Phenomenon*, Benjamin wrote: "Without you, Christine, none of this would have happened."[11]

Growing up in the Bronx, the young George was teased for his "girlish qualities," and was greatly conflicted by his homosexuality:

> One question was especially troubling for George: He had learned at church and from his school friends that homosexual relationships were considered sinful and immoral. In the Jorgensen household, the word was never spoken. Among his

[9] Elbe et al. (2020, p. 203); quoted in Joyce (2021, p. 17). Lili apparently had no regrets, writing in June 1931, "The price which I have paid seems to me very small" (Elbe et al., 2020, p. 198). On regret, see Section 13.4. The 2015 movie *The Danish Girl*, starring Eddie Redmayne, is loosely based on Einar/Lili's story.
[10] Stryker (2000, pp. v-vi).
[11] Jorgensen (1967, p. xi).

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> neighbors, “homos” or “queers” were thought to be unacceptable, even dangerous people. Hence, a series of romantic attractions to other young men became his greatest teenage conflict. Try as he might to avoid these crushes, George persistently fell in love with other male youths of his age. This conflict would contribute to episodes of depression, low self-esteem, low aspiration for success, and much personal unhappiness.[12]

George himself fixated on a hormonal explanation for his femininity and same-sex attraction—a “glandular imbalance”[13]—and was also (wrongly) convinced that his genitals were “underdeveloped.”[14] It is a plausible conjecture that George found an English translation of Lili Elbe’s autobiography while hunting in New York City libraries, “hoping to find other keys to my dilemma.”[15] In any event, in search of the hormonal and surgical treatment he felt he needed, George went to Denmark on a one-way ticket in 1950. There the “Bronx youth” became a patient of Christian Hamburger, a Copenhagen endocrinologist:[16]

> Perhaps Hamburger felt a special compassion for homosexuals because his sister was a lesbian. Despite Denmark’s comparatively liberal national policies, Hamburger surely knew from his sister’s experience how discrimination against gays and lesbians could be profoundly troubling for a homosexual. He could offer no medical intervention to help his sister, but he believed there might be some steps he could take to help George Jorgensen, and he was willing to try.[17]

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[12] Docter (2013, pp. 25-26).
[13] Docter (2013, p. 63).
[14] Docter (2013, p. 46).
[15] Jorgensen (1967, p. 80); for the conjecture, see Docter (2013, p. 38).
[16] Hamburger had a distinguished career (Pedersen-Bjergaar, 1964). Contrasting with Hamburger’s academic record, before Benjamin became interested in transsexuality he was a prominent proponent of endocrine “rejuvenation therapy,” a medical fad. In 1931 he sued the editor of the *Journal of the American Medical Association* (*JAMA*) “for calling his treatment quackery,” and lost (Pettit, 2013, p. 1070).
[17] According to Hertoft & Sørensen (1979), a “sex change” was not the original plan: “the Danish team regarded Chris Jorgensen as a homosexual man suffering from his homosexuality and since he himself asked for castration, they would not deny him this operation. Not until afterwards, when the press published the case, did the team behind the procedure accept it as a sex change. The rest of the story is well known” (p. 168). Hamburger is said to have denied that Jorgensen was a homosexual in Christine’s autobiography (Jorgensen, 1967, p. 101). See also Docter (2013, p. 81).

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In a case report he later wrote for the *Journal of the American Medical Association* (*JAMA*) Hamburger described George's desire "with medical assistance to be able to obtain permission to live on 'as nearly a woman as possible.'"[18] Hamburger prescribed estrogen, and George's application for castration to the Danish Ministry of Justice was approved in 1951.[19] Castration was followed by penectomy and a later unsatisfactory attempt at creating an artificial vagina. "As a nationally recognized personality, Christine Jorgensen's flame burned with exceptional brilliance for about thirty years,"[20] dimming in the 1980s. A heavy drinker and smoker, Christine died of cancer in 1989, at the age of 62.

3.3 "Dear Dr. Hamburger"

After the "sensational publicity" over George Jorgensen's metamorphosis into Christine, Hamburger received "a unique collection of letters from a considerable number of men and women who desire to change their sex."[21] He analyzed all 756 of them, from 465 people, and published the results in a European endocrinology journal, *Acta Endocrinologica*. His correspondents wrote from all over the world. Over three quarters were men, and some of the letter writers were young teenagers. Not everyone mentioned their sexual orientation, but the women were the most forthcoming, with 71% offering at least some information. Fewer than half the men gave "any information about their sexual impulses."[22] Homosexuality predominated[23] among the men and was universal among the women:

> It is remarkable that not one single woman admits to heterosexuality, which is the case in 22 per cent of all male letter writers … Not a single woman mentions attraction to men; on the contrary. Women who have experienced shorter or longer periods of married life, felt the physical part of matrimony to be intolerable. Completely different are the transvestic men: they do not appear to have felt any

[18] Hamburger et al. (1953, p. 393).
[19] Jorgensen (1967, pp. 114-116).
[20] Docter (2013, p. 255).
[21] Hamburger (1953, p. 361).
[22] Hamburger (1953, p. 368).
[23] Of the 45% of men who disclosed information about their sexual orientation, Hamburger classified 65% as homosexual (Hamburger, 1953, Table 3).

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> aversion to the female body, although the erotic attraction, if any, is stated to have declined with passing years, or to have led to impotence.[24]

A 16-year-old American girl wrote:

> I've always acted like a boy and did the things they did. When I was smaller I used to wear my brothers [sic] clothes and I even do now sometimes when no one is home. This isn't the worst of it though, ever since I've been in High School I've been in love with a girl! and as much as I try to forget this love the more I realize I don't want to forget it. - - - I've also read about transvestites who only wanted to dress like the opposite sex but that's not how I feel. I want to dress like a boy yes, but it's not so bad that I can't control it.[25]

Childhood gender-nonconformity is strongly associated with later homosexuality.[26] Because childhood- or early-onset gender dysphoria (GD)[27] involves extreme gender-nonconformity, young children distressed by their sexed bodies will likely grow up to be same-sex attracted. As the current *Diagnostic and Statistical Manual* (DSM-V-TR) puts it, "Studies have shown a high incidence of sexual attraction to those of the individual's birth-assigned gender, regardless of the trajectory of the prepubescent child's gender dysphoria."[28] Harry Benjamin put his own spin on George Jorgensen's homosexuality: "since the psychological status of a transsexual male is that of a female, it is natural that sex attraction centers on a male."[29]

Despite the sensational publicity, in the 1960s the "transsexual phenomenon" was still in its infancy. By 1965, Benjamin had seen 307 cases of which he deemed 220 "true transsexuals," the remainder being classed as "transvestites." Almost 90% of the transsexuals were male. Only 62 males and 11 females had had surgery.[30] Reflecting

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[24] Hamburger (1953, p. 369).
[25] Hamburger (1953, p. 370).
[26] Bailey & Zucker (1995); R. Green et al. (1987); Steensma et al. (2013).
[27] Ristori & Steensma (2016); Singh et al. (2021). For other forms of GD, see Bailey & Blanchard (2017); Zucker et al. (2016). See also Section 4.3.1.
[28] American Psychiatric Association (2022, p. 516).
[29] Benjamin (1967a, p. ix).
[30] Benjamin (1966, p. 163).

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this imbalance, *The Transsexual Phenomenon* had only one slim chapter on "the female transsexual."

By 1979, the demand for "sex change" became significant enough for clinicians caring for this patient population to form a professional association, the Harry Benjamin International Gender Dysphoria Association (HBIGDA), which published the first *Standards of Care* in 1979. In that short typewritten document, "Principle 2" of 32 was: "Hormonal and surgical sex reassignment are procedures requiring medical justification and are not of such minor consequence as to be performed on an elective basis."[31]

In the third edition of the DSM in 1980, the disorder of "transsexualism" was said to be "apparently rare."[32] In 1994 DSM-IV reported: "Data from smaller countries in Europe with access to total population statistics and referrals suggest that roughly 1 per 30,000 adult males and 1 per 100,000 adult females seek sex-reassignment surgery."[33] The "transgender tipping point"[34] had not yet arrived.

3.4 Outcomes of adult transitions

Pediatric medical transition began in the Netherlands, which had offered adult treatment in an academic hospital starting in the 1970s, with the costs of a medical transition reimbursed through the Dutch national health insurance system.[35] The availability of comprehensive and reliable medical records gave clinicians the opportunity to study how patients fared, and a paper detailing the results was published in 1988: "Sex reassignment surgery: A study of 141 Dutch transsexuals." The research was led by the psychologist Peggy Cohen-Kettenis, who had worked earlier with adult transsexuals at the Department of Sexology at Utrecht University. In 1987 she moved to the Department

[31] Harry Benjamin International Gender Dysphoria Association (1979).
[32] For the diagnostic criteria, see Appendix 2. The first two versions of the DSM fleetingly included "transvestism" (American Psychiatric Association (1952, p. 39) and "transvestitism" (American Psychiatric Association (1968, p. 44). See also Drescher & Yarbrough (2024).
[33] American Psychiatric Association (1994, p. 535). See also Dhejne et al. (2014). According to the first *Standards of Care*, "As of the beginning of 1979, an undocumentable estimate of the number of adult Americans hormonally and surgically sex-reassigned ranges from 3,000 to 6,000" (Harry Benjamin International Gender Dysphoria Association, 1979).
[34] The title of a *Time* cover story in 2014 (Steinmetz, 2014).
[35] Bakker (2021, p. 29).

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of Child and Youth Psychiatry at the Academic Hospital Utrecht (now UMC Utrecht), where she began to see children and adolescents with GD.[36]

Cohen-Kettenis and her co-author and student Bram Kuiper sent recruitment letters to all 229 patients diagnosed by the Netherlands Gender Care Foundation (NGCF) as "transsexuals and who … had at least started hormone therapy." The 141 who agreed to participate were "36 FMs (female-to-male transsexuals) and 105 MFs (male-to-female transsexuals)."[37] They were at varying stages of medical transition. Some had completed surgery, while others had just started on CSH; follow-up time from the start of treatment ranged from one month to more than 10 years. The patients' average ages were late-20s (the FMs) and mid-30s (the MFs). They were assessed by interview, and all but three were interviewed in their homes.

On the positive side, 65% reported feeling happy or very happy, while 11% said they were unhappy or very unhappy. Almost all the FMs and nearly 80% of the MFs described their ability to "pass as a member of the newly assumed gender" as good or very good. None of those who had had surgery "felt any significant doubts about the decision to get rid of their own primary and secondary sex characteristics and to have the body surgically adjusted to the characteristics of the opposite sex," except for one FM who nonetheless had no regrets about living as a man.[38]

On the other hand, while the self-reported subjective outcomes were good, objective measures told a different story. One in seven MFs and one in 36 FMs had attempted suicide after treatment began. (Of the total number of patients seen at the NGCF in the previous 10 years, three had committed suicide after treatment.) 60% of the MFs and 37% of the FMs were unemployed and 59% of the MFs and 33% of the FMs had no romantic partners.[39] Commenting on previous studies of SRS, the researchers noted: "it is possible to discern a trend in these reports that the subjective well-being of the

[36] Bakker (2021, p. 113).
[37] Kuiper & Cohen-Kettenis (1988, p. 442).
[38] Kuiper & Cohen-Kettenis (1988, p. 450).
[39] Kuiper & Cohen-Kettenis (1988, p. 447).

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transsexuals has increased, whereas an 'improvement' in their actual life situation is not always observed."[40]

Did medical transition at least alleviate gender dysphoria? Interestingly, there was no relationship between reported happiness and stage of transition:

> Although a fair number of persons attribute their feelings of happiness to SRS, there appears to be no direct relation between the subjective well-being and the phase of therapy. Those who have completed SRS are not happier or less happy than those who are still in the initial phase of therapy. In other words, a person's positive evaluation of his/her life-in-its-totality is not directly related to his/her progress in physical adjustment to the opposite sex.[41]

The researchers speculated that this might be due to an expectation effect:

> However, it does not seem justifiable to conclude that it is irrelevant to a person's happiness whether physical adjustment has or has not taken place and that the operations could therefore just as well have been omitted. One has to bear in mind that in general the [FMs and MFs who had not completed treatment] are happy in the knowledge that the operations will be performed within a reasonable time. They are taking a loan on the future.[42]

Although the researchers claimed that "there is no reason to doubt the therapeutic effect of sex reassignment surgery," they were clear that there were significant costs:

> SRS is no panacea. Alleviation of the gender problems does not automatically lead to a happy and lighthearted life. On the contrary, SRS can lead to new problems.[43]

Why were the MFs, in particular, doing so poorly? Three possible explanations were floated. One was that "passing" is easier for FMs, because of the power of

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[40] Kuiper & Cohen-Kettenis (1988, p. 440). Dhejne et al. (2011) examined the long-term outcomes of 324 people in Sweden receiving sex-reassignment surgery (SRS) over the period 1973-2003 (191 MFs, 133 FMs). Dhejne et al. concluded: "Persons with transsexualism, after sex reassignment, have considerably higher risks for mortality, suicidal behaviour, and psychiatric morbidity than the general population."
[41] Kuiper & Cohen-Kettenis (1988, p. 454).
[42] Kuiper & Cohen-Kettenis (1988, p. 454).
[43] Kuiper & Cohen-Kettenis (1988, p. 455).

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testosterone.[44] Second, "society in general is inclined to take a milder view of women who dress and/or behave like men."[45] Finally, the MFs had transitioned later and were more likely to have married and to have children, with a consequent "heavier burden of a past life as a person of the original gender."[46,47]

One possibility that the Dutch researchers did not consider was that the FMs were doing better because their romantic relationships were easier to preserve after transition. As Hamburger reported from his correspondence in 1953, "No less than 10 women say, in so many words, that they want their sex changed in order to be able to marry their female friend or to have the relationship legalized."[48] Also apparently ignored was the related possibility that transition may appeal to young gay men and lesbians suffering from social disapproval of their homosexuality.[49]

3.5 The rationale for youth gender transition

Medically transitioning earlier gave patients a better chance to "pass" and reduced the "burden of a past life," so perhaps intervening at younger ages would improve transsexuals' quality of life. Cohen-Kettenis thought so. As sociologist Michael Biggs explains,

> Cohen-Kettenis believed that transsexuals would experience better outcomes if they started treatment before adulthood. By the mid-1990s, she was referring some patients aged 16 and 17 to the Amsterdam clinic for endocrinological intervention prior to cross-sex hormones … Johanna, for example, "fulfilled all necessary requirements for early treatment": she did not favor girly things (though neither did her sisters), she was fond of soccer, she never dated in school (perhaps not surprising given that she was homosexual), and her parents discovered her wearing a tight t-shirt to conceal her breasts … Brought to the clinic at 17, she was prescribed progestin for four months and then testosterone.

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[44] This works both ways. First, testosterone can dramatically transform the female body; second, the effects of pubertal testosterone on the male body are hard or impossible to undo. See Section 7.4.
[45] Kuiper & Cohen-Kettenis (1988, p. 455).
[46] Kuiper & Cohen-Kettenis (1988, p. 456).
[47] See also Smith et al. (2005, p. 97).
[48] Hamburger (1953, p. 370).
[49] See Barnes (2023, pp. 159-164).

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> Within two years Jaap (as Johanna had become) underwent mastectomy, hysterectomy, and oophorectomy, and obtained a new birth certificate.[50]

In 1991 Cohen-Kettenis and her colleague Louis Gooren lowered the eligible age for CSH to 16, but Cohen-Kettenis was not yet recommending puberty blockers (PBs).[51] The Dutch pediatric endocrinologist Henriette Delemarre-van de Waal had treated the first patient with blockers some years earlier, in 1987. "FG" was a girl with early-onset gender dysphoria:

> From the age of 5, FG "had made it very clear that I was supposed to be a boy." It later transpired that FG was sexually attracted to women. FG's father, an Italian with traditional views on gender, disapproved of his daughter's masculinity, and serious conflict ensued. Extensive psychotherapy did not improve matters; FG wrote a suicide note at the age of 12.[52]

At age 13, FG was prescribed puberty blockers and remained on them until age 18, after which many surgeries followed, including mastectomy and hysterectomy.

FG had come to the Utrecht gender clinic three years after starting PBs; as Cohen-Kettenis recounts:

> I'll never forget that first boy treated with Decapeptyl[53] by Henriette Delemarre. He made an impression with his boyish appearance at 16—naturally, because he hadn't entered puberty. Henriette and I embarked upon the adventure. No one knew what the long-term effects of administering puberty blockers would be. Yes, I was nervous: suppose you've got it wrong with an adolescent like that and you have to reverse it![54]

With the collaboration of Cohen-Kettenis and Delemarre-van de Waal, the "Dutch Protocol" for youth medical transition was born.[55] As of 1997, for carefully selected

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[50] Biggs (2023b, p. 350).
[51] Bakker (2021, p. 118).
[52] Biggs (2023b, p. 350).
[53] The brand name of triporelin, a gonadotropin releasing hormone agonist (GnRHa); triptorelin acts on the pituitary gland, blocking puberty in adolescents. See Section 7.3.
[54] Bakker (2021, p. 115).
[55] Delemarre-van de Waal & Cohen-Kettenis (2006).

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"juvenile transsexuals," with early-onset GD worsening at puberty, PBs could be given as early as 12.[56] Cross-sex hormones could be administered at 16, with surgeries at 18.[57] Patients were required to be otherwise mentally healthy and have family support.

FG was followed up 22 years later at age 35:[58]

> FG did not regret transition, but scored high on the measure for depression. Owing to "shame about his genital appearance and his feelings of inadequacy in sexual matters," he could not sustain a romantic relationship with a girlfriend. Ironically, a "strong dislike of one's sexual anatomy" is one of the diagnostic criteria for gender dysphoria in children (according to DSM-5), and so in this respect it is not clear how the dysphoria had been resolved … Now aged 48, FG has given two recent interviews. FG's situation seems to have improved, and he now has a serious girlfriend. He describes puberty suppression as "life-saving" in his case … but also recommends that it should require a significant assessment process.[59]

3.6 The spread of the Dutch Protocol and the rise of "gender-affirming care"

In the United States, HBIGDA endorsed puberty blockers in their sixth version of their clinical guideline, the *Standards of Care* (SOC-6, 2001):

> Two goals justify this intervention: a) to gain time to further explore the gender identity and other developmental issues in psychotherapy; and b) to make passing easier if the adolescent continues to pursue sex and gender change. In order to provide puberty delaying hormones to an adolescent, the following criteria must be met:

[56] Bakker (2021, p. 121).
[57] In fact, surgery was mandatory until 2014 (Gregory, 2021).
[58] Cohen-Kettenis et al. (2011).
[59] Biggs (2023b, p. 355).

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1. throughout childhood the adolescent has demonstrated an intense pattern of cross-sex and cross-gender identity and aversion to expected gender role behaviors;

2. sex and gender discomfort has significantly increased with the onset of puberty;

3. the family consents and participates in the therapy.[60]

SOC-6 also erroneously characterized PBs as "fully reversible" (see Chapter 7). As Biggs points out, "the published evidence for the benefits of puberty suppression then comprised a single case study of one patient—FG—awaiting final surgery."[61]

In the U.S., PBs were first prescribed for GD at Boston Children's Gender Management Service (GeMS, now Gender Multispeciality Service) around 2007, with the U.K.'s Gender Identity Development Service (GIDS) following four years later.[62] GeMs did not set a minimum age limit, and in 2015 neither did the U.K.'s National Health Service.[63] The relatively strict gatekeeping of the Dutch Protocol soon gave way to a more patient-led approach (see Section 4.1. and Chapter 11). This occurred not just in the U.S. but other countries, including the U.K.:

> From 2014, puberty blockers moved from a research-only protocol to being available through routine clinical practice … In addition, the strict inclusion criteria of the Dutch protocol were no longer followed, and puberty blockers were given to a wider range of adolescents … These included patients with no history of gender incongruence prior to puberty, as well as those with neurodiversity and complex mental health presentations.[64]

HBIGDA became the World Professional Association of Transgender Health (WPATH) in 2007. Reflecting in 2009 on the "new paradigms [that] have emerged about the nature

[60] Harry Benjamin International Gender Dysphoria Association (2001, p. 10).
[61] Biggs (2023b, p. 353).
[62] GIDS was closed in March 2024; see also Barnes (2023).
[63] Biggs (2023b, p. 354).
[64] Cass (2024a, p. 73).

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of transgender identity and experience," Lin Fraser, then President-elect of WPATH, wrote:

> The new model views gender as a continuum rather than a male/female dichotomy and calls for individualized gender trajectories, which may or may not include hormonal therapy and sex reassignment surgery.[65]

The seventh version of the *Standards of Care* (SOC-7) was published in 2012 and was a significant departure from SOC-6, moving away from medical gatekeeping and towards the "gender-affirming" model. For example, SOC-6 recommended that CSH be given only to patients aged 18 or older, who either had "real-life experience" ("living in the desired gender") or had been in psychotherapy for at least three months. SOC-7 had no age limit for CSH, only requiring that the adolescent give "informed consent" and that the parents or guardians have also "consented to the treatment and are involved in supporting the adolescent." Recommendations for psychotherapy or real-life experience were absent. SOC-7 effectively relegated the role of mental health professionals to provide assessments needed by insurance companies for reimbursement.

Another change was apparent from SOC-7's title. SOC-6 was the standards of care "for Gender Identity Disorders," but SOC-7 was "for the Health of Transsexual, Transgender, and Gender Nonconforming People." "Non-binary" would have to wait its turn, appearing for the first time in the current guideline, SOC-8 (2022), with a chapter dedicated to it.[66] The first version of the *Standards of Care* was authored by just six people and comprised slightly over 3,000 words; SOC-8 has more than 100 contributors and more than 100,000 words.

In 2011, Cohen-Kettenis and colleagues published a follow-up study of 70 adolescent patients who received PBs in the Netherlands between 2000 and 2008. The results

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[65] Fraser (2009, pp. 113-114, citations omitted). One of the citations omitted from the quotation is *The Apartheid of Sex: A Manifesto on the Freedom of Gender*, by Martine Rothblatt. Chapter 1 of that book is called "Five Billion Sexes," and begins: "There are two sexes, male and female, right? Wrong! In fact, there is a continuum of sex types, ranging from very male to very female, with countless variations in between" (Rothblatt, 1995, p. 1).

[66] A 2020 survey of U.S. youth aged 13-24 who identified as LGBTQ found that, of the 11,914 who identified as transgender or non-binary, more than 60% identified as the latter (A. E. Green et al., 2022, p. 645).

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were interpreted as encouraging: “Behavioral and emotional problems and depressive symptoms decreased, while general functioning improved significantly during puberty suppression.”[67] A 2014 study of the same patient cohort after sex reassignment surgery—but with just 55 of the original 70 subjects—contained a similarly positive conclusion: “After gender reassignment, in young adulthood, the GD was alleviated and psychological functioning had steadily improved.”[68] These two studies form the foundational evidence base of the Dutch Protocol, and are widely cited to support it. (As subsequent analysis revealed, they do not: see Section 4.3.6.)

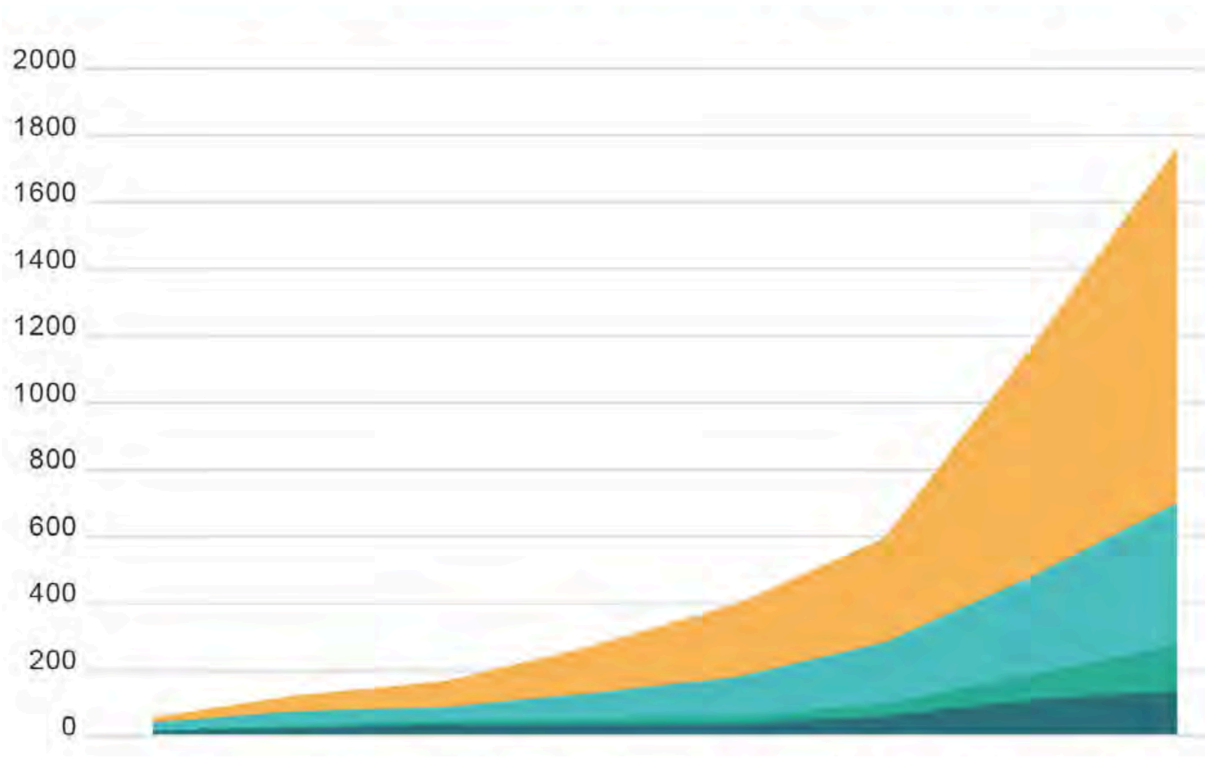
The previously observed tendency for early-onset GD patients to be gay continued with the Dutch cohort. Of the initial group of 70, only one reported heterosexuality; the other 69 reported either homosexuality (62), bisexuality (six), or “don’t know yet” (one).[69] (See also Section 13.3.1.)

Around the time Cohen-Kettenis and colleagues published their first study, clinicians started to observe a rapid increase in the pediatric patient population. More notably, the demographic profile of these patients was shifting, with adolescent females emerging as the predominant group. This trend is illustrated in Figure 3.1, which charts referrals to GIDS from 2009 to 2016.

[67] de Vries et al. (2011, p. 2276).
[68] de Vries et al. (2014, p. 696).
[69] de Vries et al. (2011, Table 1).

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Figure 3.1: Sex ratio in children and adolescents referred to GIDS in the U.K. (2009-16)[70]



	2009	2010	2011	2012	2013	2014	2015	2016
Adolescent F	15	48	78	141	221	314	689	1071
Adolescent M	24	44	41	77	120	185	293	426
Children F	2	7	12	17	22	36	77	138
Children M	10	19	29	30	31	55	103	131

In a related trend, Western countries began reporting a growing number of adolescents who, often unexpectedly, disclosed a transgender identity—frequently to the surprise of their parents.[71] The number of pediatric patients seeking medical transition can only be roughly estimated,[72] but the demand in European countries has outstripped supply, with waitlists approaching 2 years or longer. In response to the growing demand, the U.S.—characterized by its decentralized and privatized healthcare system—saw the

[70] Reproduced from Cass (2024a, p. 70); original in de Graaf et al. (2018, Figure 1).
[71] See Section 4.3.1.4.
[72] According to the Human Rights Campaign (HRC), "there are more than 300,000 high school-aged (ages 13-17) transgender youth in the United States today, *many of whom need gender-affirming care*" (Human Rights Campaign, n.d.), emphasis added). See also Williams Institute (2024).

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emergence of many new specialty gender clinics, along with a proliferation of independently practicing clinicians.[73] According to a recent conservative estimate, as of March 2023 there were 271 clinics offering PMT in the U.S., though 70 were inactive due to legislative restrictions.[74]

As clinical experience with treating youth with GD across the world has grown, concerns about the PMT model have become increasingly apparent. In response, public health authorities in several European countries have launched formal investigations into the practice. The most comprehensive is the U.K.'s 2024 Cass Review, mentioned in Chapter 1. As a result of such inquiries, some European health authorities are now restricting eligibility for medical transition and implementing new research requirements and safeguards. In the U.S., where government health authorities play a more limited role, and medical practice is primarily regulated at the state level, many states have turned to legislative measures to restrict or prohibit pediatric medical transition.[75]

As Hilary Cass observed in 2022, "it is not helpful to exceptionalise gender identity issues."[76] The consensus in pediatric gender medicine (PGM) of 10 years ago was driven by that exceptionalization, which has now begun to change. The following chapter explains why this change is underway.

[73] Levine et al. (2022a, p. 708).
[74] Borah et al. (2023, pp. 375-376).
[75] Harmon (2024).
[76] Cass (2022b).

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Chapter 4 International Retreat from the "Gender-Affirming" Model

Since the publication of the Dutch Protocol in 2006, the practice of "gender-affirming" (or "affirmative" care) has rapidly expanded. Now, a global reversal is underway. Several national health authorities have restricted hormonal and surgical interventions for minors. Section 4.1 provides a brief overview of the rise of pediatric medical transition (PMT) as the primary response to childhood and adolescent gender dysphoria (GD). Section 4.2 summarizes the ongoing practice reversal that is now taking place in an increasing number of countries. Section 4.3 explores the reasons behind these reversals.

4.1 The rise of the affirmative care model

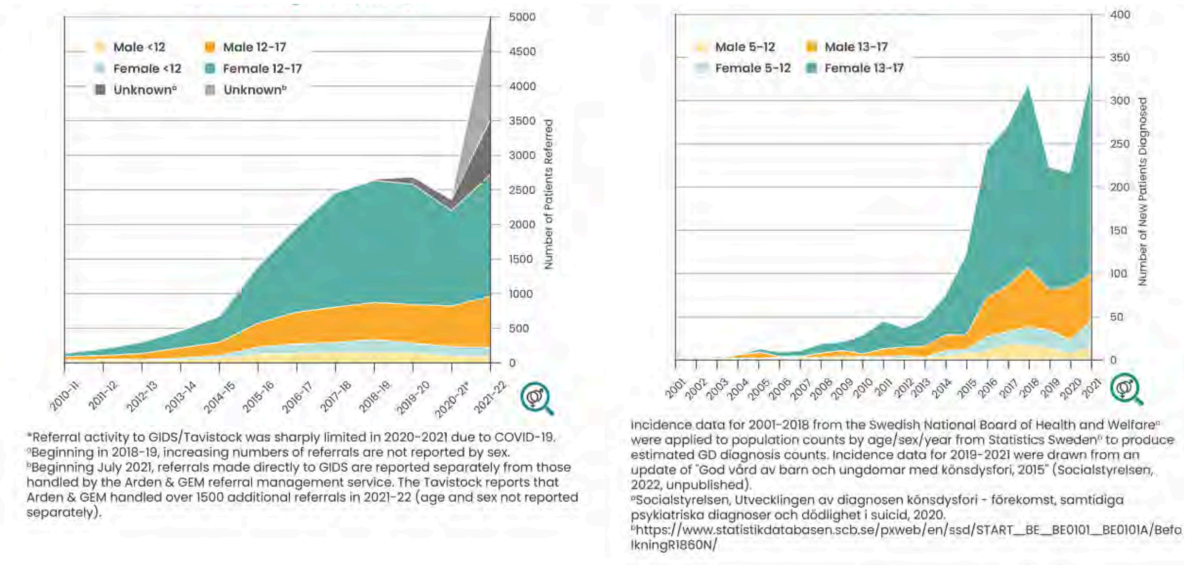
Following the publication of the Dutch Protocol in 2006,[1] puberty blockers (PBs) and cross-sex hormones (CSH) were incorporated into the Endocrine Society's 2009 clinical practice guideline (CPG),[2] which recommended that hormonal interventions should be used for certain pediatric patients with GD. This approach was also recommended by the World Professional Association for Transgender Health's (WPATH) guidelines in 2012.[3] Notably, these endorsements occurred before the final analysis of psychological outcomes from the original Dutch cohort was published in 2014[4]—and several years before the first systematic reviews of evidence (SRs) commissioned by public health authorities began to appear in 2019 and 2020.[5] During this same period, the number of children and adolescents reporting symptoms of GD and seeking medical intervention surged—a trend that has since become widespread across Western countries. At the same time, the epidemiological profile of patients changed markedly: while earlier

[1] Delemarre-van de Waal & Cohen-Kettenis (2006). Outcomes from the first patient cohort treated according to the protocol were published in 2011 and 2014 (de Vries et al., 2011, 2014).
[2] Hembree et al. (2009).
[3] The 2012 guidelines were the organization's seventh CPG (Coleman et al., 2012). The fifth and sixth CPGs, published in 1998 and 2001, briefly mentioned the potential use of "LHRH agonists" (Levine et al., 1998; Harry Benjamin International Gender Dysphoria Association, 2001), but the use of PBs as the central part of the treatment for adolescents did not emerge until the seventh version.
[4] de Vries et al. (2014).
[5] National Institute for Health and Care Excellence (2020b, 2020a); Pasternack et al. (2019).

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cohorts consisted mainly of prepubertal boys, more recent referrals have been dominated by teenage girls (see Figure 4.1 below).

Figure 4.1: Child and adolescent referrals for GD (U.K., left; Sweden, right)[6]



The scientific foundation for the rapid expansion of PMT was largely underpinned by two Dutch studies, published in 2011 and 2014,[7] which followed the same patient cohort. The first study, which focused on the use of PBs,[8] reported psychological outcomes in 70 adolescents who had completed the PB phase and were beginning CSH. The findings suggested modest "pre-post" improvements in some mental health measures following PB treatment—but notably, no improvement in GD itself, as assessed by the newly developed Utrecht Gender Dysphoria Scale (UGDS).

For more than a decade, many of the study's methodological flaws remained largely overlooked. One of the study's limitations was its retrospective selection of 70 subjects from a larger "intent-to-treat" group of 111 using non-randomized methods. This selection process inadvertently biased the sample toward cases with the most favorable prognoses, thereby limiting the generalizability of the study's findings.[9]

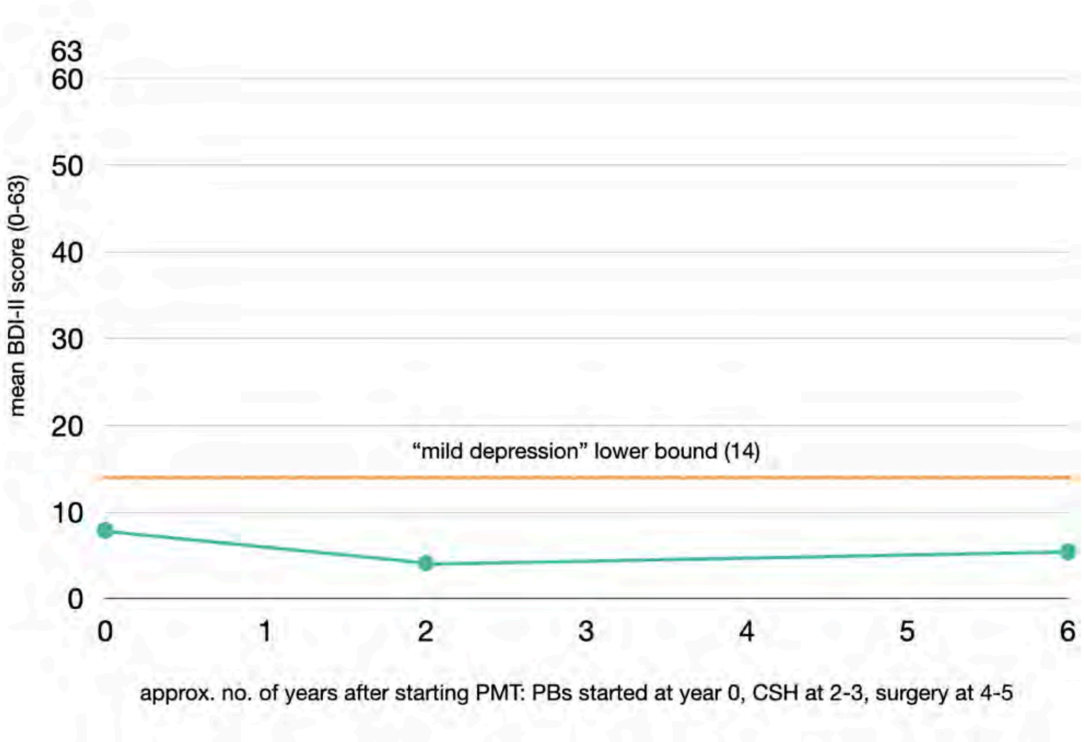
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[6] Source: Society for Evidence-Based Gender Medicine (SEGM).
[7] de Vries et al. (2011, 2014).
[8] de Vries et al. (2011).
[9] The study's inclusion criteria defined eligibility for analyzing the effects of puberty blockers (PBs) based on the start date of the subsequent phase—CSH. This approach introduced significant bias by excluding,

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In 2014, a follow-up study was published assessing the participants' functioning after CSH and surgery.[10] The sample size was further reduced to just 55 participants, and critical measures of psychological health—such as depression, anxiety, and overall functioning—were assessed in as few as 32 participants. Moreover, although the reported improvements reached statistical significance, their clinical relevance was limited (see the depression scores plotted in Figure 4.2: the orange line indicates the *threshold* for "mild depression," with 63 being the maximum score; mean scores remained below the mild depression threshold at baseline and throughout treatment).

Figure 4.2: Depression scores in Dutch cohort[11]



Noting the high-functioning status of the adolescent/young adult cohort at the end of the study, the authors concluded that the Dutch Protocol provided patients with "the

from the outset, any subjects who discontinued treatment, underrepresenting psychologically complex cases who remained in the "diagnostic" PB phase for longer periods, and skewing the sample toward older subjects. Because eligibility hinged on starting CSH at 16, only those who reached this threshold were included—potentially explaining why the average age for initiating PBs in the study was 15, despite the protocol recommending initiation around age 12 (Abbruzzese et al., 2023).

[10] de Vries et al. (2014).

[11] Graph of data contained in de Vries et al. (2011) and de Vries et al. (2014).

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opportunity to develop into well-functioning adults."[12] The study failed to consider that the subjects were already high-functioning at baseline—comparable to Dutch peers without GD.[13] This was likely attributable, at least in part, to the original Dutch Protocol's stringent selection criteria.

Moreover, the study failed to account for or appropriately consider potential signals of harm. One participant died due to post-surgical treatment complications associated with early pubertal suppression,[14] at least three were diagnosed with uncontrolled diabetes or morbid obesity while on hormones, and at least one subject discontinued treatment.

These and other serious limitations—including subject selection bias and methodological flaws (such as the post-treatment reversal of the UGDS[15])—remained largely unacknowledged, even as the study became the foundational pillar[16] of PMT protocols worldwide. Attempts to replicate the Dutch findings regarding PBs in the U.K. were unsuccessful[17]—and the publication of those unfavorable results was delayed for several years.[18] It has also been reported that the attempts to replicate the benefits of PBs in a National Institutes of Health (NIH)-funded study in the U.S. yielded less-than-favorable results.[19]

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[12] de Vries et al. (2014, p. 696).
[13] As explained in Abbruzzese et al. (2023), the requirement of psychological stability was built into the protocol, and earlier research from the same clinic had stated that "when both pre- and posttest group means were compared with Dutch normative data, all scores turned out to be within the average range" (Smith et al., 2001, p. 277).
[14] de Vries et al. (2014) noted that "1 transfemale died after her vaginoplasty owing to a postsurgical necrotizing fasciitis" (p. 697). A 2023 analysis of the original Dutch papers found that the researchers "did not mention the fact that this death was a consequence of puberty suppression: the patient's penis, prevented from developing normally, was too small for the regular vaginoplasty and so surgery was attempted with a portion of the intestine, which became infected" (Biggs, 2023b, p. 8). See also Negenborn et al. (2017).
[15] The reversal of the GD scale post-surgery may have entirely invalidated the study's key finding of the resolution of GD post-treatment (Abbruzzese et al., 2023). Of note, another clinical research study in this field (López de Lara et al., 2020) also switched GD and body image scales.
[16] One of the authors of the original Dutch research noted, in 2022, that those papers are "still used as main evidence for provision of early medical intervention including puberty blockers in transgender youth" (de Vries, 2022, p. 109). The Cass Review's final report described that instead of the usual, slow evolution of clinical practice over "many years before strongly positive research findings are incorporated … the reverse happened in the field of gender care for children. Based on a single Dutch study … the practice spread at pace to other countries …" (Cass, 2024a, p. 13).
[17] Carmichael et al. (2021).
[18] See Chapter 6.
[19] Ghorayshi (2024c).

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Spurred on by the belief in the success of the Dutch Protocol and its central premise—reliance on PBs —the expanding availability of PMT services was met by a surge in demand: "first gradually, then suddenly."[20] By 2015, nearly every European country was reporting a dramatic increase in the number of gender-dysphoric youth seeking hormonal interventions at pediatric gender medicine (PGM) clinics—a trend whose underlying cause remains the subject of ongoing debate. The endorsement of PMT was further solidified by the publication of the 2017 Endocrine Society (ES) guidelines,[21] co-authored by psychologist Peggy Cohen-Kettenis—the pioneer of the original Dutch Protocol—who had first introduced the recommendations for PMT into the 2009 ES guidelines, and later reinforced them in the 2012 WPATH *Standards of Care 7* guidelines (SOC-7).[22]

One striking characteristic of the surge of adolescents presenting with a wish to undergo medical transition is the disproportionate number of female adolescents without prior childhood history of GD who present with high rates of comorbid mental health conditions. This pattern drew the attention of Finnish researchers, who were the first to publish on these changing demographics and to raise concerns that the Dutch Protocol might not be helping—and might even be harming—patients.[23] Finland subsequently became the first country to revise its national guidelines,[24] sharply limiting medical interventions based on the findings of an SR.[25] In the years that followed, other countries began conducting their own evaluations of the evidence and arrived at similar conclusions. A global trend has since emerged, away from use of PBs, CSH, and surgeries in youth with GD. This ongoing reversal is explored in greater detail in the following section.

4.2 The international practice reversals

Starting in 2020, PMT began to face growing scrutiny from public health authorities worldwide, resulting in substantial reversals of clinical protocols in an increasing number

[20] Abbruzzese et al. (2023, p. 12).
[21] Hembree et al. (2017).
[22] Coleman et al. (2012); Hembree et al. (2009).
[23] Kaltiala et al. (2020); Kaltiala-Heino et al. (2015).
[24] Council for Choices in Health Care Finland (2020a, 2020b, 2020c).
[25] Pasternack et al. (2019).

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of countries. The most influential effort to date has been the Cass Review—a four-year independent evaluation of PGM that was published in April 2024.[26] The findings of the Cass Review led to the closure of the U.K.'s PGM clinic, the Gender Identity Development Service (GIDS), which had been given a rating of "inadequate" by the Care Quality Commission in 2021.[27] The Cass Review recommended a restructuring of the care delivery model—away from the centralized "gender clinic" model of care toward a more holistic framework centering psychosocial support, to be delivered through regional hubs. The Cass Review's findings also led the U.K. to ban the use of PBs outside clinical trials,[28] and to significantly restrict CSH.[29] While CSH are still officially an available treatment, the National Health Service (NHS) recently revealed that since the Cass Review was published, no minor has been found eligible to receive CSH according to the updated policy.[30] In the U.K., minors have never received GD-related surgery through the NHS.

Finland was the first country to curtail PMT, issuing revised national guidelines in 2020.[31] In 2022, Sweden's National Board of Health and Welfare concluded that, for most young people, the potential harms of hormonal interventions outweigh the benefits, and subsequently restricted both to research settings or exceptional cases.[32] Denmark followed Sweden's lead in 2023, restricting the use of endocrine intervention in minors,[33] and Norway's public health agency (the Norwegian Healthcare Investigation Board) advised that PBs and CSH should be considered experimental treatments.[34] Most recently, hormonal interventions have been restricted in Brazil,[35] Chile,[36] the province of Alberta in Canada,[37] and the state of Queensland in Australia.[38]

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[26] Cass (2024a).
[27] Care Quality Commission (2021).
[28] Department of Health and Social Care (2024).
[29] National Health Service England (2024c).
[30] Spencer (2025).
[31] Council for Choices in Health Care Finland (2020a, 2020b, 2020c).
[32] Socialstyrelsen (2022a, 2022b, 2022c).
[33] Hansen et al. (2023). See also Society for Evidence-Based Gender Medicine (2023b).
[34] Block (2023b).
[35] AFP (2025).
[36] Lane (2024).
[37] Government of Alberta (2024).
[38] Australian Associated Press (2025).

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At the same time, several other countries are in the process of determining how best to care for youth with GD. In Australia, following Queensland's statewide pause in January 2025 on initiating PBs and CSH for new patients under 18, the Australian Government commissioned the National Health and Medical Research Council with developing new clinical practice guidelines for youth with GD. The guidelines are expected to be completed within three years, with interim recommendations on PBs available in 2026.[39] In Italy, the Italian Bioethics Committee updated its position on the use of PBs for GD,[40] and a formal guideline development process is underway.[41] France is expected to release new national guidelines in 2025, which are expected to spark considerable debate due to anticipated endorsement of PMT[42]—a position previously criticized by the French National Academy of Medicine.[43]

Germany recently published guidelines[44] that continue to generate considerable debate in German-speaking countries, including Austria and Switzerland. The controversy stems from concerns about the non-evidence-based nature of the recommendations, their *a priori* reliance on WPATH positions, and deep divisions in the professional community[45] regarding the appropriate approach to caring for youth with GD. Even the Netherlands—the birthplace of the Dutch Protocol—has not been immune to debate.[46] In May 2024, the Dutch Minister for Medical Care formally requested that the Health Council of the Netherlands produce an independent scientific advisory report on healthcare for minors with GD. This ongoing review will include an evaluation of the Dutch Protocol and a comparison with other countries' guidelines.[47]

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[39] Australian Government National Health and Medical Research Council (2025).
[40] Italian National Bioethics Committee (2024). See also Society for Evidence-Based Gender Medicine (2024d).
[41] Curridori (2024).
[42] Sugy (2024).
[43] Society for Evidence-Based Gender Medicine (2022a).
[44] German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP) (2025).
[45] Zepf, Buchmann, et al. (2024).
[46] Society for Evidence-Based Gender Medicine (2023c).
[47] Health Council of the Netherlands (2024).

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4.2.1 The Cass Review and its reception

The Cass Review has had a profound influence on international debates. Commissioned by NHS England, the Cass Review assessed the safety, efficacy, and delivery of PGM services for children and adolescents. Conducted over four years under the leadership of Hilary Cass, pediatrician and a past president of the Royal College of Paediatrics and Child Health, the review engaged a broad range of stakeholders and relied on SRs from the National Institute for Health and Care Excellence (NICE)[48] and the University of York,[49] as well as additional research. The Cass Review identified significant limitations in the evidence base for PBs and CSH. It recommended that PBs be offered only as part of a clinical trial until further data are available, and that all potential interventions should be tested within a research context.[50] The review emphasized a multidisciplinary, developmentally-informed model of care for youth with GD that prioritizes psychological support and the development of "an explicit clinical pathway … for non-medical interventions."[51]

Recent criticisms of the Cass Review—particularly claims that it fails to meet CPG standards—reflect a misunderstanding of the Cass Review's purpose and scope. The Cass Review was not a CPG; it was an "independent review." This is a U.K.-specific process of conducting a service-level evaluation intended to inform policy, not prescriptive clinical decisions. Such processes are invoked when an area of clinical care begins to operate in ways that compromise care quality and threaten patient safety.[52]

Criticism of the Cass Review appears to stem largely from a U.S.-based group of motivated advocates for the continued legality of PMT.[53] The critiques are ridden with

[48] National Institute for Health and Care Excellence (2020a, 2020b).
[49] Hall et al. (2024); Heathcote et al. (2024); Taylor, Hall, Heathcote et al. (2024a, 2024b); Taylor, Hall, Langton et al. (2024a, 2024b); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024).
[50] "The overarching conclusion from the evidence presented in this Review is that the puberty blocker trial, which is already in development, needs to be one part of a much broader research programme that seeks to build the evidence on all potential interventions, and to determine the most effective way of supporting these children and young people" (Cass, 2024a, p. 197). See "Recommendation 6" (Cass, 2024a, p. 35).
[51] Cass (2024a, p. 157).
[52] Cheung et al. (2025).
[53] Of these, the white paper McNamara et al. (2024), produced by the Yale Integrity Project, has been most influential.

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misrepresentations of the Cass Review and contain multiple factual errors.[54] In the U.K., the Cass Review has been widely accepted as a foundational document for realigning pediatric gender medicine (PGM) with the principles of evidence-based medicine (EBM) and child safeguarding.[55] It has been welcomed by both major political parties in the U.K., and was fully accepted by the NHS for implementation, which is well underway.[56]

4.3 Rationale for international reversals

A defining feature of these global reversals has been the rejection of the "gender clinic" model, which typically promotes PMT. Internationally, this model is increasingly being supplanted by more traditional, holistic approaches to adolescent distress. Rather than referring youth with GD to specialty clinics oriented toward transition, emerging models emphasize standard mental health services, where young people receive comprehensive psychosocial and psychotherapeutic support—and, when indicated, psychiatric care.

The global reversals away from PMT can be attributed to six main factors: a significant shift in the patient population; uncertainty surrounding the natural history and prognosis of GD; increasing recognition of the risks associated with medical interventions; a more accurate understanding of the suicide risk; the collapse of the original treatment rationale; and a weak underlying evidence base. The following subsections (1-6) examine each of these factors in turn.

4.3.1 Changes in the patient population

The population of young people for whom the Dutch Protocol was originally developed differs significantly from those presenting for care today.

4.3.1.1 Epidemiological shifts

Over the past decade, the population presenting to PGM clinics has changed in two key ways: a rapid increase in numbers and a significant shift in demographic composition. Before hormonal interventions became widely available, pediatric referrals for GD were

[54] Cheung et al. (2025); McDeavitt et al. (2025).
[55] Abbasi (2024).
[56] National Health Service England (2024a).

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relatively rare,[57] and the majority were prepubertal boys with early-onset GD.[58] Over the past decade, the increase in patients has been described as exponential,[59] a trend driven primarily by adolescent females who typically have no childhood history of GD.[60]

4.3.1.2 Mental illness and neurodevelopmental diagnoses

The current patient population has a high rate (relative to the general population) of comorbid mental health problems, including depression, anxiety, suicidality, self-harm, and eating disorders; as well as neurodevelopmental conditions like autism spectrum disorder (ASD).[61] Importantly, register-based research conducted in Finland, which has national databases, found that 75% of patients presenting to PGM clinics in the mid-2010s had severe mental health problems that appeared to have *predated* the emergence of GD.[62] High rates of comorbid mental illness have been documented in the U.S. and other countries.[63]

The high prevalence of ASD among youth presenting with GD has been recognized for some time.[64] At the U.K.'s clinic, ~35% of patients had comorbid moderate-to-severe autistic traits (compared to <2% of the general population).[65] Although some researchers have postulated that the social difficulties in youth with these co-occurring conditions may not result from ASD but instead from GD and may be ameliorated by targeting this distress,[66] limited research thus far has not supported this hypothesis.[67] In

[57] For example, the U.K.'s clinic saw 12 total patients in 1994 and 24 in 1996; it saw 150 total patients between its opening in 1989 and the year 2000 (Barnes, 2023, pp. 15-16).
[58] Steensma et al. (2018).
[59] E.g. Coleman et al. (2022, p. S9, S43); Baker & Restar (2022); de Vries et al. (2021); Olson-Kennedy, Okonta et al. (2018). The figure in McDeavitt et al. (2025) shows that the rate of increase in referrals to the U.K.'s clinic (for example) is well-approximated by an exponential. A Reuters investigation did not describe exponential growth but did find that referrals to PGM clinics have sharply increased in the U.S. (Respaut & Terhune, 2022).
[60] See Kaltiala-Heino et al. (2015, 2018); Taylor, Hall, Langton et al. (2024b); Thompson et al. (2022a); Wagner et al. (2021); Wood et al. (2013); Zhang et al. (2021). One study in this field claimed that there was no disproportionate increase in female adolescents (Turban, Dolotina et al., 2022). However, this finding was based on a survey in which there was "uncertainty as to whether transgender students responded to the sex question with their sex or gender identity" (Johns et al., 2019).
[61] See Becerra-Culqui et al. (2018); Kaltiala-Heino et al. (2015), (2018); Kozlowska et al. (2021); Taylor, Hall, Langton, Fraser, et al. (2024b); Thompson et al. (2022b).
[62] Kaltiala-Heino et al. (2015).
[63] E.g., Becerra-Culqui et al. (2018); Kozlowska et al. (2021).
[64] E.g. de Vries et al. (2010); Strang et al. (2018).
[65] Barnes (2023, p. 156).
[66] E.g., Ehrensaft (2016); Edwards-Leeper & Spack (2012); J. L. Turban (2018).
[67] Russell et al. (2021).

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2018, recognizing the clinical entity of co-occurring GD and ASD traits, researchers published preliminary guidelines for this specific population of children and adolescents,[68] recommending that "due to differences in social communication, insight and flexible thinking … extended diagnostic periods should be considered in cases where [ASD] is suspected or diagnosed."[69]

4.3.1.3 Nonbinary identities

The original Dutch research did not study patients with nonbinary identities; such patients were not deemed to be appropriate candidates for medical transition.[70] However, nonbinary identities now feature prominently in contemporary clinical settings and research populations. In a 2020 research project funded by the Trevor Project, for example, 63% of the 11,914 survey respondents identified as nonbinary.[71] In a study of youth who received mastectomies, 11% identified as nonbinary or "other."[72] This creates a new set of ethical challenges, as patients seek interventions that have never before been contemplated, including keeping patients in puberty-suppressed states for extended periods of time to allow them to maintain a sex-ambiguous appearance. The risks of such interventions may be considerable.[73]

4.3.1.4 Social influence

The role of social influence is a likely factor in these epidemiological changes. In 2018, physician and researcher Lisa Littman popularized the phrase "rapid onset gender dysphoria," or ROGD, in the peer-reviewed literature, describing the clinical picture of

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[68] Strang et al. (2018).
[69] See description in Russell et al. (2021, p. 2074). In contrast to the 2018 Dutch guidelines that recommended more caution for patients with co-occurring ASD, leading specialists in the United States have criticized parents who are reluctant to consent to PMT for their autistic children. They have proposed clinicians "depend on drawings" for severely autistic, nonverbal adolescents who cannot speak but are able to draw pictures (Transparency Podcast, n.d.). See also: whistleblower account of therapist Tamara Pietzke (Section 11.4.3).
[70] de Vries et al. (2006, p. 88): "Adolescents whose wish for sex reassignment seems to originate from factors other than a genuine and complete cross-gender identity are served best by psychological interventions."
[71] A. E. Green et al. (2022).
[72] Ascha et al. (2022).
[73] In 2020, researchers published a case report in which clinicians considered the possibility of keeping an "agender" patient with low bone density on PBs for at least seven years in order to provide affirmation for this identity (Pang, Notini, et al., 2020). Contemporary WPATH guidelines have eliminated barriers to hormonal interventions and surgeries for minors with nonbinary and other identities.

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"adolescent-onset or late-onset gender dysphoria where the development of gender dysphoria is observed to begin suddenly during or after puberty in an adolescent or young adult who would not have met criteria for gender dysphoria in childhood."[74] This phenomenon has also been described in research from the U.K.,[75] the Netherlands,[76] Finland,[77] and Canada.[78] Other terms have been used—e.g. "adolescent onset gender dysphoria," "postpuberty adolescent-onset transgender histories"[79]—for pubertal-onset gender dysphoria disproportionately affecting female adolescents.

Research into experiences of detransition and regret (detransition refers to stopping or reversing transition after having received medical and/or surgical interventions; it can overlap with but is not synonymous with regret) have suggested social influence or pressure have played a role in the transient transgender identifications of some patients.[80] Concerns about the possible role of social influence underlying epidemiological shifts in presentations have been articulated elsewhere in the literature,[81] including by some proponents of PMT.[82] WPATH's guidelines note that "susceptibility to social influence impacting gender may be an important differential to consider" for some adolescents; the guidelines also acknowledge "situations in which a young person experiences very recent or sudden self-awareness of gender diversity and a corresponding gender treatment request, or when there is concern for possible excessive peer and social media influence on a young person's current self-gender concept."[83]

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[74] Littman (2018, p. 2). This research surveyed 256 parents of children with adolescent-onset GD, finding that in roughly half the cases, the rapid onset of GD appeared to have coincided with the onset of similar distress within the children's friend groups, and with an increase in social media/Internet use. "Rapid onset gender dysphoria" appeared in scholarly work a year earlier, in a poster abstract by Littman in the *Journal of Adolescent Health* and (following Littman's research) also in Marchiano (2017).
[75] de Graaf et al. (2018); Hutchinson et al. (2020).
[76] de Vries (2020).
[77] Kaltiala-Heino et al. (2018); Kaltiala-Heino & Lindberg (2019).
[78] Zucker (2019).
[79] Kaltiala-Heino & Lindberg (2019); de Vries (2020).
[80] Littman (2021); Littman et al. (2024).
[81] Bailey & Diaz (2023); Wood et al. (2013).
[82] Edwards-Leeper & Anderson (2021); Shrier (2021b).
[83] Coleman et al. (2022, p. S45, S58).

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4.3.2 Unclear natural history and prognostic uncertainty

Prior to the widespread availability of hormonal interventions, most cases of childhood GD resolved naturally by the end of puberty, with the majority of patients having a homosexual sexual orientation in adulthood.[84] The Dutch Protocol was developed on the assumption that only GD that persisted into adolescence would likely be permanent.[85] As referrals shifted toward patients with adolescent-onset distress, this assumption of permanence was generalized to all adolescent GD regardless of whether it *intensified* in adolescence or *appeared for the first time* in adolescence. The belief that any GD in adolescence is likely permanent and warrants medical treatment remains "central to the rationale for medical intervention" in adolescents.[86]

4.3.2.1 New evidence about the natural history of gender dysphoria

Recent close examination of the literature has called into question the assumptions regarding the permanence of adolescent GD.[87] Although the natural history of GD—i.e., its course absent medical interventions—is currently impossible to measure given the wide availability of interventions, new evidence suggests that GD has a low diagnostic stability. For example, a German longitudinal analysis of an insurance claims database showed that over 70% of adolescent females aged 15-19 no longer had the diagnosis

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[84] The largest such study was Singh et al. (2021), which included a comprehensive overview of prior research on persistence of childhood GD (pp. 2-4). Some have argued that changes to diagnostic criteria—from the older "Gender Identity Disorder" (for which dysphoria, described as "discomfort," was a criterion) to the contemporary "Gender Dysphoria" diagnosis—render findings of older studies irrelevant (Temple Newhook et al., 2018). These arguments have been effectively countered (Zucker, 2018). (For the diagnostic criteria, see Appendix 2.) Low persistence rate of childhood GD has been recognized in the literature: e.g. "gender variant children, even those who meet the criteria for GID prior to puberty, for the most part are not gender dysphoric at a later age" (de Vries & Cohen-Kettenis, 2012, p. 306); also see Ristori & Steensma (2016, p. 6); Cohen-Kettenis & Gooren (1999).

[85] E.g. Cohen-Kettenis & Pfäfflin (2003); de Vries et al. (2006); de Vries & Cohen-Kettenis (2012); de Vries et al. (2014).

[86] Rosenthal (2021a, p. 585): "Longitudinal studies have indicated that the emergence or worsening of gender dysphoria with pubertal onset is associated with a very high likelihood of being a transgender adult. This observation is central to the rationale for medical intervention in eligible transgender adolescents."

[87] Byrne (2024a).

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five years later.[88] Another recent study from the Netherlands found that "gender non-contentedness" continues to decline steadily into the early twenties.[89]

4.3.2.2 Concerns about identity development

There is considerable concern that "pubertal suppression may alter the course of gender identity development, essentially 'locking in' a gender identity that may have reconciled with biological sex during the natural course of puberty."[90] This concern is not new. Some early critics of the Dutch approach pointed out that initiation of hormonal interventions in early to mid-puberty "might affect the further development of gender identity, or … even iatrogenically induce persistence [of GD]."[91] In 2024, the European Academy of Pediatrics cautioned that puberty suppression may undermine long-term autonomy by creating a path dependency that leads to cross-sex hormones and surgery.[92] Several studies have suggested continuation rates from PBs to CSH exceed 90%.[93] The perception of PBs has shifted—from being seen as a reversible "pause button" to more like a "gas pedal" that accelerates medical transition.

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[88] Bachmann et al. (2024) was an insurance claims study looking at the International Classification of Diseases, tenth version (ICD-10) code F64 ("Gender Identity Disorder"), which was the billing code used in Germany over the course of the study period (Society for Evidence-Based Gender Medicine, 2024c). A recent *BMJ* analysis of claims data and medical records concluded that for some groups, including young people, "GD is not a permanent diagnosis" (Sun et al., 2023).

[89] Rawee et al. (2024, p. 1813). "Gender non-contentedness" was defined based on endorsement of item 110 in the Youth Self Report/Adult Self Report (YSR/ASR), "Wishes to be the opposite sex." Although item 110 is not synonymous with the diagnosis of GD, it is frequently used as a rough proxy for the clinical diagnosis as it captures the primary criterion of the desire to be the opposite sex. See Zucker (2005).

[90] Jorgensen et al. (2022, p. 1005). See also the Cass Review's final report: "Blocking [puberty] means that young people have to understand their identity and sexuality based only on their discomfort about puberty and a sense of their gender identity developed at an early stage of the pubertal process. Therefore, there is no way of knowing whether the normal trajectory of the sexual and gender identity may be permanently altered" (Cass, 2024a, p. 178).

[91] Korte et al. (2008, p. 839).

[92] Brierley et al. (2024).

[93] E.g., Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018). Some have claimed that "the most likely explanation for why most youth who receive early, supportive interventions [i.e., puberty blockers] continue onto gender-affirming hormone therapy [is] that they are indeed transgender. It is not ... puberty-pausing medications that drive a persistent transgender identity" (McNamara et al., 2024, pp. 20-21). However, the very research studies that comprise the evidence base in this area recognized the possibility that the intervention may induce persistence; e.g., "Due to the observational character of the study, it is not possible to say if [puberty blocker] treatment itself influenced the outcome" (Brik et al., 2020, p. 2611); "[there is] the potential that treatment could influence the continuation of their GD" (Carmichael et al., 2021).

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Social transition in childhood may have similar effects, with some low-quality studies suggesting the majority of children who socially transition[94] before puberty progress to medical interventions.[95] These patients "are likely [to] seek blockers or hormones."[96] Prepubertal transition was not recommended in the original Dutch approach (the researchers actually recommended *against* the practice),[97] but was originally championed by American clinicians.[98]

Prepubertal social transition is now recommended for certain patients, including in the Netherlands.[99] However, there are no reliable methods to distinguish which patients will experience long-term GD.[100] There is growing concern about administering irreversible treatments that may lead to lifelong medical dependency for a condition that, in many cases, may naturally resolve.

4.3.3 Concerns about treatment-associated risks and harms

Awareness of the risks and potential harms of PMT is growing.[101] Concern has been raised about the unknown or potentially harmful effects of suppressing normally timed puberty on adolescent physical and mental health, especially with regard to bone mineralization and brain development.[102] Hormonal interventions can lead to infertility and impaired sexual function, and in some cases, if the patient proceeds to genital

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[94] In this context, social transition refers to "a 'complete' binary social transition ... including changing their pronouns to the binary gender pronouns that differed from those used at their births" (Olson et al., 2022, p. 2), not to changes in hairstyle, clothing, etc.
[95] Olson et al. (2022, 2024). See also Society for Evidence-Based Gender Medicine (2022b).
[96] Olson et al. (2022, p. 4).
[97] E.g., "In a qualitative follow-up study, several youths indicated how difficult it was for them to realize that they no longer wanted to live in the role of the other gender and to make this clear to the people around them… Another reason we recommend against early transitions is that some children who have done so (sometimes as preschoolers) barely realize that they are of the other natal sex. They develop a sense of reality so different from their physical reality that acceptance of the multiple and protracted treatments they will later need is made unnecessarily difficult. Parents, too, who go along with this, often do not realize that they contribute to their child's lack of awareness of these consequences" (de Vries and Cohen-Kettenis, 2012, p. 308).
[98] E.g. Ehrensaft (2016); Olson et al. (2016).
[99] Bazelon (2022a).
[100] Cass (2024a, pp. 22, 134, emphasis added). "… clinicians have told us *they are unable to determine with any certainty* which children and young people will go on to have an enduring trans identity … Many clinicians, both nationally and internationally, have [acknowledged] that there is *no reliable way to accurately predict* which young people might benefit from a medical transition and which might benefit from alterative pathway(s) or interventions(s)."
[101] See Chapter 7 for detailed discussion.
[102] E.g., Baxendale (2024); Biggs (2021).

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procedures, riskier operations.[103] Surgical procedures themselves carry the risk of complications.

The emergence of detransitioners has brought renewed attention to a risk acknowledged in the original Dutch Protocol, which is that initiating medical transition while a young person's identity is still developing carries the risk of "false positives"—patients who undergo irreversible hormonal and/or surgical interventions but ultimately do not continue to identify as transgender.[104] In the past five years, a growing body of research and peer-reviewed literature has examined the phenomena of detransition and regret.[105] Personal accounts from detransitioned patients who report having been harmed by PMT have played a significant role in drawing public and regulatory attention to these issues.[106]

4.3.4 More appropriate understanding of suicide

Proponents of PMT often describe it as lifesaving.[107] Some physicians recommending PMT have urged anxious parents to consent to irreversible interventions for their distressed children, warning that not doing so may increase the risk of suicide.[108] Such claims are not supported by the evidence and have been criticized as unethical.[109]

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[103] See Lee et al. (2023), for example.
[104] Delemarre-van de Waal & Cohen-Kettenis (2006, p. S132). "It is conceivable that lowering the age limit increases the incidence of 'false positives.'"
[105] E.g. Entwistle (2020); Littman (2021); MacKinnon, Expósito-Campos et al. (2023); Roberts et al. (2022).
[106] According to a Reuters investigation, a patient told her gender clinic at age 16 that she was "sure of my identity … I thought nothing would change my mind." After starting CSH she experienced worsening mental health and had several suicide attempts and psychiatric hospitalizations. She detransitioned at age 20 and identifies as a lesbian: "I do wish my doctors had said to me, 'It's OK to feel disconnected from your body. It's OK to like girls. It's OK to be gender non-conforming'" (Respaut et al., 2022). For an overview of the role of detransitioner Keira Bell in drawing regulatory attention to pediatric gender medicine in the U.K., see Cass (2024a, pp. 78-80).
[107] E.g., ACLU (2021); Boerner (2022, 3/31/2025 update); Georges et al. (2024); Lee & Rosenthal (2023); Sandhu et al. (2025); Szilagyi (2022b); The Lancet Child & Adolescent Health (2021). See also Section 1.2.
[108] In 2011, Johanna Olson-Kennedy, pediatrician and leader in the field of pediatric gender medicine, told ABC News that "We often ask parents, would you rather have a dead son than a live daughter?" (ABC News, 2011). See also Singal (2018).
[109] E.g., Clayton (2023); Levine et al. (2022a).

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Adolescents and adults with GD do exhibit higher rates of suicidality—including suicidal thoughts, self-harm, and suicide attempts—compared to the general public.[110] However, completed suicide among adolescents with GD remains rare.[111] Moreover, there is no evidence that elevated suicidality can be attributed solely to GD, as it frequently co-occurs with other mental health conditions. A 2020 report by the Swedish National Board of Health and Welfare (Socialstyrelsen) concluded that "people with gender dysphoria who commit suicide have a very high rate of co-occurring serious psychiatric diagnoses, which in themselves sharply increase risks of suicide … it is not possible to ascertain to what extent GD alone contributes to suicide."[112]

Further, the evidence for whether PMT reduces *suicidality*-related outcomes in adolescents—such as self-reported frequency of suicidal thoughts, or healthcare utilization for self-harm or suicide attempts—is inconsistent.[113] When the focus turns to preventing *suicide mortality*, there is no evidence that hormonal interventions are effective. A large, register-based study from Finland found that overall suicide mortality in patients with GD was rare and that when mental health comorbidities were controlled for, the rate did not differ from that of the general population. The study authors concluded that hormonal interventions did not appear to have impacted suicide risk.[114] An SR of suicide prevention for youth with GD rated the evidence as low quality,[115] and WPATH's own SR of mental health outcomes, which focused on adult populations, acknowledged that "It was impossible to draw conclusions about the effects of hormone

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[110] E.g., Biggs (2022); Erlangsen et al. (2023); Heino et al. (2023); Marconi et al. (2023); Van Cauwenberg et al. (2021); Wiepjes et al. (2020).
[111] Biggs (2022); Ruuska et al. (2024); Society for Evidence-Based Gender Medicine (2023a).
[112] Socialstyrelsen (2020); see also Ruuska et al. (2024). Additionally, de Graaf et al. (2022) found that adolescents with GD or transgender identification had similar self-reported suicidality measures to comparator adolescents without GD who were receiving specialized mental healthcare for other psychiatric diagnoses.
[113] Small to medium-size studies have reported improvement over time in self-report scores related to suicidality (Achille et al., 2020; Allen et al., 2019) or decrease in healthcare utilization for suicidal or self-harm behavior (Kaltiala et al., 2020; Khatchadourian et al., 2014); other larger studies found the percent of patients with suicidal thoughts/behaviors increased after initiating PBs/CSH (Kuper et al., 2020) and increases in healthcare utilization related to suicidality (Hisle-Gorman et al., 2021). Kuper et al.'s before-after comparison is compromised by the unequal time periods over which suicidality was measured.
[114] Ruuska et al. (2024).
[115] Christensen et al. (2025). Similar findings were also reported in a recent narrative review focused on adults (Jackson, 2023). With respect to surgeries, evidence is limited. A recent systematic review of mastectomies in young females found very low certainty evidence with respect to effect on death by suicide (Miroshnychenko et al., 2024).

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therapy on death by suicide."[116] As summarized in the Cass Review's final report, "it has been suggested that hormone treatment reduces the elevated risk of death by suicide in this population, but the evidence found [does] not support this conclusion."[117] Consequently, claims that PMT is "lifesaving" appear to be unsupported by the evidence.

These findings also have been confirmed by the Appleby Report, commissioned by the U.K. government, which reviewed suicides among young people with GD. The report strongly criticized the way suicide and GD have been discussed on social media, characterizing it as insensitive, distressing, dangerous, and in violation of established guidance on the safe reporting of suicide. Appleby emphasized that many of the public claims made about suicide do not meet basic standards for statistical evidence. The report also urged a shift away from viewing PBs as the primary marker of supportive care, warning that such a narrow focus oversimplifies complex clinical needs.[118]

4.3.5 Collapse of clinical rationale

An original rationale for prescribing PBs, as outlined in the Dutch Protocol, was to provide adolescents with "time to think" by pausing puberty, thereby allowing for the exploration of identity without the added distress of physical development.[119] However,

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[116] Baker et al. (2021, p. 12). Another more recent systematic review also found very low certainty evidence for the effect of CSH on death by suicide (Miroshnychenko, Ibrahim et al., 2025).
[117] Cass (2024a, p. 33). An example of commonly cited evidence—e.g., American Psychological Association (2024b); The Lancet Child & Adolescent Health (2021), via reference to Rew et al., (2021); Turban (2020)—in support of this suggestion is Turban, King et al. (2020), a cross-sectional analysis of Internet-based survey data that found that respondents who had accessed PBs had lower lifetime suicidal ideation when compared to those who had wanted PBs but not accessed them. The online survey, the 2015 U.S. Transgender Survey (USTS) (James et al., 2015), had multiple methodological weaknesses. For example, it was a convenience sample, likely not representative of transgender adults in the U.S, and respondents may have confused PBs for CSH (Biggs, 2020; Clayton et al., 2021). Additionally, the survey relied on adult respondents' retrospective recall of childhood and adolescence, and such memories "are subject to confabulation, modification, bias, and simply forgetting;" for example, "31% of respondents recalled realizing they were transgender by age 5, including some who recalled they were transgender at the age of 1 and 2—long before autobiographical memories begin" (Kulatunga Moruzi & Lawler, 2024, pp. 11, 4). The Turban et al. study has also been criticized for its inaccurate assumption that PBs for GD were available in the U.S. starting in 1998, and it has been pointed out that on multivariate analysis, there were no statistically significant between-group differences on five other measures of suicidality, including history of suicide attempts (Biggs, 2020; Clayton et al., 2021).
[118] Appleby (2024).
[119] Delemarre-van de Waal & Cohen-Kettenis (2006).

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data suggest that adolescents who start PBs go on to take CSH.[120] This means that PBs may not function as a neutral pause, but rather the first step on the path to medical transition. This has prompted many experts to abandon the "time to think" rationale, a reversal reflected in more recent WPATH guidelines and professional statements.[121] PBs and CSH are now understood to be a continuous treatment pathway.[122]

Given the risk profile of PBs as outlined in Chapter 7, and the possibility that their use may lead to lifelong medical dependency carrying additional long-term risks, their role in the current treatment paradigm is unclear. In male patients, testosterone suppression can be achieved with anti-androgens alongside estrogen for feminization. In female patients, testosterone alone effectively suppresses estrogen, while also inducing masculinization. Therefore, if PBs are not being used to provide time to think, their rationale in this context remains uncertain.[123]

4.3.6 Lack of reliable evidence of benefit

The original intent behind the use of hormonal interventions in pediatrics was to improve mental health outcomes[124] by preventing sexual development and causing the development of physical characteristics typical of the other sex. This approach was

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[120] Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).

[121] Although WPATH's 2012 guidelines stated (consistent with the original Dutch research) that PBs would "[give] adolescents more time to explore their gender nonconformity and other developmental issues," (see Coleman et al., 2012, p. 177), this clinical rationale is absent in the latest version of the organization's guidelines, Coleman et al. (2022). A recent article by leaders in the field about eligibility and screening evaluations for patients interested in PBs made no mention of the "time to think" rationale (Turban et al., 2025). See also amicus brief acknowledging that PBs and CSH should not be considered separate treatment pathways because they constitute a "care continuum" and "the vast majority of adolescents with gender dysphoria who receive puberty blockers progress to cross-sex hormone therapy" (U.S. v. Skrmetti (No. 23-477), Expert Researchers and Physicians, Amicus curiae brief, 2024).

[122] There are exceptions to this understanding; some research papers and organizations still claim PBs provide time to think (e.g. Fisher et al., 2024; U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief, 2024, p. 13).

[123] The Cass Review found that although there may be "a very narrow indication for the use of puberty blockers in birth-registered males as the start of a medical transition pathway in order to stop irreversible pubertal changes," there were no other reasonable, proven rationales for use of PBs, and, notably, no indication for use of PBs in females (Cass, 2024a, p. 180). Experts have questioned "the rationale for depriving an adolescent of sex hormones for years during puberty and risking the effects on bones and brains" (Ryan, 2024b).

[124] Researchers were originally motivated to initiate hormonal interventions in children and adolescents because they were concerned about poor mental health in adult patients and hoped to mitigate this by preventing development of sex characteristics that were distressing for these adults (discussed in more detail in Chapter 3).

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based on the hypothesis that avoiding "an unfavorable physical appearance"[125] would "improve the ability to 'pass' as the desired gender."[126] While these interventions do alter physical appearance, SRs have not found credible evidence that they lead to meaningful improvement in mental health.[127] Multiple SRs have concluded that the evidence supporting the benefits of pediatric transition interventions—from PBs to CSH and surgery—is of "very low certainty." (See Chapter 5.) This means that findings from studies reporting mental health improvements[128] are not considered reliable. In contrast, all medical interventions carry the potential for harm.

Ultimately, medical interventions should be used when the balance of benefits clearly outweighs the risks. Every public health authority that has conducted a systematic review of the evidence has concluded that the benefit/risk profile of PMT is either unknown or unfavorable.

[125] Delemarre-van de Waal & Cohen-Kettenis (2006).
[126] Costa et al. (2015).
[127] The other original clinical rationale was decreasing need for future surgeries. One study has reported that female patients who started PBs early in puberty were less likely to receive mastectomies than patients who started PBs later, suggesting relative lack of breast tissue precluded need for mastectomy. However, this study also found greatly increased odds of intestinal vaginoplasty in male patients who received PBs in early puberty (van de Grift et al., 2020). One adolescent mastectomy study suggested chest-related dysphoria increased after testosterone use (Olson-Kennedy, Warus, et al., 2018). Theoretically, increasing chest dysphoria could lead to pursual of mastectomy. In the adult literature there have been reports of females undergoing hysterectomy due to pelvic pain caused by reproductive organ atrophy (e.g., Zwickl et al., 2023).
[128] Across the studies looking at mental health outcomes, statistically significant improvements have been inconsistently reported. Of longitudinal mental health outcome studies in this field, some reported improvements in one or more mental health outcomes (Achille et al., 2020; Allen et al., 2019; Chelliah et al., 2024; Chen et al., 2023; de Vries et al., 2011, de Vries et al., 2014; Fisher et al., 2024; Kaltiala et al., 2020; Kuper et al., 2020; Lavender et al., 2023; López de Lara et al., 2020; Olson-Kennedy et al., 2025); the largest study found worsening in mental health outcomes (Hisle-Gorman et al., 2021), while others reported no change (Becker-Hebly et al., 2020; Cantu et al.. 2020; Carmichael et al., 2021; Eisenberg et al., 2024; Khatchadourian et al., 2014; Russell et al., 2021; Tordoff et al., 2022). One study reported similar improvement in a group treated with PBs and a group treated with psychotherapy only (Costa et al., 2015).

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PART 2

EVIDENCE REVIEW

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Chapter 5 Overview of Systematic Reviews

This chapter reviews the best available information regarding the risks, benefits, and uncertainties of interventions commonly used to address gender dysphoria (GD) in youth. It summarizes the findings of the overview of systematic reviews (SRs) (also known as an "umbrella review") conducted for this Review. Section 5.1 defines some terminology and describes the methodology used to produce the overview of SRs. Sections 5.2-5.6 summarize the overview's findings for the following interventions: social transition; puberty blockers (PBs); cross-sex hormones (CSH); surgery; and psychotherapy. The chapter concludes with a discussion section (5.7).

Chapter 6 explains the limitations of SRs and the need—especially in the context of pediatric gender medicine (PGM)—to consider other types of scientific evidence. Chapter 7 is an overview of those other types of evidence, including evidence from basic science, from known mechanisms of drug action, and from endocrinological disorders that approximate the effects of medical transition. This broader base of evidence allows for a more comprehensive assessment of potential harms. Chapter 8 briefly summarizes the implications of these findings for decision-makers.

5.1 Methodology

A fundamental principle of evidence-based medicine (EBM) is that optimal decision-making "requires awareness of the best available evidence, which ideally will come from systematic summaries of that evidence."[1] The cornerstone of EBM is the *systematic review*,

> [which] attempts to collate all empirical evidence that meet prespecified eligibility criteria in order to answer a specific research question. It uses explicit, systematic methods that are selected with a view to minimizing bias, thus providing more reliable findings from which conclusions can be drawn and decisions made.[2]

[1] Guyatt et al. (2015, p. 10).
[2] Higgins et al. (2019, p. xxiii).

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The conclusions of any individual study will be limited by study design and other factors. Collating, synthesizing, and assessing all relevant studies on the topic of interest, using systematic and reproducible methods to minimize biases and mistakes, makes possible more reliable conclusions.

SRs sit atop of the "hierarchy of evidence."[3] However, not all literature reviews are SRs, even when titled as such, so it is important to evaluate the process used in the production and reporting of any evidence review that claims to be an SR. For example, the "Cornell Review" has been extensively cited in the field of PGM to support a claim of low regret, but that review's findings do not support that conclusion.[4]

An overview of SRs essentially applies the methodology of SRs to SRs themselves, making the SRs the unit of analysis, rather than individual primary studies. In the present case, an overview of SRs was prepared because the field is already saturated with SRs, many of which evaluate the same studies. By assessing the quality of these SRs, an overview allows for a clearer understanding of the overall strength, consistency, and gaps in the evidence base.

The methodology of the overview followed the recommendations for overviews of SRs in the *Cochrane Handbook for Systematic Reviews of Interventions*.[5,6] Medline, Embase, and the psychological database PsycINFO were searched for SRs on the effects of social transition, PBs, CSH, surgeries, and psychotherapy for youth with GD up to age 26 years.[7] A complementary literature search was also conducted for "grey

[3] See Appendix 3.
[4] Cornell University & What We Know Project (2017). The Cornell Review claimed that "regrets are most likely to result from a lack of social support after transition or poor surgical outcomes using older techniques." But this review did not properly synthesize evidence from included studies, nor assess the quality of the evidence. The review findings should therefore be interpreted with caution. The Cornell Review was not included in the present overview because the target population was mature adults, and thus is not clearly applicable to children and adolescents with GD (see Section 4.3.1.1).
[5] Higgins et al. (2019).
[6] See Appendix 4 for the detailed methodology and results of this overview.
[7] SRs in this area have usually involved patients under 18 or under 26. To encompass the inclusion of those aged 18, the Review made the decision to search for SRs for patient populations below the age of 26. This balances the comprehensiveness and the directness (applicability) of evidence review. Though there is concern regarding the directness of evidence, the evidence for <18 and patients who are older than 18 years did not identify any significant differences in outcomes.

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literature"[8] and reference lists of eligible SRs. Two reviewers independently screened titles and abstracts, and then full texts, to determine study eligibility. Reviewers resolved disagreement by discussion. The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) was used to assess the included SRs.[9] Data extraction and risk of bias assessment were completed by one reviewer and checked by a second. ROBIS assesses the quality of the SR in four domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis of findings. Additionally, ROBIS assesses the overall risk of bias in an SR's process. SRs with concerns identified in the four domains can still be assessed at low risk of bias if the SRs have properly addressed those concerns in the evidence interpretation.

The following five sections of this chapter summarize the outcome data across SRs published in English and classified at low risk of bias. The evidence synthesis was organized by the outcomes of interest for each treatment strategy. These outcomes included GD, mental health and well-being, physiologic effects (e.g., suppression of sex hormones for PBs), need for or progression to further treatment, safety outcomes including side effects and adverse outcomes, and regret. For each outcome, this overview summarized the effect estimates and the quality of evidence (the confidence in the effect estimates), following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.

In GRADE, quality of evidence is equivalent to certainty of evidence.[10] Quality of evidence can be downgraded for various reasons: risk of bias (study limitations), inconsistency (unexplained variation in results), indirectness (evidence not directly applicable), imprecision (wide confidence intervals or small samples), and publication bias (selective reporting).[11] Conversely, quality may be upgraded if there is a large

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[8] "Gray literature" refers to research and information produced outside of traditional academic publishing channels and therefore may not be formally peer-reviewed or indexed in major databases.
[9] Whiting et al. (2016).
[10] "The quality of evidence is very low" is equivalent to "the certainty of evidence is very low" (Balshem et al., 2011; Guyatt et al., 2008).
[11] Balshem et al. (2011); Guyatt et al. (2008); Guyatt, Oxman, Kunz, Brozek et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter et al. (2011); Guyatt, Oxman, Kunz,

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effect size, a clear dose-response relationship, or if confounding factors would likely reduce the observed effect but the effect was nonetheless observed.[12]

Evidence is then classified into four categories by level of quality: high, moderate, low, or very low.[13] High quality evidence means that "we are very confident that the true effect lies close to that of the estimate of the effect." Very low quality evidence indicates that "we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect." This overview summarizes the GRADE ratings from the original SRs for the respective outcome wherever it is available. Nevertheless, two modifications were made:

1. Where a formal GRADE appraisal had not been performed by the SR, but expressions such as "we are very uncertain" or "no conclusions could be drawn" were used in the SR's conclusions, these were considered equivalent to a "very low quality" GRADE assessment.[14]
2. Where SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale.

After screening, 17 SRs met the inclusion criteria. These examined the effects of social transition (n = 2),[15] PBs (n = 9),[16] CSH (n = 8),[17] surgery (n = 3),[18] and psychotherapy (n = 5)[19] among children or adolescents with GD. Of the 17 included SRs, ten were rated

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Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou et al. (2011); Guyatt, Oxman, Montori, et al. (2011); Guyatt, Oxman, Vist et al. (2011).
[12] Guyatt, Oxman, Sultan et al. (2011).
[13] Balshem et al. (2011). See also Appendix 3.
[14] Balshem et al. (2011); Santesso et al. (2020).
[15] Dopp et al. (2024); Hall et al. (2024).
[16] Chew et al. (2018); Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan et al. (2025); Ramos et al. (2021); Rew et al. (2021); Taylor, Mitchell, Hall, Heathcote et al. (2024); Thompson et al. (2023); Zepf, König et al. (2024).
[17] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024); Thompson et al. (2023); Zepf, König et al. (2024).
[18] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[19] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).

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as having a low risk of bias overall.[20] SRs rated as a "low risk of bias" nevertheless may still have limitations in one or more domains. Seven SRs were rated as having a high risk of bias overall,[21] often due to limited or poorly defined research questions and eligibility criteria, lack assessment for risk of bias, and inadequate synthesis of findings. The variation in methodological rigor highlights the need for cautious interpretation of findings, especially from reviews rated at high risk of bias.

Of note, this overview excluded two SRs performed by the National Institute for Health and Care Excellence (NICE) in October 2020 to inform the Cass Review.[22] These were excluded because several subsequent SRs commissioned from the University of York to inform the Cass Review were published. The latter SRs are more comprehensive and updated the findings of the two NICE SRs.

This overview also excluded the 2021 SR by Baker et al.,[23] because participants in most of the included studies for that SR were mature adults. Notably, the Baker et al. review was cited to support Statement 2.1 in the World Professional Association for Transgender Health's *Standards of Care for the Health of Transgender and Gender Diverse People*, Version 8 (WPATH SOC-8).[24] That statement—"We recommend health care systems should provide medically necessary gender-affirming health care for transgender and gender diverse people"—was then cited in support of the recommendations in SOC-8's Adolescent chapter. Because of the way this SR has been relied on in the field of PMT, Baker et al. was subjected to a separate ROBIS analysis which found it to be at high risk of bias due to limitations in ROBIS domains of "data collection and study appraisal" and "synthesis and findings." The ROBIS assessment of Baker et al. is included in Section 2.3 of Appendix 4, while Appendix 3 provides an

[20] Dopp et al. (2024); Hall et al. (2024); Heathcote et al. (2024); Ludvigsson et al. (2023); Miroshnychenko et al. (2024); Miroshnychenko, Ibrahim et al. (2025); Miroshnychenko, Roldan et al. (2025); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024); Zepf, König et al. (2024). SRs conducted by the same research group generally followed the same methodology approach.
[21] Chew et al. (2018); Expósito-Campos et al. (2023); Karalexi et al. (2020); Malpas et al. (2022); Ramos et al. (2021); Rew et al. (2021); Thompson et al. (2023).
[22] National Institute for Health and Care Excellence (2020b, 2020a).
[23] Baker et al. (2021).
[24] Coleman et al. (2022).

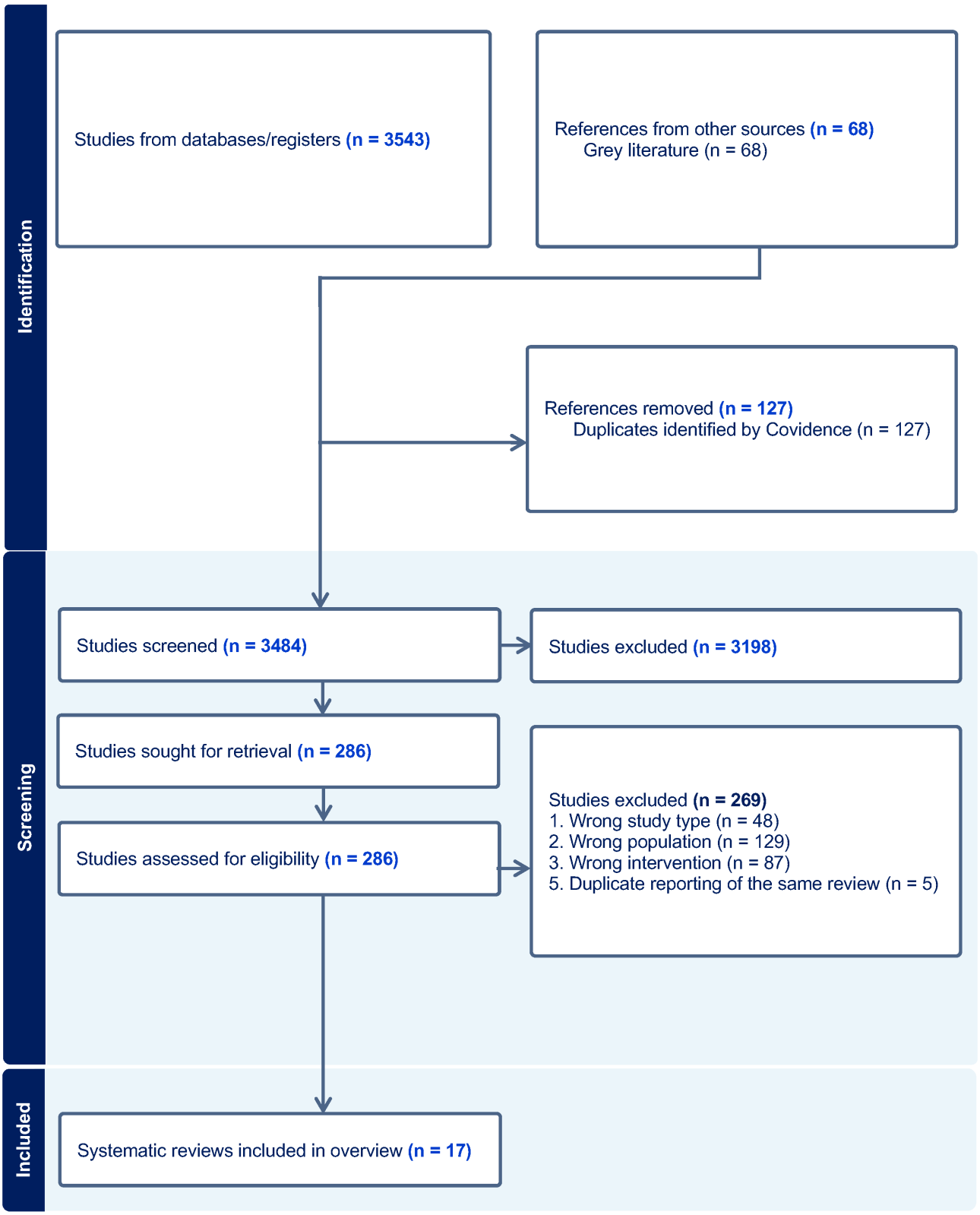
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introduction to SRs and EBM. Figure 5.1 below provides a flow diagram for the searching, screening, and inclusion process.

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Figure 5.1 Searching, screening, and inclusion process



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5.2 Outcomes of social transition

Social transition involves changing one or more aspects of one's presentation or expression, such as name, appearance, or behavior, with the goal of being perceived and treated as a member of the other sex, or to avoid being perceived and treated as a member of one's own sex. As noted in the Cass Review, even though social transition is undertaken outside healthcare settings, "it is important to view [social transition] as an active intervention because it may have significant effects on the child or young person in terms of their psychological functioning and longer-term outcomes."[25]

This overview identified two SRs evaluating the impact of social transition. Both are assessed at low risk of bias.[26] The results suggest that the impact of social transition on long-term GD, psychological outcomes and well-being, and future treatment decisions such as hormones or surgeries remains poorly understood. Evidence on regret associated with social transition is extremely limited. The certainty of evidence for these outcomes is very low.

Significant evidence gaps remain in the evaluation of social transition as an intervention for children and adolescents with GD. Most available studies are cross-sectional and there are no prospective longitudinal studies with appropriate comparison groups, making it unclear whether observed associations reflect the effects of social transition or other underlying factors. Additionally, published studies often do not disentangle the effects of social transition from concurrent interventions such as psychotherapy or medical treatments, further complicating interpretation.

5.3 Outcomes of puberty blockers

Gonadotropin-releasing hormone agonists (GnRHa), known as "puberty blockers" (PBs), are used to prevent or arrest the development of sex characteristics in peripubertal and pubertal children and adolescents with GD. This overview identified nine SRs that assessed the treatment effects of PBs. Among these four were English-

[25] Cass (2024, p. 158).
[26] Dopp et al. (2024); Hall et al. (2024).

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language SRs[27] assessed at low risk of bias. The eligibility criteria and number of included studies varied in these four SRs, and the certainty of evidence is very low regarding the effect of PBs on GD (or gender incongruence), improvement in mental health, and safety. There is high certainty evidence that PBs exert physiological effects (such as sex hormone suppression) and often cause infertility when followed by CSH, depending on the patient's pubertal stage and sex.[28] Low certainty evidence suggests that PBs may compromise bone health.[29] A high proportion of youth proceed to CSH after PBs, though the certainty of evidence regarding any causal role PBs play in this progression is very low.

Important gaps remain in both the range and quality of outcomes assessed across the existing literature. Many primary studies were not adequately designed for measuring or reporting on the outcomes related to PBs. For example, few primary studies included in the SRs assessed the impact of PBs on outcomes such as GD or mental health. Although PBs are frequently described as a "pause button,"[30] no studies have systematically examined their role in the decision-making process or the outcomes of those who discontinue treatment.

When outcomes were assessed, the focus was largely on short-term psychological or physiological changes, or surrogate outcomes—such as suicidal ideation or bone mineral density, rather than on endpoints like suicides or fractures. The evidence is particularly limited regarding long-term outcomes related to fertility, growth, and neurocognitive development.

While studies suggest a high proportion of youth proceed to CSH after puberty suppression,[31] there is minimal evidence on the impact of this combined pathway

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[27] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan et al. (2025); Taylor, Mitchell, Hall, Heathcote et al. (2024).
[28] See subsequent discussion of fertility in Chapter 7.
[29] See subsequent discussion of physiologic mechanisms whereby induced hypogonadotropic hypogonadism negatively impacts bone development.
[30] See, for example, a puberty blocker fact sheet from Cambridge Health Alliance/Harvard Medical School Teaching Hospital (Cambridge Health Alliance, n.d.).
[31] In the systematic reviews that were assessed at low risk of bias, only two studies (Carmichael et al., 2021; Karakılıç Özturan et al., 2023a) reported data on this outcome, each reporting progression rates from PBs to CSH of >95%. Other studies not captured by this overview, cited elsewhere in this Review,

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compared to CSH alone, or on how this pathway affects longer-term outcomes such as undergoing surgery. Furthermore, no studies have clearly examined the physical or psychosocial trajectories of the small minority of those who undergo PBs but do not proceed to CSH. As a result, there is little data on what happens after treatment ends, and the assumption that the effects of PBs are reversible remains largely untested. Another important limitation is that most of the primary studies have not distinguished the effects of PBs on females versus males. Overall, the absence of long-term, high-certainty evidence on these critical outcomes (including suicides, fractures, fertility, growth, and neurocognitive development) leaves substantial uncertainty about the effects of PBs.

5.4 Outcomes of cross-sex hormones

Estrogen for males and testosterone for females are used off-label to induce physical changes in the sex characteristics of youth with GD. This overview identified eight SRs on the treatment effects of CSH, among which four were in English language and assessed at low risk of bias.[32] The certainty of evidence is very low regarding the effect on GD or incongruence, improvement in mental health, and safety metrics including fertility and bone health. There is high certainty evidence that CSH exert physiological effects.

As with PBs, important evidence gaps exist for CSH. Many studies were not specifically designed to capture the full range of long-term outcomes and have primarily concentrated on short-term psychological or physiological changes. Key outcomes such as effects on GD, other mental health outcomes, and quality of life have been inconsistently measured and, when reported, often are derived from small, observational studies with limited follow-up. Critically important long-term outcomes remain poorly understood. Sexual dysfunction, despite being highly relevant to long-

also reported >90% progression rate from PBs to CSH: Brik et al. (2020); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).

[32] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024).

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term well-being, has been infrequently assessed. Although a few studies have reported cardiovascular event rates, long-term follow-up is needed to evaluate cumulative risk.[33]

Evidence on fertility is sparse, with little data on whether reproductive effects vary by age at treatment initiation or whether these effects are reversible. Furthermore, the compounded effects of sequential (and sometimes concurrent, especially among males) treatment with PBs followed by CSH—such as their impact on bone health recovery, final adult height, or the likelihood of requiring surgical interventions—have not been adequately investigated. As with PBs, the lack of methodologically rigorous, long-term studies significantly limits researchers' understanding of the broader health implications of CSH use during adolescence. A lack of primary studies that separately evaluate the effects of estrogen in males and testosterone in females is a significant limitation, as hormone-sex interactions may meaningfully influence outcomes.

5.5 Outcomes of surgery

Masculinizing mastectomy for adolescent females is the most frequently performed surgery in the context of youth with GD. This overview identified three SRs on surgeries for children or adolescents with GD, with most primary studies considering mastectomy only.[34] Two SRs were assessed at low risk of bias.[35] There is high certainty evidence that mastectomy is associated with predictable surgical complications such as necrosis and scarring. The certainty of evidence is very low regarding the effect of surgery on GD or incongruence, improvement in mental health including suicidality and depression, and long-term outcomes such as sexual function, quality of life, and regret.

There are substantial gaps in the evidence on surgeries for adolescents with GD. Most studies are case series or small observational designs, with limited or no comparator groups, and thus are unable to isolate the effects of surgery from prior medical or psychosocial interventions. Outcomes such as effects on GD, mental health, and quality

[33] This is particularly true for pediatric medical transition (due to starting CSH in adolescence, the duration of treatment will be longer than for previously studied populations of adults).
[34] Dopp et al. (2024) included 18 studies; more than half of the included studies were on mastectomy. Miroshnychenko et al. (2024) included 39 studies and only assessed the effects of mastectomy. The other SR included 25 participants receiving surgeries, of which 24 received mastectomy. See Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[35] Dopp et al. (2024); Miroshnychenko et al. (2024).

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of life are inconsistently reported and often lack validated measures. Long-term outcomes, including the durability of psychological benefits, sexual function, need for revision surgeries, as well as satisfaction and well-being into adulthood, remain poorly characterized. Furthermore, while regret is a frequent topic of public discussion, existing studies do not provide robust data on the factors influencing regret. There are also knowledge gaps for other types of surgeries, including genital surgeries.

5.6 Outcomes of psychotherapy

Discussions about the role of psychotherapy in the treatment of youth with GD suffer from internal inconsistencies in the field of gender medicine, whereby psychotherapy is both recognized as an important tool but is also stigmatized if its aim is the resolution of GD (Chapter 14). The overview identified a total of five SRs assessing psychotherapy among children or adolescents with GD. Only two were assessed at low risk of bias.[36]

The evidence on the effects of psychotherapy is limited. A 2024 review conducted by Dopp et al. included one randomized controlled trial (RCT) evaluating the effects of "coping-oriented brief videos" on suicidality, which did not provide direct evidence about the effect of psychotherapy in youth with GD. There are no other RCTs. Both SRs found that psychotherapy interventions were delivered through a range of formats, highlighting considerable heterogeneity in delivery. Formats for both face-to-face and online interventions varied widely, including individual, group, family-based, and combined approaches. Face-to-face interventions took place in diverse settings, such as specialist gender services, community programs, community mental health clinics, a weekend retreat, and an acute residential treatment program. These heterogeneities limit the generalizability of evidence. For mental health outcomes, the certainty of evidence was very low. However, no harms were reported.

The overview found no evidence on the effect of psychotherapy on GD itself. This evidence gap may be due to a conflation of psychotherapy with "conversion therapy." As noted by the Cass Review, "[the] role of psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an

[36] Dopp et al. (2024); Heathcote et al. (2024).

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unhelpfully polarised debate around conversion practices."[37] There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with childhood or adolescent GD,[38] including depression, anxiety, eating disorders, self-harm, and suicidality. Early reports often did not isolate the effects of psychotherapy from those of other concurrent interventions such as social transition, PBs, or CSH, making it difficult to attribute observed outcomes to psychotherapy alone. There is little understanding of which therapeutic approaches may be more or less effective for specific subgroups. The lack of robust research was acknowledged by the Cass Review, which noted that "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[39]

Of note, although the direct evidence for psychotherapy in children and adolescents with GD is limited, there is available evidence to support the role of psychotherapy in treating children and adolescents with other mental health problems, including depression, anxiety, eating disorders, self-harm, and suicidality (See Section 14.5.1).

5.7 Discussion

5.7.1 Findings of this overview

This overview of SRs includes 17 SRs evaluating the effects of interventions for children or adolescents with GD. For social transition, the certainty of benefits and harms is very low due to problems in the study designs. While studies suggest that early social transition is associated with a high rate of persistence of GD and a >90% rate of continuation to PBs and CSH,[40] from a methodological perspective there is uncertainty due to very low-quality evidence about causal explanations/pathways. Specific to medical transition, this overview highlights a consistent pattern across interventions for children or adolescents with GD: while PBs, CSH, and surgeries reliably produce expected physiological changes, there remains substantial uncertainty about their psychological and long-term health impacts. High-quality evidence confirms that PBs suppress pubertal development and CSH induce changes to sex characteristics. There

[37] Cass (2024a, p. 150).
[38] See Chapter 14.
[39] Cass (2024a, p. 155).
[40] Hall et al. (2024).

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is low quality evidence suggesting that PBs compromise bone health.[41] However, the quality of evidence for outcomes such as GD, mental health, quality of life, and regret remains very low across all intervention types. The interpretation of many of the SRs' findings should be approached with caution, particularly given the sources of uncertainty, the robustness of this overview's conclusion, and the methodological limitations inherent in the evidence reviews.

5.7.2 Sources of uncertainty in evidence

Across the included SRs, the quality (certainty) of evidence is predominantly limited by lack of methodologically rigorous studies. For instance, across all primary studies included in the nine SRs on PBs, there were no eligible randomized controlled trials.

The lack of proper controls is another common methodological limitation in the studies. This overview found that across all primary studies in the nine SRs on PBs, only six were observational studies with parallel control groups that compared PBs with no PBs among children or adolescents with GD.[42] However, the overall certainty of evidence was influenced not only by methodological shortcomings, but also by factors such as small sample size and small or no effects, which signify imprecision in GRADE terminology. For instance, the sample sizes of the six comparative observational studies addressing PBs were small, with three studies which each included fewer than 100 participants. One SR downgraded the quality of evidence on the effect of PBs on global function for imprecision, noting that the evidence "suggests both a possibility of a benefit or a harm in the outcome."[43]

Inconsistent study findings are another frequently cited concern that lowers the quality of evidence. For instance, one SR of CSH found "limited or inconsistent evidence regarding GD, body satisfaction, psychosocial and neurocognitive outcomes, fertility, height/growth, bone health and cardiometabolic effects."[44] Similar limitations were

[41] Physiological mechanism for PBs' effect on bone mineralization is discussed in Chapter 7.
[42] Becker-Hebly et al. (2021); Costa et al. (2015); Grimstad et al. (2021); Jensen et al. (2019); McGregor et al. (2024); Tordoff et al. (2022).
[43] Miroshnychenko, Roldan et al. (2025).
[44] Taylor, Mitchell, Hall, Langton et al. (2024).

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observed across studies evaluating other medical and surgical interventions for youth with GD.

Thus, it is important to clarify that the absence of high- or even moderate-quality evidence is not only due to a lack of randomized controlled trials (RCTs). The quality of evidence could have been improved through well-conducted observational studies,[45] which can provide moderate and even high-quality evidence when effects are large, consistent, and clearly attributable to the intervention.

5.7.3 Robustness of this overview's conclusion

Although this overview focused on English-language SRs assessed at low risk of bias, another low risk of bias SR, published in German, reached similar conclusions, reinforcing the overall patterns identified here.[46] As stated earlier, this overview did not include the NHS-commissioned SRs on PBs and CSH in 2020, as they were superseded by the SRs published in 2024 to inform the Cass Review. However, these two earlier SRs also concluded that the evidence was of very low quality,[47] and their inclusion would not have altered the conclusions of this overview.

Furthermore, it is also important to note that while this overview focused on SRs assessed at low risk of bias, this designation does not imply that these SRs were without methodological limitations. The "low risk of bias in the systematic review" in ROBIS allows for some flexibility. The included SRs still had shortcomings, such as limited search strategies, outdated literature searches,[48] or lack of precision in evidence assessments. In contrast, SRs assessed at high risk of bias consistently exhibited serious methodological flaws, including poorly defined eligibility criteria, absence of risk of bias assessments for included studies, and unsystematic synthesis approaches. These SRs were judged to be too biased to inform reliable conclusions. The findings

[45] See the checklist for ways to improve observational research in this field in Ludvigsson et al. (2023).
[46] Zepf, König et al. (2024).
[47] National Institute for Health and Care Excellence (2020b, 2020a).
[48] According to the Cochrane Handbook, reviews should be as up-to-date as possible. However, as recency is not the sole consideration, SRs with outdated search strategies can still be considered at low risk of bias overall (Higgins et al., 2019).

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presented in this overview, therefore, reflect a deliberately cautious approach, drawing only from the most trustworthy sources currently available.

Finally, rather than extending beyond what the evidence can support, this overview is confined to summarizing the conclusions of SRs. As a result, it may not include some of the most recently published studies (due to the timing of the SRs' literature searches). However, a targeted search[49] of recently published studies did not reveal any published or ongoing studies that would significantly change the conclusions, especially those pertaining to benefits. This is due to ongoing problems such as an absence of comparison groups, inadequate sample sizes, and limited follow-up. Should the contemplated U.K. RCT trial of PBs[50] receive ethics approval, it might improve the evidence base for short-term (24 month) effects of PBs on certain outcome measures. However, based on the elements of the study design publicly disclosed to date, it might not provide information about the effect of treatment when PBs are followed by CSH—a clinical trajectory which appears to occur more than 90% of the time.[51] Such combination use would have a different risk/benefit profile than the use of PBs alone, both in terms of possible benefits and possible harms. Finally, the anticipated short-term follow-up will not adequately address the key question of long-term outcomes.

Without a meaningful shift toward more robust research designs—such as RCTs that test each intervention as it is currently provided (i.e., sequential treatment of PBs followed by CSH), prospective cohorts with suitable comparators, or natural experiments—the quality of evidence likely will remain low.[52] Conducting new SRs to answer the same research questions in the near future is unlikely to yield novel insights. This dearth of robust research and evidence has direct implications for clinical guidance

[49] A targeted search in this field identified recent publications based on observational studies from the U.S. (Hidalgo et al., 2024; Olson-Kennedy et al., 2025; Wittlin et al., 2025), Canada (Lawson et al., 2024), the Netherlands (van der Meulen et al. 2025), and the U.K. (Morandini et al., 2023). These studies have similar limitations (including study design, small sample size, short-term follow up, etc.) to the primary studies included in the SRs.
[50] National Institute for Health and Care Research (2024).
[51] Brik et al. (2020); Carmichael et al. (2021); van der Loos, Klink, et al. (2023); Wiepjes et al. (2018).
[52] There is debate about whether high-quality research on effects of PBs/CSH in minors should be pursued. Ethical deliberations factor into this debate. Some have argued that research should focus on patients who already received PBs, CSH or surgery (Ryan, 2024b). The Cass Review called for more robust research into psychotherapeutic approaches to GD, which is a promising treatment approach so-far neglected by research (Cass, 2024a).

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and policy development, where expectations of benefit must be weighed against the persistent uncertainty of the evidence documented in the literature.

5.7.4 Limitations and strengths of this overview

All SRs and overviews of SRs have limitations. SRs aim to capture all relevant research that meets predefined eligibility criteria. However, this objective may be undermined by reporting (or non-reporting) bias — a form of bias that arises when the decision to publish, delay, or selectively report study results is influenced by the statistical significance, size, or direction of the findings.[53]

As discussed in Chapter 6 of this Review, research in the field of PGM suffers from significant publication and reporting bias. The extent of the problem is difficult to quantify due to widespread poor methodology and a lack of consistency in reporting effect sizes.[54] Notably, publication bias has not been considered as a reason for downgrading the certainty of evidence in the included SRs.

Another limitation is that SRs serve to answer well-defined research questions which have prespecified outcomes, but cannot detect signals or generate hypotheses. Many studies in PGM focus on psychological outcomes but only inconsistently track other outcomes that may be signals of the intervention's adverse effects. When outcomes are not reported using rigorous methodological standards—such as being clearly listed in a dedicated outcomes table—but instead are only mentioned in the discussion section, SR methodologies are unlikely to flag the study as relevant to that outcome during the screening process. As a result, important adverse effects may go unnoticed. This issue is discussed at some length in the next chapter.

A key characteristic of SRs and overviews of SRs is their emphasis on population-level epidemiological data,[55] often with limited integration of mechanistic evidence or considerations of biological plausibility. This narrow scope limits the ability of this

[53] Guyatt, Oxman, Montori, Vist et al. (2011).
[54] Publication bias is notoriously hard to measure, and the existing statistical tools have significant limitations (Afonso et al., 2024).
[55] Guyatt et al. (1992, 2015).

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overview to elucidate potential causal pathways or to fully interpret observed associations—or their absence.

This overview of SRs has other limitations. Like all overviews, it is constrained to synthesizing published SRs and does not reanalyze primary studies. The scope of this overview was intentionally narrow, focusing on young patients and excluding indirect evidence from adult populations that may provide insight into long-term effects.

Strengths included systematic evaluation of the risk of bias across SRs using the ROBIS tool. Thus, this overview offers a transparent assessment of the reliability of each SR's conclusions. It also allows for comparison across SRs with overlapping but differently scoped studies, helping to identify consistent findings, methodological gaps, and areas of agreement or divergence.

5.7.5 Conclusion

This overview synthesizes the best available clinical evidence from population-level data, highlighting a consistent pattern across interventions for children and adolescents with GD. The benefits and harms of social transition remain unknown; PBs, CSH, and surgeries consistently produce certain physical and physiological effects; and there is considerable uncertainty regarding their psychological and long-term health outcomes.

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Chapter 6 Limitations of Systematic Reviews

As reported in the overview of systematic reviews (SRs), the quality of evidence for benefits of the interventions used in pediatric medical transition (PMT) is very low. Nevertheless, the practice has continued to expand rapidly. The “very low” quality of evidence for benefits demands additional scrutiny of the potential harms in order to arrive at a proper understanding of the risk/benefit ratio.

It is well-established that SRs are better at detecting benefits than harms.[1] Consequently, the absence of evidence of harms in published studies is not equivalent to evidence of absence of harms. In pediatric gender medicine (PGM), inadequate harm detection is amplified by the following factors:

- Insufficient time has elapsed since the widespread adoption of PMT;
- Short-term before-and-after observational studies that comprise the bulk of the evidence often have high ‘loss to follow up’ rates and do not systematically look for, track, or completely report harms;
- Publication bias impedes the recognition of harms.

The first three sections of this chapter (6.1-6.3) consider how these factors affect the ability of SRs to detect harms, with a summary in Section 6.4.

A comprehensive examination of harms associated with PMT is necessary to inform clinical practice. Harms associated with surgeries that remove healthy body parts are easy to recognize, as are some of the adverse effects of hormonal interventions. The latter are noted both in the Food and Drug Administration (FDA) drug labels[2] and on informed consent or assent forms parents and children sign prior to initiating treatment.[3] Use of these drugs off-label in PGM may add additional risk. It is well-established in adults that for the same drug, off-label uses are associated with considerably higher

[1] Loke et al. (2007); Mayo-Wilson et al. (2023); Qureshi et al. (2022).
[2] Testosterone is one of the most widely used drugs in the field and is classified as a Schedule III controlled substance due to the risk of psychological dependence and abuse.
[3] E.g. Cornell Health (n.d); Fenway Health (2024a, 2024b, 2025).

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rates of adverse effects, especially when strong scientific evidence is lacking.[4] Clinical trials have never been conducted for using puberty blockers (PBs) to stop normally-timed puberty; such use will have a different risk profile than the use of PBs to temporarily stop abnormally early (precocious) puberty.

Additional uncertainty arises from the fact that, in studies, PBs are followed by cross-sex hormones (CSH) over 90% of the time;[5] this de facto combination therapy introduces new and potentially serious risks (e.g., concerning fertility) and has never been subjected to any FDA-regulated clinical trial for any population. Further, research shows that when the evidence supporting a particular off-label use is of very low certainty—as is the case for PMT—the already elevated risk of adverse effects associated with off-label use is increased even further.[6]

6.1 Insufficient elapsed time

Although the Dutch Protocol was first published 20 years ago,[7] it was not until the late 2010s to early 2020s that there were sufficient numbers of patients to allow for studies that can estimate rates of harms and benefits.[8] In addition, because the emergence of harms may be delayed by a decade or longer, SRs conducted relatively early in the field's tenure are more likely to understate these outcomes.[9] The average patient is still quite young—typically in their teens or early twenties—at the time of follow-up. This compounds problems with risk detection, since the effect of hormones on health may be cumulative (e.g., effects of hormones on cardiometabolic disease or malignancies) and may not fully manifest until later in life.

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[4] Eguale et al. (2016).
[5] E.g., Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[6] Eguale et al. (2016).
[7] de Vries et al. (2006); Delemarre-van de Waal & Cohen-Kettenis (2006). See Chapter 3.
[8] Respaut & Terhune (2022).
[9] A study in gender medicine with longer-term follow up found "poorer outcome[s] … [which] might also be explained by longer follow-up period (median 10 years) compared to previous studies. In support of this notion, the survival curve (Figure 1) suggests increased mortality from ten years after sex reassignment and onwards" (Dhejne et al., 2011).

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6.2 Short-term observational studies

The Cass Review recognized continued reliance on poorly-designed observational studies as a "key limitation to identifying … safety of gender-affirming hormones for children and adolescents."[10] A key problem that disadvantages SRs in their detection of harms is the fact that the entire body of evidence in PGM is largely composed of short-term "before and after" observational studies that are particularly prone to bias. Such studies focus on demonstrating benefits while inconsistently reporting harms.[11] Unlike the intended benefits of an intervention, which are hypothesized before the study begins and investigated as primary outcomes,[12] harms are not always expected, surveilled, or reported. Therefore, SRs are limited by being able to identify only those outcomes reported by primary studies.[13]

An example of the difficulty in identifying harms pertains to whether PBs represent a harmless "pause button" providing "time to think"[14] or a powerful intervention that promotes iatrogenic persistence of GD and promotes continuation to CSH. At least five studies indicate >90% rate of progression from PBs to CSH.[15] As the Cass Review noted, "These data suggest that puberty blockers are not buying time to think, given that the vast majority of those who start puberty suppression continue to masculinizing/feminising hormones, particularly if they start earlier in puberty."[16] Because the high rate of persistence from PBs to CSH is often mentioned only in the text of a study (and not delineated in outcome tables or abstracts), SRs may overlook this information at the screening stage. Only one low risk of bias SR assessed the proportion of CSH use after PBs, identifying only two studies.[17]

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[10] Cass (2024a, p. 76).
[11] Loke et al. (2007); Mayo-Wilson et al. (2023); Qureshi et al. (2022).
[12] In the case of prospective studies.
[13] Researchers may want their intervention to lead to beneficial outcomes, and may be reluctant to look for or focus on harms.
[14] See Chapter 4 for discussion of the "time to think" rationale.
[15] Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[16] Cass (2024a, p. 176).
[17] Miroshnychenko, Roldan et al. (2025) was the SR that identified Carmichael et al. (2021) and Karakılıç Özturan et al. (2023a).

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There are other examples of inappropriate reporting of adverse effects.[18] Three notable ones are profiled below.

6.2.1 de Vries et al., 2011, 2014[19]

The pair of seminal Dutch studies that launched PMT worldwide can serve as an example of how harms can go unreported. The 2014 study's conclusion that treatment with PBs, CSH and surgery "leads to improved psychological functioning"[20] did not comment on the finding that at least four of the original 70 young patients experienced adverse effects during treatment. Three adolescents were diagnosed with obesity and diabetes, which disqualified them from continuing to surgery, and one patient died from complications following surgery after early pubertal suppression.[21] These serious adverse events were not reported as formal outcomes,[22] precluding any discussion of whether they were caused by the experimental intervention or occurred incidentally. More recently published evidence suggests that the postsurgical death was likely directly related to the practice of early pubertal suppression.[23] Further, because these adverse effects were noted only in the context of accounting for the reduced postsurgical sample size, the study may not have attempted to detect and report less severe adverse effects that were not disqualifying for further participation.

Inadequate reporting of harms in the Dutch study was compounded when SRs excluded this study due to its unreliable design (e.g. the study comingled the CSH and surgery phases, making it impossible to determine which outcomes were associated with which

[18] This is not atypical in medicine. Researchers who invent innovative treatments are likely to focus on the apparent benefits.
[19] de Vries et al. (2011); de Vries et al. (2014).
[20] de Vries et al. (2014, p. 703).
[21] See Chapter 4 for discussion of the weaknesses in the original Dutch Protocol research.
[22] These outcomes were only discussed in the "methods" section (de Vries et al., 2014).
[23] de Vries et al. (2014) had 15 missing cases from the original cohort of 70 participants. Of these 15 participants, three were disqualified from the study because they developed obesity and/or diabetes. One dropped out of treatment, and one died from a surgical complication that was a likely consequence of pubertal suppression (Biggs, 2023b; Negenborn et al., 2017). Several others failed to return postsurgical questionnaires for unknown reasons.

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intervention).[24] Thus, the serious harms reported incidentally by the study authors were entirely omitted from the SRs due to the study's poor design.

6.2.2 Tordoff et al., 2022[25]

Inadequate reporting of harm is also evident in more recent research. A highly influential 2022 study from Seattle Children's Gender Clinic by Tordoff et al. focused exclusively on psychological outcomes, where benefits had been hypothesized. It did not study or report physical health outcomes, where harms would have been more likely to occur.

The study by Tordoff et al. reported mental health outcome data for adolescents and young adults aged 13-20 years who were treated with PBs or CSH for up to one year. The study claimed to provide "quantitative evidence" of mental health improvements; however, the rates of depression in youth who started PBs or CSH remained unchanged—about 6 in 10 youth were moderately-to-severely depressed both pre- and post-intervention.[26] These data were reported in a supplement which was available only online. The study finding of improved mental health was derived from the odds ratios: 60% lower odds of depression and 73% lower odds of suicidality in patients treated with PBs or CSH as compared to those who were not. However, major methodological issues, including potential selection bias and confounding,[27] inappropriate statistical

[24] de Vries et al. (2014) was excluded from the systematic review of CSH by the SR conducted by the U.K.'s National Institute for Health and Care Excellence (NICE). The stated reason for exclusion was: "Exclude on intervention – all participants had surgery after gender-affirming hormones. Unable to determine whether changes were due to hormones or surgery. Complete data only available for 40 patients. Details of gender-affirming hormones are poorly reported" (National Institute for Health and Care Excellence, 2020a, p. 72). This study was also excluded from the SR by Miroshnychenko, Ibrahim et al. (2025) on CSH. Though it was included in the SR by Taylor, Mitchell, Hall, Langton et al. (2024) on CSH, it was classified as a low-quality study and not included in the evidence synthesis.

[25] Tordoff et al. (2022). This research was conducted in the U.S. at Seattle Children's Hospital/Washington State University.

[26] Raw Patient Health Questionnaire (PHQ-9) and Generalized Anxiety Disorder-7 (GAD-7) data was not reported, even in the online-only supplement.

[27] Of 104 youth aged 13-20, 62 initiated treatment with PBs or CSH during the 12-month study, and 7 were already on treatment at baseline. Participants who initiated treatment during the study contributed to both "treated" and "untreated" groups at different times, complicating interpretation.

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modeling,[28] missing participant data,[29] and selective reporting[30]—raise serious concerns about the reliability of the reported findings.

The impressive-sounding odds ratios were thus calculated by relying on progressively smaller denominators in the untreated "comparator" group. The supplementary online-only data revealed that only seven cases from the "comparator group" of patients not treated with PBs or CSH remained enrolled in the study by its end.[31] It was also unclear if or to what extent this "comparator" group could be considered representative of all untreated patients. It appears that the "untreated" group comprised youth whose mental health problems and GD issues resolved who dropped out from the gender clinic and the study (representing 80% of the total "untreated group"); the patients who were about to cross-over to the treated group after a short assessment; and the 8 patients (7 of whom provided follow-up data) who continued to attend the gender clinic 12 months later, but for an unknown reason were not starting hormonal interventions.[32]

Two recent systematic reviews have assessed Tordoff et al. for risk of bias, using two different tools (the Newcastle Ottawa Scale and ROBINS-I).[33] While both analyses identified some methodological weaknesses (e.g., short follow-up, high attrition rate), the study's inclusion of untreated youth as a comparison group somewhat boosted its

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[28] Rather than analyzing individual mental health trajectories before and after treatment, the study performed cross-sectional comparisons at various time points, leading to potential bias.
[29] At 12 months, data are missing for 17% of medicalized youth (12 of 69) and an astounding 80% of non-medicalized youth (28 of 35). It is likely that non-medicalized participants without mental health distress, including those whose gender distress resolved, would be least likely to return to the clinic
[30] The authors performed analyses following multiple strategies, reporting in the abstract only the version of the analysis that produced the most dramatic results (strongest aOR [adjusted odds ratio] and smallest p-values), raising concerns about data-dredging.
[31] Based on eTable 3 in the supplementary material, the estimated prevalence of depression in the control group was 59% at baseline, 76% at month 3, 58% at month 6, and 86% at month 12. The substantial fluctuation across time points indicates that the estimates for the control group were unstable and likely influenced by random error.
[32] There was incomplete data for 80% of patients in the untreated group. It is possible that patients whose GD resolved stopped attending appointments. Additionally, the 7 untreated patients with follow-up data at one year may not have been approved for medical transition because they did not have sufficient capacity for consent—the only scenario under which this pediatric gender clinic would not recommend medical transition if desired by the patient, according to the study's lead author ("In practice, the only instances when it would have been appropriate to delay initiation of PB/GAH is if there was a concern that a patient did not have the capacity to provide informed consent … which is exceedingly rare in adolescence" (Tordoff, 2022). Barriers to provision of informed consent can include active psychosis or mania and profound intellectual disability.
[33] Miroshnychenko, Ibrahim et al. (2025); Taylor, Mitchell, Hall, Langton et al. (2024b). ROBIS: Risk of bias in non-randomized studies - of interventions.

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quality ratings. Systematic reviews are not always able to capture serious problems with comparison groups of this type.

This study's misrepresentation of its own results, serious confounding, and the exceptionally loss-follow-up for untreated youth have been highlighted by science journalists and discussed in peer-reviewed articles.[34] Despite these well-demonstrated problems, this study, published in the *Journal of the American Medical Association* (JAMA) Open Network, continues to be uncritically described, by authoritative sources, as evidence that PBs and CSH are beneficial to mental health, medically necessary, and lifesaving.[35]

6.2.3 Chen et al., 2023[36]

Similarly, while a National Institutes of Health (NIH)-funded initiative, "The Impact of Early Medical Treatment in Transgender Youth,"[37] registered a study protocol in 2016 that included plans to evaluate the safety of PBs and CSH, researchers committed to a short follow-up of only 24 months.[38] Upon reviewing the protocol of this study, its design appears inadequate to comprehensively assess the safety of PMT. The lack of a parallel control group impairs the ability to attribute observed safety outcomes specifically to the intervention, as it becomes difficult to differentiate treatment effects from normal developmental changes. Moreover, the exclusive reliance on biochemical markers fails to capture other critical safety outcomes such as growth and fertility. Additionally, the small sample size undermines the study's capacity to evaluate rare but clinically significant harms, such as thromboembolic events. The absence of long-term follow-up

[34] E.g., Abbruzzese et al. (2023); Biggs (2023b); Singal (2022a). The university that conducted the research was made aware of the study's problems, but chose not to disrupt the very positive medical narrative that misrepresented the authors' findings Singal (2022b).
[35] E.g., American Psychiatric Association (2023); Boerner (2022); Stringer (2023); U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024). To date, this study has been cited over 300 times in other peer-reviewed publications, and viewed nearly half a million times.
[36] Chen et al. (2023). This was an NIH-funded multi-site study performed in the U.S. at Children's Hospital of Chicago, Boston Children's Hospital, and the Los Angeles Children's Hospital.
[37] The research protocol can be found in the supplementary material in Chen et al. (2023).
[38] The study recruited patients from four pediatric gender clinics: Benioff Children's Hospital, Boston Children's Hospital, Children's Hospital Los Angeles, and Lurie's Children's Hospital of Chicago. Two young patients died by suicide while taking CSH, and "suicidal ideation" was registered as the most common adverse event (Chen et al., 2023). The protocol can be found in supplementary material.

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further limits the detection of delayed or cumulative adverse effects. These methodological limitations weaken the strength of any conclusions that can be drawn regarding the overall safety of the intervention.

The study reported mental health outcome data for 315 adolescents and young adults aged 12-20 who were treated with CSH for a period of 24 months. This study, published in the *New England Journal of Medicine* (NEJM), framed its findings in a positive light: "our findings showed improvements in psychosocial functioning ... which supports the use of [CSH] as effective treatment for transgender and nonbinary youth."[39]

However, two of the study subjects died by suicide within one year of initiating hormones, representing a rate that is 30-50 times higher than expected in adolescents of similar age.[40] The only statistically significant finding was a small improvement on the "transgender congruence scale," which has not been validated in minors.[41] Critically, only four out of 19 mental health outcomes described in the study's pre-registered protocol were reported; in particular, outcomes of GD, self-harm, and suicidality outcomes were not reported, and no explanation was provided for omitting these critical data.[42] The authors claimed that depression symptoms decreased during the study period.[43] However, further subgroup analysis by sex showed that the reported outcomes in females were of questionable clinical significance, while males experienced no statistically significant improvement in the reported measures at all.

According to the study's pre-registered protocol, the authors originally hypothesized that patients would exhibit "decreased symptoms of … gender dysphoria, self-injury, trauma symptoms, and suicidality" (among other changes) over time.[44] Instead, as mentioned,

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[39] Chen et al. (2023, p. 249).
[40] For comparison of the suicide rate in Chen et al. to that of other populations (e.g., other cohorts referred to pediatric gender clinics; patients taking antidepressants) see McDeavitt (2025).
[41] Strauss et al. (2024).
[42] In Chen et al. (2023), life satisfaction/positive affect were measured with the NIH Toolbox Emotion Battery. A recent paper describing this same patient cohort published more information on these life satisfaction/positive affect results along with information on additional measures from the NIH Toolbox Emotion Battery (Olson-Kennedy et al., 2025), but it did not report the gender dysphoria, self-harm, or suicidality outcomes, nor did it reference the two patient suicides.
[43] The mean Beck Depression Inventory score improved from 15.46 to 12.92 on a 63-point scale (Chen et al. 2023).
[44] See pp. 25-26 of the study's pre-registered protocol, which is linked to the article Chen et al. (2023) on the New England Journal of Medicine's website.

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two young patients died by suicide within one year of initiating treatment, and the most frequently occurring adverse event during hormonal treatment was "suicidal ideation."[45] Thus, the findings do not support the original hypothesis.

Although a recent systematic review was able to capture issues like study attrition in its risk of bias assessment for Chen et al., methodological analyses are not able to capture serious concerns that may be more related to research ethics than to methodology (e.g., study hypotheses changing between the protocol and the published article). Peer-reviewed critiques addressing the issues with Chen et al. were eventually published by the journal, but not until nearly a year after the article first appeared.[46]

The study continues to be widely cited and uncritically described as providing evidence of benefit for hormonal transition of minors.[47]

6.3 Publication bias

It is a well-documented problem in biomedical research that positive findings confirming an original hypothesis are much more likely to be published or published expeditiously, as compared to studies with inconclusive or negative results. "Publication bias" is not unique to this field. The U.K.'s national PGM clinic, the Gender Identity Development Service (GIDS), tried to replicate the seminal 2011 Dutch study, launching its own "early intervention" study of PBs in 2011. Although the results were available in 2016-2017, they were only released in 2021 following a complaint to the U.K. Health Research Authority.[48] Once published, the study acknowledged that the outcomes reported by the Dutch were not replicated.[49] The study also found that puberty blockade was associated with impaired bone density accumulation. Subsequent reanalysis of the same data showed that up to one-third of participants experienced a deterioration in mental health while on PBs.[50]

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[45] Chen et al. (2023, p. 241).
[46] E.g., Biggs (2023a); Hare (2023); Jorgensen (2023c); Dutch PMT researchers also published a commentary on Chen et al., which acknowledged the study's many problems (de Vries & Hannema, 2023).
[47] E.g., U.S. v. Skrmetti (No. 23-477*),* Expert Researchers and Physicians*,* Amicus curiae brief (2024).
[48] Biggs (2023b).
[49] Carmichael et al. (2021).
[50] McPherson & Freedman (2023).

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A similar pattern may be unfolding in the United States. The lead investigator of a NIH-funded PB study acknowledged delaying the publication of results—apparently due to fear that the unimpressive findings would undermine the field.[51]

A similar reluctance to report on disappointing findings is evident in other places, too. According to court disclosures, the World Professional Association for Transgender Health (WPATH) suppressed publication of SRs on at least ten of thirteen topics relating to endocrine treatment of adolescents with GD.[52] The unpublished SRs evaluated harms, including the effects of PBs on "clinical outcomes and harms"; the effects of estrogen on the risk of pulmonary embolism, deep-vein thrombosis, stroke, and myocardial infarction; the effects of testosterone on uterine, ovarian, cervical, vaginal, and breast pathology; and the effects of hormone therapy on fertility and metabolic syndrome.[53]

There also are instances of SRs arriving at conclusions that contradict the underlying evidence. One SR commissioned by WPATH found only "low" and "insufficient"[54] strength of evidence regarding the effects of hormonal interventions on mental health. Nevertheless, the SR's authors came to the unsupported conclusion that this treatment pathway "is likely associated with improvements" in quality of life, depression, and anxiety. The authors also asserted that "[t]hese benefits make hormone therapy an essential component of care that promotes ... health and well-being." Notably, there was no attempt to evaluate hormone effects on physical health.[55] The content of this SR was influenced by WPATH leadership, including approving the conclusion as a condition for eventual publication. This may explain the discrepancy between the SR's optimistic conclusion and its more problematic findings. Section 10.3.2 discusses evidence suppression by WPATH in detail.

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[51] As reported in the New York Times (Ghorayshi, 2024c). Of note, the investigator, Johanna Olson-Kennedy, denied having said this in a later deposition (Deposition of J. Olson-Kennedy in LB v Premera Blue Cross NO. 2:23:Cv-00953-TSZ, 2024).
[52] See Chapter 10.
[53] Sharma et al. (2018). See also Society for Evidence-Based Gender Medicine (2024b).
[54] Baker et al. (2021, p. 13).
[55] Appendix 4 includes a ROBIS assessment of Baker et al. (2021).

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Another 2021 SR, conducted by Bustos et al., examined postsurgical regret rates.[56] This SR is often cited as evidence that the regret rate after transition-related surgery is very low, about 1%.[57] But of the 27 studies included in Bustos et al., 23 were rated as "poor" or "fair" in quality. The few higher-rated studies suffered from substantial loss to follow-up and the reported results included deaths from suicide and complications. One included study contributed nearly half the total participants but reported a 36% loss to follow-up. The study authors acknowledged that the short follow-up period was a key limitation. However, the authors failed to address the most serious criticism, namely that their central conclusion of "extremely low regret" was unsupported.[58]

6.4 Summary

The quality of SRs in the field of gender medicine varies widely, but even the highest quality SRs typically find only "low certainty" evidence for most harms. However, there are familiar and plausible explanations for why evidence of harms may not have been sought, detected or reported. Reflecting on the state of evidence in PGM, the Cass Review noted, "it has been evident that there has been a failure to reliably collect even the most basic data and information in a consistent and comprehensive manner; data have often not been shared or have been unavailable."[59]

Unless SRs specifically search for harms (and with the provisos above), they are not well-suited to detect complications or adverse effects. This is due to the relatively recent debut and rapid growth of the field of PGM, the tendency of the predominantly short-term observational studies to focus on benefits and underreport harms, and publication bias. EBM emphasizes the role of best available evidence. To address SRs' limited ability to detect harms, decision-makers must consider other sources of scientific information. That is the topic of the following chapter.

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[56] Bustos et al. (2021) reported regret rates of around 1%. This SR was not included in this Review's overview of SRs as most of the included studies did not focus on the adolescent population.
[57] See examples of such statements in Cohn (2023).
[58] For the criticism, see Expósito-Campos & D'Angelo (2021). The authors provided a reply to the critique (Escandón et al., 2021), which addressed some but not all of the key concerns.
[59] Cass (2024a, p. 39).

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Chapter 7 Evidence from Basic Science and Physiology

When clinical studies provide insufficient information about harms, and therefore systematic reviews (SRs) are unable to reliably collate information about harms, other types of evidence should be integrated. Trustworthy evidence from other sources, including basic sciences, should be considered to arrive at a more informed understanding of the plausible effects of interventions.[1] In the case of pediatric medical transition (PMT), this involves consideration of human physiology, development, and the well-established mechanisms of action of the drugs used. The consideration of such evidence aligns with the core requirement of evidence-based medicine (EBM): the judicious use of the "best available" evidence.

The following sections explain: normal pubertal development and the mechanisms of action of PMT interventions (Section 7.1); treatment of central precocious puberty with puberty blockers (PBs) (Section 7.2); biologically plausible implications of using PBs to arrest normally timed puberty and cross-sex hormones (CSH) (Sections 7.3 and 7.4); surgical implications, particularly when pubertal development has been arrested (Section 7.5); and psychological risks of undergoing PMT interventions given what is known about child and adolescent development (Section 7.6). Mortality is discussed in Section 7.7.

7.1 Puberty

This section overviews physiology and the implications of disrupting normally-timed puberty. Of note, there are three distinct waves of hypothalamic-pituitary-gonadal (HPG) axis activity over an individual's lifespan: in utero, during the first month after birth, and in late childhood-early adolescence.[2] Only the latter is referred to as "puberty."[3] Medications can be given to suppress the HPG axis.

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[1] Sackett et al. (1996).
[2] Rohayem et al. (2024).
[3] The discussion in this section focuses on normal pubertal development. Individuals with disorders (differences) of sex development (DSDs) are not a focus of this chapter because the vast majority of adolescents with gender dysphoria do not have a DSD. Among those with DSDs, approximately 5% experience identity changes (Kreukels et al., 2018). As noted in the Cass Review, "Studies of children with DSD suggest that a complex interplay between testosterone levels, external genitalia, sex of rearing and socio-cultural environment all play a part in eventual gender identity" (Cass, 2024a, p. 102).

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7.1.1 Overview of normal pubertal development

In mammals, puberty is defined as the period of time during which immature juveniles reach adult sexual maturity and become capable of reproduction. It is a transitional phase between childhood and adulthood. In humans, pubertal onset typically occurs between ages eight and 13 in females and nine and 14 in males. It is driven by increasing levels of sex steroid hormones—primarily estrogen and progesterone in females, and testosterone in males.[4]

During puberty, sex steroid hormones promote skeletal growth, muscular development, and neurologic development. In females, estrogen initiates breast development, menarche, ovulation, and changes in body composition and skeletal morphology.[5] In males, the androgenic surge results in testicular enlargement, penile growth, spermatogenesis, deepening of the voice, and the emergence of secondary sexual characteristics such as facial and body hair. Spermatogenesis in males and ovulatory cycles in females mark the attainment of fertility.

7.1.2 Tanner Stages of puberty

Physicians use a system known as Tanner Staging to document the physical progression of puberty based on a physical examination.[6] This framework delineates five stages of maturation, from a prepubertal baseline (Stage 1) to full adult development (Stage 5). Intermediate stages capture transitional morphological and physiological characteristics.

In females, Tanner Stage 2 commences with the growth of breast tissue (thelarche), followed by hair growth (pubarche), and then the first period (menarche), typically by Tanner Stage 3 or 4. Menarche typically occurs one to two years after thelarche, at an average age of 12-13 years. The first egg release (ovulation) generally occurs within the first year following menarche, typically at Tanner Stage 4. Ovulatory function stabilizes approximately one year after menarche. Female pubertal development is accompanied by bone growth, body hair growth, widening of the hips, redistribution of fat to the hips

[4] Breehl & Caban (2025).
[5] Kuohung & Hornstein (2024).
[6] Tanner (1962).

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and breasts, and enlargement of both internal reproductive organs (i.e., uterus, ovaries) and external genitalia (i.e., labia, clitoris).[7]

In males, the initiation of Tanner Stage 2 is typically identified by increased testicular volume, followed by growth of the penis, emergence of pubic and later facial hair, and a rapid increase in lean body mass and skeletal size driven by androgens. There are significant increases in bone and muscle mass and thickening and elongation of the vocal cords results in voice deepening. First ejaculations (spermarche) generally occur about one year after the onset of puberty, with full gamete maturation following approximately one year later.[8] Spermatogenesis generally occurs during Tanner Stage 4.[9]

7.1.3 Neuroendocrine regulation of puberty

Puberty is initiated and sustained by complex endocrine signaling. In the brain, the anterior pituitary, in response to pulsatile gonadotropin-releasing hormone (GnRH) release from the hypothalamus, secretes luteinizing hormone (LH) and follicle-stimulating hormone (FSH). Collectively termed gonadotropins, LH and FSH act on the gonads (ovaries and testes) to stimulate the synthesis of sex steroids and promote gametogenesis.[10]

7.2 Puberty blockers and central precocious puberty

In central precocious puberty (CPP) — a condition occurring in one out of 5,000 to one out of 10,000 children, more often in girls[11]—the pituitary gland is activated prematurely, sometimes even during infancy or early childhood.[12] This leads to early-onset, or precocious, pubertal development. CPP is associated with several potential negative

[7] Breehl & Caban (2025).
[8] Breehl & Caban (2025); Kota & Ejaz (2023).
[9] Emmanuel & Bokor (2022).
[10] In males, LH stimulates Leydig cells to produce testosterone while FSH targets Sertoli cells to facilitate spermatogenesis. In females, LH and FSH coordinate estrogen production and follicular development in the ovaries.
[11] Eugster (2019). Although there are some genetic causes of CPP, it is usually idiopathic, meaning the cause is unclear. Females are generally treated for CPP with PBs if puberty occurs at age six or younger, males are generally treated if puberty occurs at age eight or younger (Ergun-Longmire et al., 2023).
[12] E.g., Nienaber & Van Der Walt (1991); Yoon & Kim (2016).

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health outcomes, including decreased adult height due to early presence of sex hormones causing premature epiphyseal fusion.

GnRHa (puberty blockers or PBs) have been approved by the Food and Drug Administration (FDA) for use in the treatment of CPP. The evidence to date comparing large populations of untreated patients to treated patients suggests that, at least for appropriately chosen female patients, treatment of CPP with PBs is associated with increased height attainment and lower body mass index (BMI).[13]

When PBs are used for CPP, the medication is discontinued when the child reaches a more typical age for pubertal onset, allowing normal puberty to resume. The goals include facilitating normal timing of puberty, so that the patient goes through puberty alongside peers (as opposed to significantly before). Although FDA-approved for this indication, PBs—like all medications—are associated with risks and side effects, even when used for CPP.

7.3 Puberty blockers and gender dysphoria

The use of PBs to arrest normally timed puberty is the central element and original contribution of the Dutch Protocol. PBs act directly on the pituitary gland to significantly reduce the release of LH and FSH. Continuous administration of these agents desensitizes GnRH receptors, suppressing LH and FSH secretion, and consequently arresting the production of endogenous sex steroid hormones. In females, this causes the cessation of normal menstrual function, if it has begun. In males, sperm production is halted or forestalled. PBs have not been approved by the FDA for the indication of gender dysphoria (GD); they are used “off-label” in pediatric gender medicine (PGM).[14] Unlike in CPP, use of PBs for PMT is not FDA-approved and safety data are lacking.

Using PBs to stop normally timed puberty effectively induces hypogonadotropic hypogonadism (HH), a condition characterized by the failure of the pituitary to

[13] Luo et al. (2021).
[14] GnRHas have been approved by the U.S. Food and Drug Administration (FDA) for various indications, with effects that can differ significantly depending on their application. For instance, the GnRHa leuprolide (commonly marketed as Lupron) is FDA-approved for androgen deprivation therapy in adult males with prostate cancer and for estrogen deprivation in adult females with endometriosis. It has also been FDA-approved to treat central precocious puberty (CPP).

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appropriately release gonadotropins. As a result, the gonads are unable to produce the sex-specific hormones testosterone or estrogen. Pubertal development is disrupted, halting the progression of physical and reproductive maturity. Left untreated, clinical research shows HH is associated with a range of risks including infertility and decreased bone mineral density, elevating the risk of osteoporosis and fractures.[15]

Although PBs for GD are typically indicated for short-term use (about two years), this time range may be considerably longer for some patients.[16] The reasons for the apparent deviation from the original Dutch Protocol in regard to the length of PB use remain unstudied, but may include increasingly younger social transition ages which 'necessitate' pubertal blockade at increasingly younger ages to allow young patients to continue living in "stealth,"[17] as well as the medical treatment of youth who identify as nonbinary and wish to maintain a sex-ambiguous appearance for an extended period of time.[18]

7.3.1 Developmental risks of blocking normal puberty

One of the key rationales for using PBs in CPP is to allow the child to experience normative psychosocial development alongside same-age peers. By contrast, in PMT, patients are maintained in a prepubertal or early pubertal stage while their peers developmentally progress. This has potential sequelae for the adolescent's psychosocial development.[19]

7.3.2 Bone mineral density and skeletal development

Puberty is recognized as providing a critical window for the accrual of peak bone mass. Sex steroid hormones play an essential role in the mineralization of the skeleton.[20] Failure to reach peak bone density may lead to increased risk of osteopenia,

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[15] Zhu & Chan (2015).
[16] A Cambridge Health Alliance fact sheet, for example, discusses using puberty blockers for up to four years (Cambridge Health Alliance, n.d.).
[17] The Cass Review's qualitative research program found that for prepubertal children who underwent full social transition "living in stealth appears to increase a child's level of stress and anxiety with resultant behaviour and mental health problems. These included social withdrawal, with children becoming increasingly isolated, including resorting to home-schooling or tutoring and even rarely leaving their house" (Cass, 2024a, p.159).
[18] Notini et al. (2020).
[19] This is noted in Vrouenraets et al. (2022), for example.
[20] Elhakeem et al. (2019).

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osteoporosis, and fractures later in life, including debilitating fractures of the spine and hip. In older adults, hip fractures are particularly concerning, as they significantly elevate the risks of morbidity and mortality.[21]

Because of the known physiological role of sex steroid hormones in skeletal development, the original Dutch research acknowledged the possibility of negative effect on bone mineralization. Researchers measured 'Z-scores,' a measure comparing individual bone density to age- and sex-matched population norms, and these scores decreased after PBs in the original Dutch cohort.[22] Since then, multiple longitudinal, observational studies on pediatric patients undergoing medical transition have consistently demonstrated decreases in Z-scores with PB use.[23] In addition to decreases in the *average* scores, a re-analysis of the United Kingdom (U.K.) data found that one third of the puberty-blocked patients had a Z-score of below -2 (indicating osteoporosis) for hip, and more than one quarter of patients had low Z-scores for spine.[24] Fracture rates have not been reported alongside Z-scores in this literature.[25]

When PBs are followed by CSH, as has occurred in studies over 90% of the time, bone mineralization will increase, but a critical developmental window for bone density accrual during adolescence may have been missed or foreshortened, as bone density accrual slows during the 20s and then begins to decline. These patients may never reach the peak bone density they otherwise would have achieved. Research on medium and long-term outcomes is limited.[26] Due to the novel nature of PMT no studies have yet followed patients into middle age or late adulthood.

7.3.3 Neurocognitive and psychosocial development

The human brain undergoes substantial reorganization during adolescence, including synaptic pruning and myelination, processes that are influenced by sex steroid

[21] Bentler et al. (2009).
[22] Delemarre-van de Waal & Cohen-Kettenis (2006).
[23] E.g., Boogers et al. (2023); Carmichael et al. (2021); Ciancia et al. (2024); Delemarre-van de Waal & Cohen-Kettenis (2006); Joseph et al. (2019); Klink et al. (2015); Navabi et al. (2021); Schagen et al. (2020); Stoffers et al. (2019); Van der Loos, Vlot et al. (2023); Vlot et al. (2017).
[24] Biggs (2021).
[25] E.g., Roy et al. (2024).
[26] Two longer-term studies (Schagen et al., 2020; van der Loos et al., 2023) found Z-scores returned to pre-treatment baseline after 3-11 years of subsequent CSH treatment in females, but not in males.

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hormones. Research suggests that sex steroid hormones impact brain regions associated with executive function, emotion regulation, and social cognition.[27] The precise neurocognitive effects of puberty suppression remain understudied,[28] and researchers in this field have recognized the limitations of the evidence in this area.[29] A recent literature review concluded that the effect of PBs on neurocognitive development is unknown, but that "there is some evidence of a detrimental impact of pubertal suppression on IQ [intelligence quotient] in children."[30] However, a 2022 Dutch study found that in patients treated with PBs the associations between pretreatment IQ and eventual education achievement were similar to population norms (the study did not longitudinally measure IQ).[31] The Cass Review has raised concern over the potential harm and unknown effects of pubertal suppression on the developing brain,[32] noting that "[t]here is increasing evidence that the changes in brain maturation described above are driven by a combination of chronological age and sex hormones released through puberty."[33]

7.3.4 Reproductive maturation

By halting the development of sex characteristics, PBs interrupt the maturation of reproductive anatomy and function. Suppression of the HPG axis can impair gametogenesis, potentially resulting in permanent infertility if CSH are started thereafter, particularly when gonadal maturation is not completed prior to the interruption of normally-timed puberty.

In adult males initiating estrogen for medical transition, testicular atrophy results, leading to impaired fertility or infertility that may be irreversible (even if estrogen were to

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[27] Cservenka et al. (2015); Gonnabathula & Yakubu (2023); Macoveanu et al. (2016); Pillerová et al. (2022).
[28] One cross-sectional study (which cannot methodologically suggest causation) found poor executive functioning in patients taking PBs >1 year, but their baseline functioning before PBs was unknown (Strang et al., 2022). Another cross-sectional study reported similar executive functioning between patients on PBs and patients not on PBs (Staphorsius et al., 2015). Arnoldussen et al. (2022), another study, is discussed in the text.
[29] Chen et al. (2020).
[30] Baxendale (2024).
[31] Arnoldussen et al. (2022).
[32] Cass (2024a, p. 115).
[33] Cass (2024b, p. 104).

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be discontinued).[34] However, adult males may choose to cryopreserve sperm prior to initiation of estrogen. This is not the case with children or early adolescents.[35] Spermatogenesis generally occurs in Tanner Stage 4 of puberty.[36] In PMT, if PBs are started in Tanner Stage 2, prior to gamete maturation, and estrogen is started thereafter (as is likely), cryopreservation of sperm cannot be completed beforehand.[37] Additionally, fertility may be affected in females initiated on PBs who proceed to take testosterone.[38] Effect of testosterone on the reproductive tract makes the likelihood of conception, pregnancy, and birth uncertain.[39] Maternal and fetal outcomes under these circumstances are also poorly studied.

It is possible that CSH use after pubertal arrest could permanently damage the immature gonadal tissues, leading to sterilization.[40] If the gonads are arrested in an immature state due to prolonged use of PBs, and this is followed by administration of CSH, there is no proven physiological mechanism by which fertility can reliably be re-established. The likelihood of permanent infertility will be substantially increased.[41,42]

With respect to fertility preservation (FP), techniques can range from relatively simple to technically challenging to not currently viable, depending on the patient's sex and Tanner Stage of development. For example, males who have undergone spermarche can produce a semen sample for long-term storage. However, males who have puberty

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[34] Cheng et al. (2019); Deutsch (2020a).
[35] Fertility preservation for natal males in early puberty remains a theoretical and experimental undertaking, with no clinically validated protocol currently available (Laidlaw et al., 2025).
[36] See above, Section 7.1.2.
[37] The original Dutch research acknowledged that infertility would result for males initiated on PBs in Tanner Stage 2 and on estrogen thereafter: "In early pubertal boys, the hypogonadotrophic state will block the development of fertility" (Delemarre van de Waal & Cohen-Kettenis, 2006, p. S134).
[38] Cheng et al. (2019). Although pregnancies can occur in adult females taking testosterone, less is known about pregnancy in females who underwent PMT in childhood/adolescence.
[39] Laidlaw et al. (2025).
[40] See the subsequent section for specific effects of CSH.
[41] It should be noted that PBs for CPP does not negatively impact fertility. In pediatric medical transition, because PBs are generally the first part of a continuum including CSH, infertility is a likely result of treatment (depending on sex and Tanner Stage of patient).
[42] There is controversy regarding minors' capacity to provide informed consent to potential loss of fertility with respect to PMT. E.g., "Can these minors make adequately autonomous decisions in the present that may impact their opportunities in the future? This is less a question of decision-making capacity…than a matter of sufficient life experience to know their future desires … How to maintain an "open future" for transgender youth is a common concern of parents and healthcare professionals" (Harris et al., 2020, p. 2459). See also Jorgensen & Masson (2024). In a study of patients in their early 30's who had begun hormonal interventions at age 15, 23% expressed regret about infertility (de Nie et al., 2024).

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blocked at Tanner Stage 2 will have immature testicles; FP necessitates testicular tissue cryopreservation, which currently remains entirely experimental.[43] For the mature female patient, oocyte preservation involves an invasive procedure (and is costly). For females in early Tanner Stages, techniques such as ovarian tissue cryopreservation, although technically possible,[44] have yet to be shown to result in viable pregnancies in patients who have undergone PMT.

Most studies on FP in adolescents with GD undergoing PMT have shown very low rates, between 0% and 4.7% of patients who underwent FP.[45] One study in which male patients were able to access fertility preservation via testicular biopsy reported that 10 out of 23 patients (43%) were able to have gametes cryopreserved prior to PB initiation (Tanner Stages were not reported).[46]

7.3.5 Risks of sexual dysfunction

Concerns have been raised about the potential consequences of PMT on sexual function, particularly with regard to the ability to experience sexual pleasure and orgasm. In 2021, Marci Bowers—a leading vaginoplasty surgeon and then-president-elect of the World Professional Association for Transgender Health (WPATH)—voiced concerns that male patients who commenced PBs at Tanner Stage 2 and subsequently received CSH were physiologically anorgasmic, prior to and following vaginoplasty surgery.

Many of these patients reported no history of genital sexual sensation before undergoing vaginoplasty. After vaginoplasty, the constructed clitoris provided no meaningful tactile or erogenous response. Bowers suggested that this issue had not been adequately addressed in discussions of informed consent for youth undergoing puberty suppression.[47]

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[43] Klipstein et al. (2020).
[44] Practice Committee of the American Society for Reproductive Medicine (2019).
[45] Chen et al. (2017); Chiniara et al. (2019); de Nie et al. (2024); Nahata et al. (2017).
[46] Pang, Peri, et al. (2020).
[47] Shrier (2021b). It has been questioned "whether even highly intelligent children who have not had sexual experiences can meaningfully comprehend the loss of future sexual function and reproductive abilities" (Levine et al., 2022a, p. 720).

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Despite these concerning clinical observations, there is a striking paucity of research on sexual function outcomes in this population.[48] The potential for anorgasmia and sensory dysfunction merits serious consideration, especially given the irreversible nature of some interventions and the centrality of sexual health to overall quality of life.

There is a lack of published research regarding sexual function outcomes in females who underwent PMT with PBs followed by CSH.

7.4 Cross-sex hormones and gender dysphoria

Testosterone for females and estrogen for males are routinely used in PGM to induce changes in the secondary sex characteristics that resemble those typical of the opposite sex. In males, estrogen is frequently used alongside a testosterone blocker or PB to enhance estrogen's effects.

7.4.1 Physical effects of cross-sex hormones

As described above, puberty involves the maturation of primary sex characteristics—the male and female genitalia—and the entire reproductive system, enabling the production of mature gametes: sperm in males and ova in females. The ES guidelines for PMT describe titration of testosterone for females and estrogen for males as the "Induction of Puberty," a term that is misleading.[49] Under the influence of high doses of testosterone, females may develop facial and body hair, cystic acne, male pattern scalp hair distribution, clitoral growth, changes in musculature, thickening of vocal cords leading to voice deepening, and alterations in fat deposition. Similarly, males receiving high doses of estrogen may experience significant breast tissue growth (gynecomastia), reduced muscle mass, change in skin texture, and may develop a more typically female pattern of fat distribution. These physical changes reflect the body's response to unusually high levels of sex steroids, not actual opposite-sex pubertal development. In fact, development of reproductive capacity—definitionally, the purpose of puberty—may be

[48] Two Dutch studies have published data from one small patient cohort: Bungener et al. (2020); van der Meulen et al. (2025). Although the researchers found that for the males, sexual function outcomes after vaginoplasty were similar regardless of which Tanner Stage of puberty PBs had been started in, experts pointed out that the small study was methodologically limited due to sample size (therefore unable to reliably compare different subgroups) and that the patients frequently reported serious sexual difficulties/dysfunction (orgasm difficulties, pain, shame about genitalia) (Clayton et al., 2025).

[49] Hembree et al. (2017, p. 3884), for example. See also Coleman et al. (2022, p. S115), and Chapter 2.

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hindered. The physiological end point of puberty—sexual maturation that makes possible reproduction—is not and cannot be obtained via PMT.

7.4.2 Dosing of cross-sex hormones

In WPATH and ES guidelines, the principal goal of CSH administration is to induce physical characteristics typical of the opposite sex. When hormone levels rise beyond the typical reference range for a person's sex, they are considered supraphysiologic. ES guidelines suggest that the sex an individual identifies as—as opposed to their biological sex—should determine the target reference range for hormonal concentrations.[50] Critics have argued that perceived identity does not alter physiological processes and that such a belief can result in inappropriate and potentially dangerous hormone dosing.[51]

7.4.3 Hyperandrogenism in females

Hyperandrogenism refers to the condition of abnormally elevated androgen levels—most commonly testosterone—in the bloodstream. Among adult females, typical serum testosterone levels range between 2–45 ng/dL. In certain pathological conditions, testosterone may rise well above this range.

ES guidelines for cross-sex hormone administration in females recommend testosterone between 320–1000 ng/dL, comparable to, or exceeding levels found in endocrine disorders.[52] These concentrations represent a six to 100-fold increase above physiologic norms for females, inducing hyperandrogenism. Hyperandrogenism is also associated with health risks, discussed below.

7.4.4 Hyperestrogenemia in males

Hyperestrogenemia is defined as elevated blood levels of estrogens, such as estradiol, above the normal physiological range. In males, the standard reference range for estradiol is approximately 60–190 pg/mL. Certain disease states are known to cause

[50] Rosenthal et al. (2019).
[51] Laidlaw et al. (2021).
[52] Hembree et al. (2017).

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excess estrogen. For instance, certain adrenal tumors can elevate estrogen levels by a factor of 3 to 10.[53]

In PMT, supraphysiologic estrogen levels are intentionally induced through the off-label use of high doses of estrogen. ES guidelines advise titration of estradiol to levels between two and 43 times higher than the typical male range to induce the development of female-typical secondary sex characteristics such as breast tissue.[54]

7.4.5 Effects of testosterone on the female reproductive system

Testosterone use causes histopathological changes in the female reproductive tract.[55] Given the potential—though not well-defined—risk of cancer in the female reproductive tract, ES guidelines recommend that "health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer."[56] WPATH's clinical practice guideline[57] has not adopted the same recommendation, but there is limited reliable evidence regarding the long-term cancer risks associated with testosterone use in the female reproductive tract. Testosterone can cause reproductive organ atrophy, including thinning and atrophy of vaginal epithelium,[58] persistent pelvic pain and discomfort,[59] and pelvic floor dysfunction.[60]

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[53] Cavlan et al. (2010).
[54] Hembree et al. (2017).
[55] A review of 11 histopathologic studies of resected ovaries found that 34.9% exhibited polycystic-appearing ovaries, and 0.7% had benign ovarian neoplasms (Toland et al., 2023). In another study of females aged 18-56, 57% of 35 ovariectomy cases showed multiple bilateral cystic follicles, and 80% of 40 uterine resections displayed endometrial stromal fibrosis. Abnormal tissue growth was also noted in the vagina and cervix following hysterectomy and vaginectomy. The most common findings included transitional cell metaplasia and the development of prostatic-type glands (Lin et al., 2022). A separate study found that 100% of vaginectomy specimens contained abnormal prostatic tissue growth (Xu et al., 2022).
[56] Hembree et al. (2017).
[57] Coleman et al. (2022).
[58] In 2020, a whistleblower from Washington University in St. Louis clinic described a case in which a female minor taking testosterone called the clinic due to vaginal bleeding: "In less than an hour she had soaked through an extra heavy pad, her jeans, and a towel she had wrapped around her waist … We found out later this girl had had intercourse, and because testosterone thins the vaginal tissues, her vaginal canal had ripped open. She had to be sedated and given surgery to repair the damage" (Reed, 2023a). Reportedly, multiple patients at this clinic had problems with vaginal lacerations.
[59] Patients have sought hysterectomies due to these symptoms; e.g., Zwickl et al. (2023).
[60] Da Silva et al. (2024); Tordoff et al. (2023); Zwickl et al. (2023).

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7.4.6 Effects of estrogen on the male reproductive system

Testicles have two primary functions: producing testosterone and generating sperm capable of fertilizing an ovum. The use of estrogen in accordance with the ES and WPATH guidelines results in impairment of normal testosterone production and significant abnormal histologic changes to the male reproductive system.[61] These findings point to widespread structural reconfiguration of testicular tissue in response to prolonged exposure to the high levels of estrogen used in medical transition.

7.4.7 Cardiovascular and metabolic risks

Among the most significant long-term risks associated with CSH is an increase in cardiovascular risk factors. A 2018 review found that patients taking CSH had an elevated risk of heart attack and CV mortality compared to controls.[62]

Several studies and reviews have found increased risk of CV events like heart attacks and strokes in females taking testosterone.[63] This is thought to result from testosterone's effects on underlying metabolic factors related to CV risk. In females, testosterone can cause elevated blood pressure, polycythemia, and atherogenic

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[61] In one study of 99 testicle specimens, Leydig cells (crucial for producing testosterone) were completely absent or extremely diminished in 80% of cases. There was a significant average decrease in the diameter of the seminiferous tubules (site of spermatogenesis) when compared with controls, with 82% showing peritubular fibrosis, which interferes with tubular function (Matoso et al., 2018). In another study, 74% of specimens had abnormal basement membrane thickening (Riva-Morales et al., 2025). This mimics findings seen in conditions like cryptorchidism (undescended testes), which are associated with infertility (Mittal et al., 2017). In one of the abovementioned studies, all 125 testicular specimens showed atrophic changes and decreased spermatogenesis, with 71.2% having no sperm production at all (Riva-Morales et al., 2025). In another study, 80% of testicular tissue samples from males on estrogen showed maturation arrest, meaning that although the early stages of the sperm development may have begun, maturation to fully functioning spermatozoan did not occur (Matoso et al., 2018). These findings point to widespread structural reconfiguration of testicular tissue in response to prolonged exposure to high levels of estrogen used in medical transition. Other structures affected by estrogen (and/or androgen deprivation) include the epididymis, rete testes, and prostate (Crowley et al., 2023; Matoso et al., 2018). A long-term analysis involving 86 patients who underwent orchiectomies after a median duration of 7.5 years on estrogen therapy found a clear correlation between the length of hormonal treatment and the degree of tissue abnormality (Marins et al., 2024). This study discussed "[c]ompromise in integrity of blood-testis-barrier with *increased vulnerability to cytotoxic and immune damage*; impaired adhesion with premature detachment of spermatids from Sertoli cells, causing altered shaping in spermatids; germ cells phagocitation" as theoretical mechanisms of impaired spermatogenesis (emphasis added).

[62] Irwig (2018).

[63] E.g., Nota et al. (2019). A systematic review found moderate and high certainty evidence of some incidence of cardiovascular events in young females under 26 years old (Miroshnychenko, Ibrahim et al., 2025).

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changes in the lipid profile.[64] Longitudinal studies of PMT have reported increases in BMI (and/or fat mass) after initiation of CSH[65] and PBs.[66] Atherogenic changes to the lipid profile have also been reported.[67]

With respect to polycythemia, elevated hematocrit levels are known to increase blood viscosity, raising the risk of thromboembolic and CV complications. Among females, even modest elevations in hematocrit levels have been independently associated with heightened risks of CV disease, coronary events, and CV-related mortality.[68]

In males taking estrogen, studies have shown increased risk of CV events like venous thromboembolism and stroke.[69]

7.4.8 Other risks associated with cross-sex hormones

In both sexes, CSH use may be associated with early mortality.[70] In females taking testosterone, breast tissue undergoes structural remodeling, often with increased fibrous connective tissue and decreased glandular volume.[71] There is also some concern about possible increased risk of breast and ovarian cancer.[72] In males, some studies suggest that estrogen may increase risk of developing multiple sclerosis[73] and thyroid cancer,[74] and that it may lead to a decrease in brain volume.[75] However, research in these areas is still preliminary. While breast cancer is uncommon in natal males, data suggest that high-dose estrogen therapy increases this risk.[76] Other effects

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[64] Glintborg et al. (2024); Safer & Tangpricha (2019).
[65] Boogers et al. (2024); Jarin et al. (2017); Klaver et al. (2018, 2020).
[66] Carmichael et al. (2021); Ciancia et al. (2024); Delemarre-van de Waal & Cohen-Kettenis (2006); Fisher et al. (2024).
[67] Klaver et al. (2020); Olson-Kennedy, Okonta, et al. (2018). Millington et al. (2021) found atherogenic changes only in females, not in males.
[68] Gagnon et al. (1994). In a longitudinal cohort study of 1,073 adult females taking testosterone (Madsen et al., 2021), approximately 24% of participants developed hematocrit values ≥50%, a threshold commonly used to define severe erythrocytosis. While the study did not report prevalence in the intermediate range (hematocrit levels between 45% and 50%) it is reasonable to infer that a similar or greater proportion of individuals would fall within this bracket.
[69] Nota et al. (2019) reported a nearly five-fold (4.6x) elevation in risk of venous thromboembolism, and Getahun et al. (2018) reported a nearly ten-fold (9.9x) elevation in risk of stroke.
[70] C. J. de Blok et al. (2021).
[71] Grynberg et al. (2010).
[72] Hembree et al. (2017).
[73] Papkoor et al. (2016); White et al. (2022).
[74] Derwahl & Nicula (2014).
[75] Pol et al. (2006); Seiger et al. (2016); Zubiaurre-Elorza et al. (2014).
[76] C. J. M. de Blok et al. (2019).

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of estrogen may include diminished libido, erectile dysfunction, and loss of spontaneous erections.[77]

7.5 Surgery and gender dysphoria

WPATH provides an extensive list of surgeries it considers appropriate treatments for GD.[78] All surgeries carry risks,[79] some of which are amplified when surgery follows PBs and CSH. Further, surgeries to remove healthy and functioning organs introduce a unique set of iatrogenic harms not encountered in other areas of medicine.

7.5.1 Surgical problems related to early pubertal blockade

Males who initiate PBs at Tanner Stage 2 and then proceed to estrogen have narrowed options for future genital surgery, should this be desired. PBs arrest development of male genitalia. If PBs are started in Tanner Stage 2 and estrogen is started some time thereafter, the male genitalia will never develop beyond the prepubertal or early-pubertal state. For patients who proceed with vaginoplasty later in life, this may foreclose the surgical option of penile inversion vaginoplasty due to lack of sufficient genital tissue for this procedure. This issue was recognized in the original Dutch papers,[80] but over subsequent decades almost no research has been published on this topic. A single Dutch study found greatly increased odds of receiving intestinal vaginoplasty (compared to penile inversion) in male patients with history of pubertal blockade.[81] Intestinal vaginoplasty is a more technically complex and risky procedure.[82] One notable and tragic case involved a member of the original Dutch Protocol research cohort who died

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[77] Hembree et al. (2017). Of note, some or all of these effects on sexual function (diminished erections, for example) may be desired by certain patients.
[78] According to WPATH's SOC-8, even highly unusual surgeries such as non-binary mastectomies (where female breasts are reshaped to resemble gynecomastia in males), penis-preserving vaginoplasty, and vagina-preserving phalloplasty (to provide patients with both sets of genitals), and genital nullification procedures (involving genital removal) are considered medically-necessary procedures for some patients. Only phalloplasty for females has a minimum recommended age of 18 (Coleman et al., 2022). In 2024, a Canadian patient successfully sued a provincial health insurer, who had declined to cover "penile-preserving vaginoplasty" surgery, considering it experimental. Media coverage noted that "…the court decided that [this] procedure…[was] consistent with the World Professional Association for Transgender Health (WPATH) Standards of Care, the leading authority on gender-affirming medical and surgical care, especially as it recommends individualized treatment plans" (Arsenych, 2024).
[79] E.g., bleeding, infection, scarring, and risks related to anesthesia.
[80] Delemarre-van de Waal & Cohen-Kettenis (2006).
[81] van de Grift et al. (2020).
[82] Lee et al. (2023).

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from necrotizing fasciitis at age 18 following an intestinal vaginoplasty conducted because of inadequate genital tissue.[83]

7.6 Other risks associated with hormonal interventions or surgeries

The use of endocrine interventions affects multiple organ systems beyond the reproductive tract. In addition, there are psychological risks associated with PMT.

7.6.1 Adverse psychiatric effects

The FDA-mandated labeling for testosterone cautions about abuse potential, noting: "Testosterone has been subject to abuse, typically at doses higher than recommended for the approved indication ... Anabolic androgenic steroid abuse can lead to serious cardiovascular and psychiatric adverse reactions." These effects have been reported in males and females, including adolescents.[84]

Research on anabolic steroid misuse has demonstrated associations with severe psychiatric problems, including mood instability, psychosis,[85] and dependence.[86] The most frequently observed symptoms include irritability, aggression, euphoria, inflated self-perception, impulsivity, and risk-taking behaviors. Additional manifestations may include acute psychotic episodes, worsening of tic disorders or depression, and delirium-like states. One study assessing medium (300–1000 mg/week) and high (>1000 mg/week) anabolic steroid use found that 23% of users met diagnostic criteria for a major mood disorder, including mania, hypomania, or depression, while 3.4-12% developed psychotic features.[87]

In an analysis of the FDA's Event Reporting System (FAERS) database for people using CSH for medical transition, 88% of adverse drug reactions were classified as serious.[88] Without an idea of denominators, individual risks are not possible to quantify. Among the 83 reports regarding females using testosterone, 87.8% of the events were deemed

[83] Negenborn et al. (2017).
[84] Actavis Pharma, Inc. (2018).
[85] R. C. W. Hall et al. (2005).
[86] Skauen et al. (2023).
[87] R. C. W. Hall et al. (2005).
[88] Gomez-Lumbreras & Villa-Zapata (2024).

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serious, with two reported deaths (2.4%) and 25 hospitalizations (30.5%).[89] Reported psychological harms included anxiety, depression, mood swings, suicidal ideation and behavior, aggression, dissociation, and self-harm. More extreme symptoms, such as antisocial behavior and homicidal ideation, were also documented.[90]

A separate study from Sweden found an elevated rate of criminal convictions in natal females who had taken testosterone and undergone gender-transition surgery, compared to age-matched controls. This study also found that adults who had undergone medical and surgical transition had 19 times the rate of suicide deaths and nearly three times the rate of all-cause mortality and inpatient psychiatric care compared to age and sex-matched controls.[91] Elevated suicide rates (compared to the general population) have also been reported in other studies.[92] It is impossible to determine causation based on this data, in part due to presence of confounders like co-occurring mental health conditions.

7.6.2 Detransition and regret

In males, estrogen causes breast growth and infertility that may be irreversible even with cessation of CSH.[93] In females, irreversible virilizing effects of testosterone include face and body hair growth, deepening of the voice, clitoral growth, and male-pattern baldness.[94] Patients of any age may experience regret regarding the permanent physical and physiologic effects of CSH, regardless of how they identify. For example, stably transgender-identified patients may regret loss of fertility. Developing baldness, or chafing/discomfort caused by clitoromegaly, may lead a patient who identifies as a transgender man to regret taking testosterone.

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[89] Laidlaw & Jorgensen (2024).
[90] Laidlaw & Jorgensen (2024).
[91] Dhejne et al. (2011).
[92] C. J. de Blok et al. (2021) found that the standardized mortality ratio for suicide among transgender adults was 3.1 compared to the general population of the Netherlands. In Van Cauwenberg et al. (2021), five out of 177 adolescent patients died by suicide. All suicide deaths were in patients who had been started on CSH (Society for Evidence-Based Gender Medicine, 2024a). Biggs (2022) reported that four out of 15,032 patients referred to the U.K.'s pediatric gender medicine (PGM) clinic died by suicide over a ten-year period. Two of the suicides were in waitlisted patients (i.e., probably not taking CSH). A recent U.S. study reported a suicide rate of two out of 315 patients taking CSH over a two-year period (Chen et al. 2023).
[93] Cheng et al. (2019); Deutsch (2020a).
[94] Deutsch (2020b).

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If patients do detransition,[95] they may experience regret,[96] but some patients may integrate the physical changes into their self-concept and not experience regret.[97] Even proponents of PMT acknowledge that regret is a risk (e.g., the phrase "Some adolescents may regret the steps they have taken" in WPATH's guidelines).[98]

This serious issue has been minimized with the claim that detransition and regret rates are vanishingly low. In fact, the detransition rate is unknown.[99] The ubiquitous claim that the detransition and regret rates are vanishingly low is unsupported by the evidence.[100] A U.K. population-based study not focused on minors found that about one-fifth of patients discontinued hormonal interventions within five years, with more than half of them reporting experiences of detransition and/or regret.[101] Reasons for detransition are complex[102] and can be related to external[103] or internal[104] factors. With respect to

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[95] Detransition refers to reverting back to living as one's sex after having medically and/or surgically transitioned. For discussion of detransition as a phenomenon see Butler & Hutchinson (2020); Irwig (2022); MacKinnon, Expósito-Campos et al. (2023). For research based on survey data from detransitioners or their parents, see Bailey & Diaz (2023); Littman (2018), (2021); Vandenbussche (2022).

[96] Some detransitioners have described adverse experiences with CSH as well as regret; e.g., in a recent court case (DH v. Snyder Case: 21-15668, 07/07/2021, ID: 12164749, DktEntry: 22, n.d.) one patient described that testosterone "exacerbated her anxiety and depression" in addition to prompting increased aggression, risk-taking, and suicidal ideation (p. 22); another patient experiencing depression after several months of euphoria, (p. 24) and another described ongoing regret and distress due to a permanently deepened voice from testosterone and numb scars and absent breasts from mastectomy surgery (p. 18).

[97] MacKinnon et al. (2022).

[98] Coleman et al. (2022, p. S47).

[99] Cohn (2023).

[100] The detransition rate after PBs and CSH has been described as very low, but this is backed by little evidence. A few sources are frequently cited. One is an SR of surgery studies with limited (if any) relevance to PMT, which reported a regret rate of around 1% (Bustos et al., 2021). This SR had methodological problems, calculation errors, and included mostly studies of poor or moderate quality, many with follow-up times that were inadequate for capturing regret (Cohn, 2023; Expósito-Campos & D'Angelo, 2021). Additionally, there were issues with the ways included studies defined regret; in Wiepjes et al. (2018), for example, patients needed to report regret to their clinician and ask to start natal sex hormones. Another study was based on survey research of individuals who identified as transgender *at the time of survey completion*. Some respondents had detransitioned in the past (usually due to factors like stigma or other external difficulty) before re-identifying as transgender (Turban et al., 2021). A survey of surgeons found respondents had rarely been asked to perform reversals (Narayan et al., 2021); Cohn (2023) noted that these findings were hard to interpret because of "unclear follow-up time, loss to follow-up, and even measurement instrument (Were questions about regret routinely asked and was there a consistent definition of regret in use?)" (p. 1944). Another study of surgical regret partly quantified regret via request for surgical reversals (Jedrzejewski et al., 2023), which Cohn pointed out would have excluded patients who do not return to their surgeons.

[101] Boyd et al. (2022).

[102] MacKinnon, Gould et al. (2023).

[103] Turban et al. (2021).

[104] Littman (2021); Littman et al. (2024).

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clinical research studies of children and adolescents, one study reported a 7.1% regret rate,[105] two found low rates of CSH discontinuation or reidentification with birth sex (<5%),[106] and one found a higher rate of CSH discontinuation (25%).[107]

7.7 Mortality risk

Four population-based cohort studies have found that transgender individuals appear to have higher mortality risk when compared to members of the general population of similar age and sex. In the U.S., private insurance data from 2011 to 2019 indicated that transgender persons were nearly twice as likely to die as age- and sex-matched controls.[108] A Dutch cohort study that included five decades of data found that compared to their natal sex peers, transgender people had an elevated standardized mortality ratio (higher risk of death).[109] A 2023 cohort study from the U.K. found that compared to their natal sex peers, transgender people had higher risk of mortality (34 % higher for females, 60% higher for males).[110] Finally, a Swedish study that included three decades of data found that the mortality risk for transgender persons was 2.8 times that of age and natal sex matched population controls.[111]

This Review does not assess the methodological quality of these epidemiological studies or quantitatively synthesize their findings. The magnitude of the mortality risk for maintaining a transgender identity remains uncertain, as do the underlying causal factors (causes of death found to be elevated among transgender persons included suicide, cardiovascular disease, and HIV[112]). Moreover, in light of ongoing epidemiological shifts (see Section 4.3.1.1), it is unclear whether these findings extend to children and adolescents with gender dysphoria (GD). These studies further support a cautionary stance toward PMT, however, especially insofar as the Dutch cohort study

[105] Crabtree et al. (2024).
[106] Cavve et al. (2024); van der Loos et al. (2022).
[107] Roberts et al. (2022).
[108] Hughes et al. (2022).
[109] de Blok et al. (2021).
[110] Jackson et al. (2023).
[111] Dhejne et al. (2011).
[112] See de Blok et al., 2021; Dhejne et al., 2011; Hughes et al., 2022; Jackson et al. 2023.

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found that despite changes in care of the transgender population over five decades, the elevated mortality risk has persisted, not declined.[113]

[113] de Blok et al. (2021).

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Chapter 8 Summary and Implications of Evidence Review

Medical and surgical interventions for children and adolescents with gender dysphoria (GD) are widely promoted as essential and even lifesaving, yet the evidence base does not support strong conclusions about their effectiveness in improving mental health or reducing GD. Analysis of the biological plausibility of harms is necessary, and suggests that some short- and long-term harms are likely (in some cases expected) sequelae of treatment.

The Food and Drug Administration (FDA) also looks at risks in this manner when making a risk/benefit determination:

> Benefit-risk planning is most valuable in cases where a challenging benefit-risk assessment can be reasonably anticipated, either because the extent of benefit is expected to be modest or is highly uncertain, or when serious adverse events of the drug can be anticipated (e.g., based on a suspected class effect, understanding of the mechanism of action, and/or early-phase or non-clinical safety findings).[1]

The FDA states that with respect to risks, it is important to understand suspected class effects, meaning the types of predicted effects that are known to occur within the same class of medications. For example, the class of diuretics called thiazides are known to cause hypokalemia (low potassium), and so this potential adverse effect must be taken into account when making a risk/benefit determination regarding thiazides.

The FDA also emphasizes the importance of understanding the physiological mechanism of action, meaning the known way in which a drug affects the body. For example, medications called beta blockers affect the beta-adrenergic receptor and by their known mechanism of action cause effects such as slowed heart rate and decreased cardiac contractility. These physiological mechanisms—and the potential adverse effects of bradycardia (slow heart rate) and reduced cardiac output (amount of

[1] Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) (2023).

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blood pumped by the heart)—must be taken into account when making a risk/benefit determination regarding beta blockers.

Similarly, risk/benefit determinations regarding PMT must take into account both class effects and known mechanism of action for these interventions. Moreover, as the FDA also emphasizes, when the risks of a treatment are serious, anticipated effects must be proportionate:

> In cases where serious risks are anticipated, it is important to consider whether the risk can be outweighed by a benefit of sufficient certainty, magnitude, and clinical relevance to patients.[2]

Some of the plausible harms of PMT are serious. The likelihood of infertility when puberty blockers (PBs) are provided at the early stage of puberty and followed by cross-sex hormones (CSH) does not have to be demonstrated in a clinical trial. This is because the mechanism is well-understood and conducting a trial would amount to an unethical "parachute test."[3]

Analysis of all available data described in this section of the Review suggests that the risk/benefit profile of medical and surgical interventions for children and adolescents with GD is unfavorable.

This has implications for decision-makers—ranging from individual clinical care to guideline development, health policy, and regulation.[4] The findings of this evidence review also underscore the importance of clearly distinguishing how values and preferences are incorporated at different levels of decision-making.

At the individual level, shared decision-making must be grounded in transparency. This means that patients and their families need to be fully informed—not just about available interventions, but also about their potential benefits, harms, alternative

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[2] Center for Biologics Evaluation and Research (CBER) and Center for Drug Evaluation and Research (CDER) (2023). See Chapter 13 for discussion of ethical implications.
[3] Smith & Pell (2003). The paper highlights the limitations of "gold-standard" research designs such as randomized controlled trials (RCTs) by pointing out that no RCTs have been done on the effects of jumping from a plane without a parachute. Narrow (mis)application of EBM would conclude that there is "very low certainty evidence" of death, given the dearth of high quality studies.
[4] Zeng et al. (2023); Zhang et al. (2017).

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options, and the certainty or uncertainty of the supporting evidence. When this information is missing or inaccurate, the values and preferences people express may be influenced by incomplete understandings.[5]

At the level of clinical practice guidelines and health policy, values and preferences should reflect those of a population well-informed about the strength of evidence. Weak or uncertain evidence for benefits requires greater caution and flexibility, not stronger recommendations.[6]

At the regulatory level, because decisions must prioritize public health and safety, the strength of the evidence is especially important. When evidence for benefit is lacking or of very low certainty, regulatory frameworks should focus on ongoing evaluation, risk mitigation, and the collection of more robust data before allowing broad implementation. At all levels, responsible decision-making requires a clear grasp of what is known, what remains uncertain, and how this understanding informs ethical obligations of clinicians. Several of the other chapters in this Review explore these issues in greater depth.

[5] Zhang, Alonso-Coello, et al. (2019); Zhang, Coello, et al. (2019).
[6] Guyatt et al. (2008).

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PART 3

CLINICAL REALITIES

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Chapter 9 Review of International Guidelines

Like in other areas of medicine, clinical care for gender dysphoric (GD) youth is typically guided by clinical practice guidelines (CPGs). The aim of such guidelines is to promote practices that are proven to improve patient outcomes and reduce unwarranted variation in care. Although guidelines are not mandates and clinicians must still exercise professional judgment, they serve as important reference points that influence treatment decisions, institutional protocols, insurance coverage policies, and broader standards of medical practice.

This chapter provides an overview of CPGs that address care for youth with GD. Section 9.1 is a primer on the purpose and characteristics of trustworthy evidence-based guidelines. Section 9.2 provides an overview of the quality of the existing guidelines in the area of pediatric gender medicine as assessed by two systematic reviews (SRs). It also discusses the newest guidelines not included in the extant SRs. Section 9.3 profiles the clinical recommendations set out in the only two guidelines rated as trustworthy (both from Nordic countries).

9.1 The role and process of clinical practice guidelines

Clinical practice guidelines are a set of clinical care recommendations intended to optimize patient care.[1] While used primarily by healthcare providers, CPGs also guide hospitals in standardizing care, informing insurance coverage decisions, shaping health policy, and supporting medical education. Researchers use them to identify knowledge gaps, and legal professionals may cite them in malpractice cases. Informed patients and caregivers may also rely on CPGs to participate in shared decision-making and advocate for appropriate care.

The field of evidence-based medicine (EBM) provides several sources describing the characteristics of a trustworthy guideline.[2] According to the National Academy of Medicine (NAM),[3] trustworthy CPGs:

[1] Brignardello-Petersen et al. (2021).
[2] Brignardello-Petersen et al. (2021); Brouwers et al. (2010); Lima, Mirza et al. (2023).
[3] Formerly the Institute of Medicine.

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> should be *based on a systematic review of the existing evidence*; be developed by a knowledgeable, multidisciplinary panel of experts and representatives from key affected groups; consider important patient subgroups and patient preferences, as appropriate; be based on an explicit and transparent process that *minimizes distortions, biases, and conflicts of interest*; provide a clear explanation of the logical relationships between *alternative care options* and health outcomes, *provide ratings of both the quality [certainty] of evidence and the strength of the recommendations*; and be reconsidered and revised as appropriate when important new evidence warrants modifications of recommendations.[4]

Most guideline users will focus on two core elements of guidelines: the content of the recommendations, and their strength. One of the most widely accepted approaches to rating the strength of recommendations is the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. GRADE classifies recommendations according to their direction and strength into four categories: 1) strong recommendation for an intervention; 2) conditional or weak recommendation for an intervention; 3) conditional recommendation against an intervention; and 4) strong recommendation against an intervention.[5]

In addition, there is a GRADE recommendation known as "only in research."[6] It is used sparingly in situations in which an intervention may be promising but lacks sufficient evidence to support its general use. The "only-in-research" recommendation is appropriate when three conditions are met: 1) the available evidence is of low or very low certainty, making it unclear whether the intervention provides meaningful benefit; 2) further research has a large potential to reduce this uncertainty and produce more definitive evidence; and 3) conducting such research is deemed valuable given anticipated costs and risks. This recommendation may be accompanied by a second strong recommendation not to use the intervention outside the research context.[7]

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[4] Graham et al. (2011, p. 5, emphasis added).
[5] Andrews, Schünemann et al. (2013).
[6] Agarwal et al. (2020).
[7] Andrews, Guyatt et al. (2013, p. 724); Guyatt, Oxman, Kunz et al. (2008, p. 1051).

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In addition to interpreting evidence of benefits and harms, guideline panels that develop CPGs also must "trade off the benefits and risks, burden, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and values and preferences" to make their final recommendations and GRADE them for strength.[8] Guideline development groups must be free from or carefully manage financial, intellectual, and personal conflicts of interest, and should represent diverse and balanced views.

The credibility of guidelines should be assessed before their recommendations are accepted as trustworthy. A guideline's trustworthiness and authority depend on how closely the development group adhered to best practices for guideline development.[9] The Appraisal of Guidelines for Research and Evaluation (AGREE II) instrument is one of the most well-established validated tools for assessing the quality and methodological rigor of CPGs. The AGREE II instrument evaluates guidelines across six domains: scope and purpose, stakeholder involvement, rigor of development, clarity of presentation, applicability, and editorial independence. Each domain is rated on a standardized 7-point scale, with higher scores indicating greater methodological quality and trustworthiness. AGREE II further provides two overall assessments, one summarizing the guideline's overall quality and another evaluating whether the guideline should be recommended for implementation in clinical practice. By promoting transparency and consistency in guideline appraisal, AGREE II helps healthcare providers, policymakers, and patients identify guidelines most likely to improve patient outcomes and quality of clinical decision-making. Other approaches for evaluating the trustworthiness of CPGs emphasize related but distinct dimensions.[10]

9.2 Summary of systematic appraisals of clinical guidelines and guidance documents

At least two SRs have evaluated the quality (trustworthiness) of CPGs addressing the care of patients with GD. One focused on guidelines applying to all age groups,[11] and

[8] Guyatt et al. (2015).
[9] Graham et al. (2011).
[10] Brignardello-Petersen et al. (2021); Lima, Mirza et al. (2023).
[11] Dahlen et al. (2021).

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the other on guidelines devoted specifically to the care of youth.[12] Both relied on AGREE II.[13] This section focusses on the SR that assessed guidelines for pediatric GD, which was conducted by researchers at the University of York to inform the development of the Cass Review.[14]

The York analysis identified 23 and appraised 21 clinical guidelines and clinical guidance documents for their methodological rigor and quality. York's analysis revealed three main findings: 1) all the guidelines, with the exception of two (from Sweden and Finland), were found to be untrustworthy due to serious deviations from the methodological standards for trustworthy guideline development; 2) most international guidance documents have relied heavily on WPATH and Endocrine Society (ES) guidelines,[15] which were themselves closely linked through overlapping authors and with WPATH acting as a sponsor for the development of ES guidelines; and 3) none of the three guidance documents that have shaped the United States's approach to pediatric GD are trustworthy due to serious problems in their development methodology.[16]

9.2.1 Methodological quality of existing guidelines and guidance documents

All guidelines and guidance documents appraised by the York SRs were evaluated across AGREE II's six domains. The SR authors also provided two assessments, one on quality of the guideline overall, and the other on whether the guideline can be recommended for clinical implementation.

The reviewers noted that while generally most guidelines scored well in the domain of "clarity of scope and purpose," most scored poorly in the domains of "rigour of development," "editorial independence," and "applicability," the domains that tend to

[12] Taylor, Hall, Heathcote et al. (2024a, 2024b).
[13] Brouwers et al. (2010).
[14] Taylor, Hall, Heathcote et al. (2024a, 2024b). In this chapter, as in this two-part systematic review (SR), the word "guidelines" will be used to refer to the various documents that were appraised, some of which were not formal clinical practice guidelines (CPGs). The reviewers included "published articles or documents that [provided] at least one specific recommendation for the assessment and/or care of children and/or adolescents (age 0–18) experiencing gender dysphoria/incongruence, and which were developed by or for a professional, healthcare or government organisation or from a research study" (Taylor, Hall, Heathcote et al., 2024a, p. s66).
[15] Coleman et al. (2012); Hembree et al. (2009); Hembree et al. (2017).
[16] See Taylor, Hall, Heathcote et al. (2024a).

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most strongly influence the overall rating and the recommendation for use in clinical practice.[17]

Only the Swedish and the Finnish guidelines were rated as "recommended for implementation" by all reviewers; they also received the highest overall quality score, with Sweden rated as 6 and Finland rated as 5 (out of 7).[18] The Swedish and Finnish guidelines were the only guidelines that described how the evidence base was reviewed and that linked the evidence to clinical recommendations. All other guidelines and guidance documents scored between two and four and were not recommended for implementation by one or more reviewers.[19]

Overall, the reviewers described existing guidance documents that recommend pediatric medical transition (PMT) as "[lacking] an independent and evidence-based approach," noting that it was difficult to detect what evidence had been reviewed and how this informed development of recommendations. Moreover, they reported that the links between specific recommendations and evidence were often unclear or missing.

[17] Hoffmann-Eßer et al. (2018).
[18] See Figure 9.1 below.
[19] Taylor, Hall, Heathcote et al. (2024a, p. s65).

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Figure 9.1[20]

Guideline ID	OQA1	R1	OQA2	R2	OQA3	R3
AACAP 2012	3	No	3	No	4	Yes (mod)
American Academy of Paediatrics 2018	2	No	3	No	1	No
American Psychological Association 2015	3	No	2	No	3	No
Council for Choices in Healthcare Finland 2020	5	Yes (mod)	5	Yes	5	Yes (mod)
de Vries 2006	2	No	3	No	2	No
Endocrine Society 2009	3	No	4	No	4	Yes (mod)
Endocrine Society 2017	4	Yes (mod)	4	No	4	Yes (mod)
European Society for Sexual Medicine 2020	3	Yes (mod)	2	No	3	No
Fisher 2014	2	No	3	No	1	No
Health Policy Project 2015	2	No	1	No	2	No
Norwegian Directorate of Health 2020	3	No	3	Yes (mod)	4	Yes (mod)
Oliphant 2018	2	No	3	No	1	No
Pan American Health Organisation 2014	2	No	2	No	1	No
Royal Children's Hospital Melbourne 2018	3	No	3	No	2	No
Society for Adolescent Health and Medicine 2020	2	No	2	No	1	No
South African HIV Clinicians Society 2021	3	No	3	No	2	No
Strang 2018	3	Yes (mod)	2	No	2	No
Swedish National Board of Health & Welfare 2022	6	Yes (mod)	6	Yes	6	Yes
University California San Francisco 2016	3	No	2	No	3	No
WPATH 2012	3	Yes (mod)	3	No	2	No
WPATH 2022	3	Yes (mod)	3	No	3	No

OQA: Overall quality assessment - 1-7 where 1 is lowest possible score and 7 is the highest possible score

R: Recommend guideline for use - Possible responses are Yes, Yes with modifications (Yes (mod)), No

The numbers 1-3 refer to the three reviewers who appraised the guidelines

Abbreviations
AACAP – American Academy of Child & Adolescent Psychiatry
WPATH – World Professional Association for Transgender Health

[20] Supplementary Table S3 in Taylor, Hall, Heathcote et al. (2024a).

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Figure 9.2[21]

Table 1 Critical appraisal domain scores

Guideline ID	Scope and purpose	Stakeholder involvement	Rigour of development	Clarity of presentation	Applicability	Editorial independence
AACAP 2012	65	39	44	63	7	31
American Academy of Paediatrics 2018	70	26	12	30	6	69
American Psychological Association 2015	74	74	24	50	18	14
Council for Choices in Healthcare Finland 2020	91	69	51	72	56	0
de Vries 2006	63	31	10	74	17	6
Endocrine Society 2009	65	33	44	70	22	31
Endocrine Society 2017	63	33	42	72	21	92
European Society for Sexual Medicine 2020	63	52	39	70	7	58
Fisher 2014	65	20	12	35	17	44
Health Policy Project 2015	63	63	16	24	33	6
Norwegian Directorate of Health 2020	76	81	30	57	47	17
Oliphant 2018	44	39	12	33	21	0
Pan American Health Organisation 2014	52	44	13	31	21	0
Royal Children's Hospital Melbourne 2018	81	59	19	41	19	14
Society for Adolescent Health and Medicine 2020	41	24	17	41	7	0
South African HIV Clinicians Society 2021	59	59	21	43	24	69
Strang 2018	87	31	18	37	15	19
Swedish National Board of Health & Welfare 2022	91	87	71	83	25	36
UCSF 2016	70	41	23	37	26	0
WPATH 2012	85	61	26	56	17	17
WPATH 2022	83	63	35	56	24	39

≥70%, 31%–69%, ≤30%.
AACAP, American Academy of Child & Adolescent Psychiatry; UCSF, University of California, San Francisco; WPATH, World Professional Association for Transgender Health.

9.2.2 Interdependence of the existing guidelines and guidance documents

The SR authors noted an unusual interdependence between much of the published guidance supporting the management of children and adolescents with GD.[22] There was a marked pattern of "circular referencing and mutual endorsements"[23] between guidelines recommending PMT for routine care, with WPATH and the ES guidelines influencing all other guidelines and guidance documents.

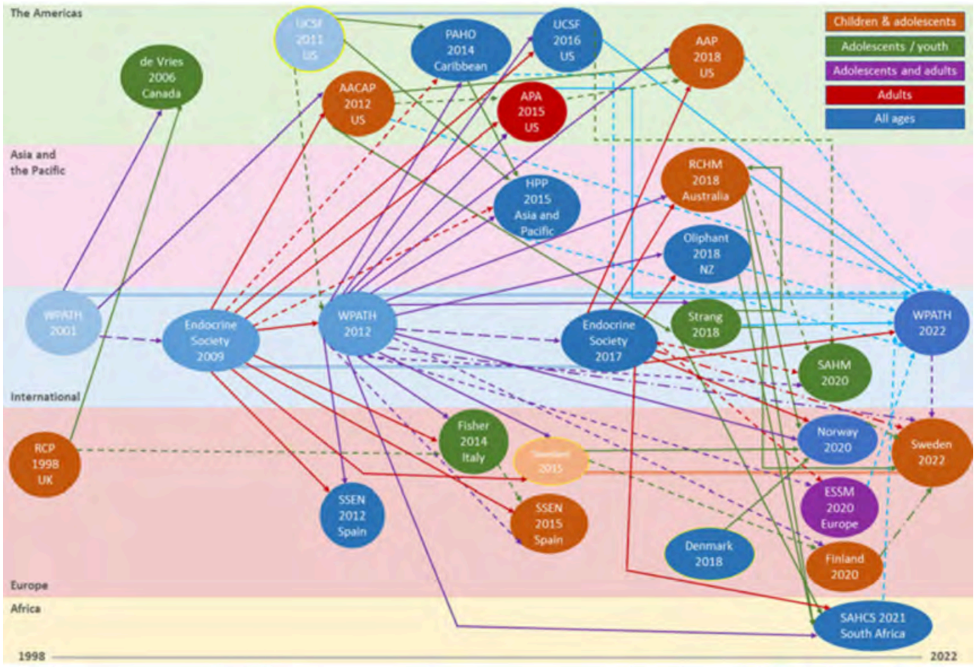
The pattern of "links and influences between guidelines"[24] had been established early in the field's tenure with the ES 2009 and WPATH 2012 guideline versions.[25] The pattern persisted as both ES and WPATH updated their guidelines in 2017 and 2022 respectively.[26] Moreover, the 2009 and 2017 ES guidelines state that WPATH was a guideline sponsor.[27] The University of York reviewers noted that this represents

[21] Taylor, Hall, Heathcote et al. (2024a, Table 1).
[22] Taylor, Hall, Heathcote et al. (2024a, pp. s69-s70).
[23] Donkin et al. (2025, p. 3).
[24] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[25] Coleman et al. (2012); Hembree et al. (2009).
[26] Coleman et al. (2022); Hembree et al. (2017).
[27] Hembree et al. (2009); Hembree et al. (2017).

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problematic circularity, "with WPATH adopting Endocrine Society recommendations in its own guideline and acting as a cosponsor for and providing input on drafts of the Endocrine Society guideline."[28]

Figure 9.3[29]



The Cass Review emphasized the interdependence and circularity of the guidance documents:

> The circularity of this approach may explain why there has been an apparent consensus on key areas of practice despite the evidence being poor … the guideline appraisal raises serious questions about the reliability of current guidelines.[30]

9.2.3 WPATH, Endocrine Society, and the American Academy of Pediatrics (AAP) guidelines and practice statements

The most influential sources of clinical guidance for treating pediatric GD in the U.S. are the WPATH and ES CPGs and the American Academy of Pediatrics' (AAP) guidance

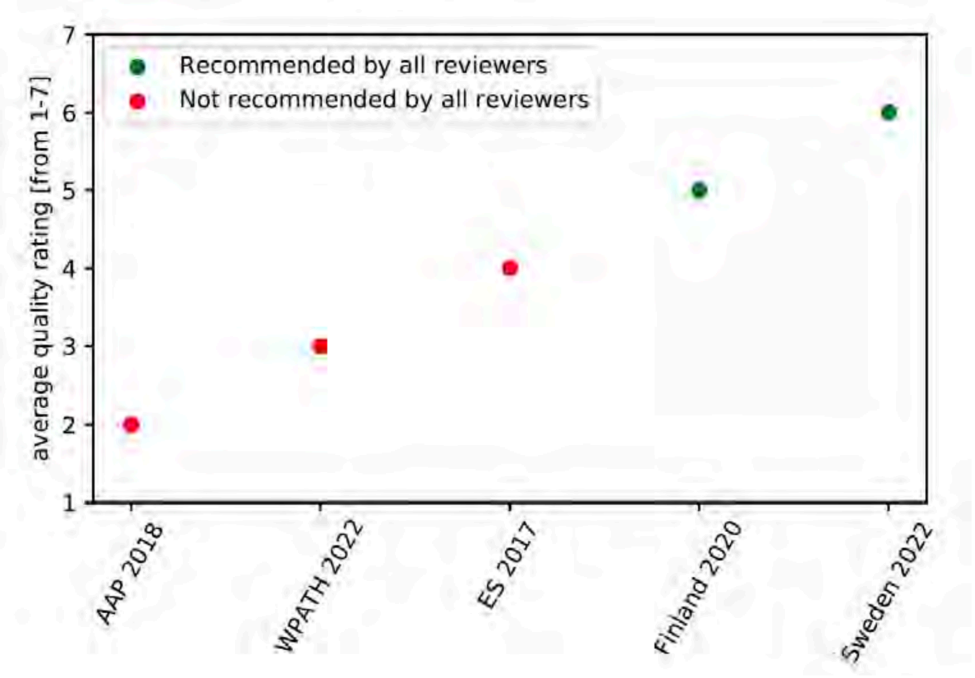
[28] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[29] Taylor, Hall, Heathcote et al. (2024a, p. s69).
[30] Cass (2024a, pp. 129-130).

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document.[31] The York SR assessed all three documents as very low quality and did not recommend them for implementation.

Figure 9.4 plots the overall rating of the quality of these three guidance documents relative to the only two guidelines that have been recommended for implementation by the York SRs.[32]

Figure 9.4[33]



Legend**:** AAP: American Academy of Pediatrics; WPATH: World Professional Association for Transgender Health; ES: The Endocrine Society

The York appraisals found that WPATH's guideline, *Standards of Care*, Version 8 (SOC-8) and the ES guidelines were both "[lacking] in developmental rigour." SOC-8 was given an overall score of 3 out of 7; the ES guideline scored 4 out of 7. The extensive problems in the SOC-8 development process, which included the failure to base recommendations on SRs and numerous other serious limitations in the process,

[31] The American Academy of Pediatrics' (AAP) 2018 Policy Statement was reaffirmed in 2023 (Rafferty et al., 2018); the Endocrine Society's (ES) published in 2017 represents the most recent published version (Hembree et al., 2017); the World Professional Association for Transgender Health's (WPATH) most recent clinical practice guideline is *Standards of Care*, Version 8 (SOC-8) (Coleman et al., 2022).
[32] Taylor, Hall, Heathcote et al. (2024a).
[33] Figure 9.4 plots data from Supplementary Table S3 in Taylor, Hall, Heathcote et al. (2024a).

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ultimately led to this low rating and the status of "not recommended for implementation." These problems are discussed in more detail in Chapter 10.

The ES 2017 guideline, which used the GRADE framework, has been criticized for making strong recommendations for hormonal interventions in the setting of a weak evidence base.[34] Notably, none of the systematic reviews that supported the ES guidelines were based on outcomes for children or adolescents.[35] The ES recommendation to initiate puberty blockade using GnRH as was derived by putting a higher value on achieving a "satisfactory physical appearance" while putting the lowest value on avoiding physical harms.[36] The ES recommendation for the initiation of cross-sex hormones no earlier than age 16 was justified by placing a higher value on adolescent's purported ability to meaningfully consent to cross-sex hormones (CSH) and placing a lower value on avoiding harm from potentially prolonged pubertal suppression.[37]

The AAP 2018 policy statement is not technically a CPG but has been widely cited in the U.S. as influential in establishing how pediatricians respond to children and

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[34] E.g. Block (2023c). If such recommendations are made, which the GRADE framework allows in specific circumstances, the reasoning for this must be clear. The ES guidelines did not do this.

[35] Maraka et al. (2017); Singh-Ospina et al. (2017); Of note, the only study of adolescents included in these systematic reviews, Klink et al. (2015), concluded that puberty blockers impede the development of bone mass density (BMD) and cross-sex hormones fail to bring up BMD to its pretreatment potential: "Between the start of GnRHa and age 22 years the lumbar areal BMD z score (for natal sex) in transwomen decreased significantly from 0.8 to 1.4 and in transmen there was a trend for decrease from 0.2 to 0.3. This suggests that the BMD was below their pretreatment potential and either attainment of peak bone mass has been delayed or peak bone mass itself is attenuated" (Klink et al., 2015, p. E270).

[36] Full quotation: "These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression" (Hembree et al., 2017, p. 13). Published gender-affirming care literature has also described a prioritization of aesthetic outcomes, e.g., a research paper noted gender-affirming care can be beneficial because (among other reasons) "The combination of pubertal suppression and cross-sex hormones] may … increase the concordance of youths' appearance with cisgender norms …" (McGregor et al., 2024, p. 5).

[37] Full quotation: ""The recommendation to initiate pubertal induction [cross-sex hormones] only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/ harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers" (Hembree et al., 2017, p. 3885).

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adolescents with GD.[38] Because the document offers extensive clinical recommendations regarding every step of PMT—from social transition to PBs, CSH, and surgery—the York team assessed the trustworthiness of the AAP guidance using the same criteria they applied to CPGs. Using the AGREE II criteria, the AAP policy statement received the second-lowest average score among all international guidelines: 2 out of 7.

As noted in Chapter 2, the AAP's policy statement's use of "gender diverse" casts a very wide net regarding which patients the organization considers eligible for medical intervention. The statement has been heavily criticized in peer-reviewed articles, which have pointed out that it is rife with referencing errors and inaccurate citations.[39] Despite persistent advocacy among its members, who have petitioned the organization to release updated, evidence-based guidance for treating pediatric GD,[40] the organization chose to reaffirm their policy statement in 2023.[41]

9.2.4 More recent international guidelines

Since the publication of the York reviews, several new European guidelines have been issued in final or draft form, including those from the German AWMF, the French Society of Pediatric Endocrinology and Diabetology, the Polish Sexological Association, the European Society for Paediatric Endocrinology (ESPE), and the forthcoming final version of the French National Authority for Health (HAS) guidelines.[42] These reviews have been developed amid growing international awareness of the weaknesses of WPATH's SOC-8 and the outdated nature of the Endocrine Society's guidelines,

[38] Rafferty et al. (2018).
[39] E.g., Cantor (2020); McDeavitt (2025).
[40] See description of efforts led by pediatrician Julia Mason in Block (2023c).
[41] Block (2023c).
[42] The AWMF German guidelines (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy [DGKJP], 2025) are comprehensive; the guidelines by the French Society of Pediatric Endocrinology and Diabetology (SFEDP; Brezin et al., 2024) are limited to hormonal interventions and is currently available only as a preprint; the Polish guidelines, supported by the Polish Sexological Association, the Polish Psychiatric Association, and the Polish Society of Paediatric Endocrinology and Diabetology cover most aspects of PMT but are almost entirely derivative (Gawlik-Starzyk et al., 2025); the ESPE guidelines (Hannema et al., 2024) primarily focus on endocrine (medical/hormonal) interventions; the draft French national HAS guidelines became publicly available when a French newspaper published a draft in November 2024 (Sugy, 2024); the final version has not yet been released.

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reflecting the need to have defensible, localized, up-to-date guidelines that set the standards of care for youth with GD.

Unfortunately, these recently-published (or as yet to be finalized) guidelines suffer from the same or similar methodological weaknesses that have rendered the WPATH and the Endocrine Society's guidelines not trustworthy and not recommended for implementation. All suffer from non-evidence-based approaches to guideline development and exhibit one or more of the following problems: 1) guideline development groups are composed of individuals with unmanaged conflicts of interest relating to the provision of pediatric gender transition services; 2) the guideline takes an a priori WPATH-aligned position that medicalized pathway of hormones (and surgery) is the recommended treatment approach;[43] 3) the recommendations are not based on rigorously-conducted systematic reviews of evidence[44] 4) individual studies that drive treatment recommendations are not appraised for quality, and their conclusions are accepted at face value; 5) the recommendations are not graded for strength, resulting in ambiguity in clinical decision-making.

While some guidelines, in response to criticism of the draft version, have added references to systematic reviews of evidence, it is apparent that SRs were not utilized to make treatment recommendations, with apparent and unreconciled contradictions between the findings of the SRs and the treatment recommendations. [45] Alternatives such as psychological support are in nearly all cases marginalized or even entirely absent. Ongoing reliance on the "consensus-based" non-evidence-based process

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[43] For example, the German AWMF guidelines state that the members of the guideline development group adhere to the WPATH positions (Society for Evidence-Based Medicine, 2025).The Polish guideline explicitly bases itself on WPATH SOC-8, without independent review, stating, "This document is based on the Standards of Care for the Health of Transgender and Gender Diverse People, Version 8 (2022) [1] and an Endocrine Society Clinical Practice Guideline … The person conducting psychological or sexological assessment and care should be familiar with the content of the current standards of care of the World Professional Association for Transgender Health and comply with them" (Gawlik-Starzyk et al., 2025, pp. 4, 8).

[44] The German guidelines methodological report explicitly states that no evidence-based recommendations were developed (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP), 2025, p. 6).

[45] Society for Evidence-Based Gender Medicine (2025).

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underlines the trustworthiness of these guidelines, raising questions about the rigor of guideline development in pediatric gender medicine not just in the U.S., but worldwide.

9.3 Overview of recommendations in the high-quality guidelines

Of the 23 guidelines that were appraised in the systematic evidence review, only two were recommended for practice by all three reviewers: the guidelines from Finland (which were scored five out of seven), and those from Sweden[46] (which were scored six out of seven). Both guidelines recommend that psychotherapy—not hormones or surgeries—should be the standard of care for youth with GD, and that any use of hormones should be limited to nationally overseen research or exceptional circumstances. As described in the systematic review, the two Scandinavian guidelines were the only ones that based their treatment recommendations on systematic evidence reviews, a key element of trustworthy clinical practice guidelines.

9.3.1 Finland

In 2020, Finland's Council for Choices in Health Care (PALKO/COHERE) issued national guidelines for treating gender dysphoria in minors, representing a major shift away from the model endorsed by WPATH's *Standards of Care* Version 7.[47] Finland's guidelines emphasize that the first-line treatment for adolescents experiencing gender distress should be psychosocial support and psychotherapy, not early medical intervention.[48]

Following an SR, Finnish authorities concluded that the body of evidence supporting puberty blockers and cross-sex hormones for youth is inconclusive. Importantly, the guidelines explicitly state that "in light of available evidence, gender reassignment of minors is an experimental practice."[49] While medical transition remains possible, it is restricted to highly select cases—specifically, adolescents with persistent, childhood-

[46] In 2022, Sweden's healthcare authority, Socialstyrelsen, issued guidelines recommending that "Psychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures" (Socialstyrelsen, 2022b, p. 45).
[47] Council for Choices in Health Care Finland (2020a). There is an official English-language summary (Council for Choices in Health Care Finland, 2020c), as well as an unofficial English translation of the complete guideline document (Council for Choices in Healthcare Finland, 2020b).
[48] Council for Choices in Healthcare Finland (2020a).
[49] Council for Choices in Healthcare Finland (2020b, p. 8).

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onset gender dysphoria, no major psychiatric comorbidities, and stable identity development through adolescence.

Surgery is not offered to minors in Finland. Furthermore, the guidelines stress that psychiatric conditions must be treated and stabilized before considering hormonal interventions. Special caution is placed on the use of puberty blockers, given emerging evidence about their potential impact on brain maturation and long-term decision-making capacity.

Adherence to this strict protocol is assured because Finland has only two centres that provide assessments and approve treatment indications for youth with GD, with highly coordinated clinical teams that adhere to the Finnish strict protocol.

Since the publication of the Finnish guidelines, two major register studies have provided additional support for their cautious approach. One explored psychiatric needs among gender-referred individuals, finding high rates of psychiatric comorbidities and suggesting that the rising number of referrals includes increasingly complex clinical cases.[50] The second examined suicide mortality among individuals under 23 and found that, after adjusting for psychiatric needs, there was no statistically significant difference in suicide rates between gender-referred youth and matched controls from the general population.[51]

Finland's cautious, evidence-focused guidelines stand in stark contrast to the WPATH model. Rather than expanding access amid uncertain outcomes, Finland has re-centered pediatric care around rigorous assessment, psychotherapeutic exploration, and prioritizing long-term health.

9.3.2 Sweden

In 2022, Sweden's National Board of Health and Welfare (Socialstyrelsen) issued an update to its national guidelines for the treatment of children and adolescents with

[50] Kaltiala et al. (2023).
[51] Ruuska et al. (2024).

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gender dysphoria.[52] This update was motivated in part by shifts in epidemiology and uncertainty about the recent rise in cases, and limited data regarding rates of detransition or regret among young adults. Grounded in a systematic review of the evidence,[53] the new framework departs sharply from the SOC-8. Unlike WPATH's affirmation-based model, Sweden's guidelines conclude that the risks associated with puberty blockers and gender-affirming treatments likely outweigh the expected benefits for young people. As with Finland, such interventions are now restricted to research settings, with exceptions permitted under strict clinical oversight.

The Swedish guidelines prioritize a comprehensive psychosocial evaluation and support. Clinicians are instructed to conduct thorough assessments of psychological, psychosocial, and psychiatric factors, utilizing validated instruments, investigative interviews, and detailed life histories from both the young person and their guardians.[54] Rather than presuming a fixed outcome, the guidelines emphasize the importance of supporting the open-ended exploration of gender identity.[55] Systematic screening for neurodevelopmental conditions, including autism spectrum disorder (ASD) and attention deficit hyperactivity disorder (ADHD), is required early in the evaluation process, with full neuropsychiatric assessments initiated when indicated.[56] Moreover, concurrent psychiatric conditions must be identified and addressed as early as possible, ensuring that psychosocial support and psychiatric interventions are available to bolster overall mental health throughout the evaluation.

Medical and surgical interventions are subject to equally rigorous restrictions. Treatment with puberty blockers (GnRH analogues) is confined to the context of clinical research. Until such research protocols receive ethics board approval, puberty blockers may be administered only in exceptional cases under the updated guidelines.[57] Similarly, the use of cross-sex hormones—testosterone or estrogen—is permitted solely within

[52] The official Swedish-language guidelines are Socialstyrelsen (2022c). Page numbers in this section refer to a certified, complete, unofficial translation that was submitted as evidence in a U.S. court case (Socialstyrelsen, 2022b). There is also an official English-language summary (Socialstyrelsen, 2022a).
[53] Swedish Agency for Health Technology Assessment and Assessment of Social Services (2022).
[54] Socialstyrelsen (2022b, p. 63).
[55] Socialstyrelsen (2022b, p. 66).
[56] Socialstyrelsen (2022b, p. 69).
[57] Socialstyrelsen (2022b, p. 85).

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research studies, with narrowly defined exceptional cases allowed.[58] Only adolescents who meet stringent eligibility criteria for gender-affirming hormone therapy may be considered for surgery, again under exceptional circumstances.[59] Across all interventions, the emphasis is on minimizing risk and ensuring that treatment decisions are based on the best available evidence.

Sweden's 2022 guidelines represent a marked shift away from affirmation-driven PMT model. Anchored in a systematic review of the literature, they embody a precautionary approach grounded in the principles of evidence-based medicine. Sweden's approach signals an important recalibration in gender medicine, reinforcing that interventions involving youth must be guided by systematic evidence appraisal, ethical responsibility, and a focus on long-term health trajectories.

9.3.3 United Kingdom

Currently, there is no finalized clinical practice guideline for pediatric gender medicine available from the National Institute for Health and Care Excellence (NICE) for England and Wales, or the Scottish Intercollegiate Guidelines Network (SIGN) for Scotland.[60]

NICE was commissioned by NHS (National Health Service) England[61] to perform a systematic evidence review evaluating treatments for gender dysphoria among children and adolescents. NICE's evidence reviews identified significant limitations in existing research, concluding that the available evidence was of very low quality (as assessed by the GRADE methodology) [62] and therefore insufficient to support the development of a formal clinical guideline.

These two SRs were cited as part of the Terms of Reference for an independent review that NHS England commissioned, led by Dr. Hilary Cass.[63] Released in 2024, the Cass Review aimed to thoroughly evaluate pediatric gender medicine services in the U.K. and provide clear recommendations on clinical practices and service delivery. Rather than

[58] Socialstyrelsen (2022b, p. 90).
[59] Socialstyrelsen (2022b, p. 95).
[60] Silver et al. (2025, p. 2).
[61] On March 13, 2025 it was announced that NHS England would be merged with the Department of Health and Social Care (DHSC).
[62] National Institute for Health and Care Excellence (2020b, 2020a).
[63] Cass (2024a, Appendix 1).

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providing explicit clinical guidelines, the Cass Review is a detailed, independent, investigative assessment based on multiple, commissioned, peer-reviewed systematic reviews.[64]

The Cass Review identified critical issues within the existing pediatric gender services, such as inadequate clinical assessments, insufficient long-term outcome data, and significant concerns over rapidly increasing referrals of young people with gender incongruence. Overall, it identified a significant gap between the available evidence and the clinical justifications for medical interventions for gender dysphoria in young people[65] and emphasized the necessity for comprehensive psychological support and thorough, individualized assessments.

In response to the Cass Review, NHS England introduced major policy changes. Puberty blockers are no longer routinely commissioned due to insufficient evidence regarding their long-term safety and effectiveness. Instead, they will only be accessible through structured clinical research trial, which is currently being designed. Additionally, CSH (masculinizing or feminizing hormones) are available to young people around the age of 16, contingent upon strict eligibility criteria and detailed assessment protocols by specialist multi-disciplinary teams and a new national Multi-Disciplinary Team (MDT) review process.[66] As reported most recently, no adolescent was prescribed cross-sex hormones in the last year. The NHS recently revealed that since the Cass Review was published, no minor has been found eligible to receive CSH according to the updated policy.[67]

Without a finalized clinical practice guideline, clinicians must follow the current policies directly informed by the Cass Review. These interim standards prioritize patient safety, rigorous clinical evaluation, ongoing research, and holistic care approaches, significantly revising the clinical pathways for young individuals experiencing gender incongruence.

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[64] Archives of Disease in Childhood (2024).
[65] Cass (2024a, pp. 22, 29, 32-35).
[66] National Health Service England (2024a); a review of adult services was also announced (National Health Service England, 2024b).
[67] Spencer (2025).

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9.4 Conclusion

The current landscape of CPGs for treating youth with GD underscores significant variability in methodological rigor and trustworthiness. Rigorous appraisals consistently demonstrate that only a select few guidelines, notably those from Finland and Sweden, meet high standards for evidence-based clinical decision-making. These Scandinavian guidelines emphasize cautious approaches grounded firmly in systematic evidence reviews, advocating psychotherapy and psychosocial interventions as first-line treatments, and restricting medical interventions to carefully monitored research settings or exceptional circumstances.

In contrast, many internationally influential guidelines, including those from WPATH, the Endocrine Society, and the American Academy of Pediatrics, have been criticized for substantial methodological shortcomings and conflicts of interest, resulting in recommendations not reliably supported by rigorous evidence. This pattern of circular referencing and mutual endorsement among these guidelines further compromises their credibility and has likely perpetuated a perceived consensus in pediatric gender medicine that belies the actual paucity of high-quality evidence.

Given the ethical implications and lifelong consequences of medical interventions in youth, it is imperative that future guidelines in pediatric gender medicine adhere strictly to established standards of evidence-based medicine. Guideline developers must prioritize transparency, methodological rigor, independence from vested interests, and systematic evidence appraisal. Only through such disciplined approaches can clinical practice guidelines fulfill their intended role of safeguarding the health and well-being of youth with GD, promoting informed decision-making among clinicians, families, and policymakers alike.

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Chapter 10 WPATH's *Standards of Care* 8

As shown in Chapter 9, the guidelines issued by the World Professional Association for Transgender Health (WPATH) have been rated among the lowest in quality and have not been recommended for implementation by systematic reviews of guidelines. Despite their lack of trustworthiness, for more than a decade WPATH guidelines have served as the foundation of the healthcare infrastructure for gender dysphoric (GD) youth in the United States. The WPATH *Standards of Care* guidelines are embedded in nearly all aspects of healthcare including clinical education, delivery of care, and reimbursement decisions by private and public insurers.

This chapter focuses on the current Version 8 of the WPATH *Standards of Care* guidelines (SOC-8),[1] published in 2022.[2] Section 10.1 describes WPATH's central role in shaping the treatment of youth with GD in U.S. healthcare settings. Section 10.2 provides a brief overview of the rationale for the development of SOC-8, highlighting how it differs significantly from earlier guideline versions with particular emphasis on the new Adolescent chapter. Section 10.3 examines the development process of SOC-8, considering both internal dynamics and external pressures, and analyzes its multipurpose role as a clinical guideline, a tool to secure insurance coverage, and a legal instrument aimed at promoting broad access to pediatric medical transition (PMT). Section 10.4 highlights one critical downstream consequence of the guideline's flawed development process: the elimination of all minimum age requirements for endocrine and surgical interventions (except phalloplasty) in minors. Section 10.5 discusses the implications of continued reliance on WPATH.

10.1 Influence of WPATH in the United States

There is no accredited subspecialty in "gender medicine" in the U.S. Instead, the practice of PMT typically involves a series of handoffs among different providers: a pediatrician or an adolescent medicine specialist[3] first assesses whether PMT may be

[1] Coleman et al. (2022).
[2] Portions of this evaluation necessarily rely on internal WPATH communications made publicly available through subpoena. See Boe v. Marshall, No. 2:22-cv-00184, (M.D. Ala.). Some material from Boe v. Marshall was previously released in Voe v. Mansfield, No. 1:23-Cv-00864: 100-1 (M.D.N.C.).
[3] American Board of Pediatrics (2024).

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warranted; mental health professionals diagnose GD or a related condition and recommend PMT; endocrinologists prescribe hormonal interventions (i.e., puberty blockers and cross-sex hormones); and various surgical specialties including plastic surgeons, urologists, and gynecologists perform a range of surgical procedures to alter the adolescent's sex-specific physical characteristics.

The multidisciplinary nature of PMT combined with the absence of a single medical specialty responsible for overseeing patient care has resulted in an oversight gap WPATH has filled. WPATH has successfully positioned itself as the leading authority in the field of gender medicine, including pediatric gender medicine. The first version of WPATH's Standards of Care was published in 1979. Subsequent updates followed in 1980, 1981, 1990, 1998, 2001, and 2012.[4] The most recent version, SOC-8, was published in 2022.[5] Chapter 3 provides a brief history of gender medicine and the role of WPATH, which was originally formed (under a different name, the "Harry Benjamin International Gender Dysphoria Association") to focus on the gender transition wishes of mature adults, but after pediatric transitions were pioneered in the Netherlands, increasingly shifted its attention to children and adolescents.

10.1.1 WPATH's role in clinical practice

Although some medical societies involved in providing PMT have issued guidance documents on specific aspects of care for youth with GD,[6] no professional society has published a comprehensive, up-to-date, evidence-based clinical guideline covering the full PMT pathway. Instead, medical societies have largely deferred to WPATH, adapting their own clinical positions to WPATH's most recent recommendations.[7] Unlike the U.K., Sweden, Finland, and other countries with centralized medical policymaking bodies that

[4] SOC-7 was released in 2011 and published in 2012.
[5] Coleman et al. (2022).
[6] The most notable documents are discussed in Chapter 9 and include the Endocrine Society's guidelines (Hembree et al., 2017) and the American Academy of Pediatrics position statement (Rafferty et al., 2018). Both are significantly outdated.
[7] In August 2024, WPATH was presented in a court case as "the leading association of medical professionals treating transgender individuals." It was further asserted that "[t]he Nation's leading medical and mental health organizations recognize [SOC-8] as reflecting the accepted standard of care for treating gender dysphoria." See U.S. v. Skrmetti (No. 23-477), Brief for the petitioner (2024, p. 3).

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issue independent, authoritative clinical care guidelines,[8] in the United States, WPATH's influence has been outsized and largely uncontested—primarily due to the fragmented healthcare system and the complexity of the U.S. regulatory environment.[9] WPATH's influence on clinical protocols for the care of youth with GD is pervasive within U.S. medicine. Its *Standards of Care* have become the primary framework embedded in clinical protocols and hospital operating procedures for the diagnosis and treatment of youth with GD.[10]

10.1.2 WPATH's role in medical education and training

WPATH has become the dominant influence shaping the education and training of U.S. healthcare providers who treat youth with GD. Indeed, it is virtually coterminous with the field itself. Because there is no officially accredited medical subspecialty in gender medicine in the U.S., and no formal board certification process as exists in fields like adolescent medicine, endocrinology, or psychiatry, training in PMT remains informal, variable, and largely organized through WPATH-affiliated medical education efforts.

WPATH's Global Education Initiative (GEI) offers certified courses that serve as the core curriculum for clinical training in the U.S. and worldwide. WPATH GEI's official collaborators include pediatric gender clinics and hospitals, the American Medical Student Association, and the World Health Organization (WHO).[11] Major U.S. hospitals and medical schools have embedded WPATH-aligned standards into their residency, fellowship, and continuing medical education programs.[12] Gender clinics reference

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[8] When NHS England moved to remove puberty blockers for GD from clinical practice, it received complaints that the decision was "not consistent … with the WPATH standards of care for trans children." NHS England responded: "The policy proposition has been developed following a review of peer reviewed published evidence as per NHS England Policy Development Methods. NHS England does not commission based upon guidelines or treatment protocols e.g. WPATH 8.0 [SOC-8] or practices in other countries. The not for routine commissioning position has been concluded based on 'insufficient clinical benefit to the patient of which evidence of harm is one aspect'" (National Health Service England, 2023, p. 4).

[9] The U.S. lacks a centralized medical policy-making body, resulting in what has been described as a "bewildering regulatory maze" (Field, 2008, p. 607).

[10] For an example, see Seattle Children's Hospital (n.d.). Note: it appears some pediatric gender clinics have recently removed public references to WPATH and have also removed the backups of the websites, making them inaccessible to citation.

[11] See World Professional Association for Transgender Health (n.d.).

[12] For example, Mt. Sinai's transgender psychiatry fellowship: "Fellows are provided time and financial compensation to attend the U.S. Professional Association for Transgender Health or World Professional

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WPATH's *Standards of Care* in clinical protocols and physician training.[13] WPATH-certified trainers further extend WPATH's reach into professional training at institutional and community levels.[14] WPATH certification not only is encouraged but also in some cases mandated.[15] This widespread integration has effectively established WPATH as the de facto authority for defining clinical competency, treatment eligibility criteria, and ethical frameworks across much of U.S. medicine.

10.1.3 WPATH's role in insurance reimbursement

Many U.S. public and private health insurers and regulatory bodies rely on SOC-8 when making coverage determinations. Requirements for credentialing, assessing medical necessity, and making coverage decisions almost universally reference WPATH's *Standards of Care*. Major U.S. private insurers, including Anthem,[16] Kaiser,[17] Aetna,[18] Cigna,[19] and UnitedHealthcare,[20] explicitly reference SOC-8 to define medical necessity, eligibility criteria, and coverage decisions.

Association for Transgender Health bi-annual conferences" (Icahn School of Medicine at Mt. Sinai, n.d.-b). Mt. Sinai's transgender surgery fellowship attending faculty includes Marci Bowers, the former president of WPATH (Icahn School of Medicine at Mt. Sinai, n.d.-a). Oregon Health and Sciences University's gender surgery fellowship program director is "the surgical lead for the World Professional Association for Transgender Health (WPATH) and the United States Professional Association for Transgender Health (USPATH) meetings" (OHSU School of Medicine Surgery, n.d.).

[13] For example, the Stanford Medicine Children's gender clinic website states, "the expert members of the Gender Clinic team consists [sic] of providers from pediatric endocrinology, adolescent medicine, pediatric urology and social services, supporting each child's or adolescent's gender identity. All our providers are members of the World Professional Association for Transgender Health (WPATH)" (Stanford Medicine Children's Health, n.d.). Fenway Health references WPATH as the authority in the field: "The World Professional Association of Transgender Health (WPATH) monitors current research and new knowledge about evidence-based medicine for transgender people. It publishes Standards of Care and Ethical Guidelines for health care providers, which 'articulate a professional consensus about the psychiatric, psychological, medical, and surgical management of gender dysphoria' to guide clinicians in providing quality care for transgender and gender diverse people, including children and adolescents" (Fenway Health, n.d.).

[14] See Harvard Medical School's continuing medical education (Harvard Medical School, n.d.), led by senior WPATH leaders involved in the production of SOC-8 (e.g., Sari Reisner, WPATH board member). Also see the following training initiatives: Gender Health Training Institute (n.d.); Silver Hill Hospital/World Professional Association for Transgender Health (n.d.).

[15] For example, the Washington State Department of Corrections mandates that physicians providing "gender-affirming care" must be WPATH-certified or obtain certification within two years (Washington State Department of Corrections, 2025). The Oregon Health Authority is another example (see following section).

[16] Anthem (2023). WPATH is referenced 35 times as the basis for all recommendations.

[17] Kaiser Permanente (2023). Transition and detransition policies require "WPATH letters."

[18] Aetna (2024). Adolescents are to meet "WPATH criteria" for hormonal interventions.

[19] Cigna (2025).

[20] Stroumsa & Kirkland (2020).

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Government payers, such as Medicaid programs, also commonly rely on WPATH guidelines as the primary basis for developing their medical policies. In 2024, Oregon became the first state to officially adopt SOC-8 as its standard of care, committing the Oregon Health Authority to cover treatments based entirely on WPATH guidelines. Oregon additionally requires that if a patient is denied coverage for medical or surgical intervention related to gender transition, the clinicians reviewing the patient appeal must complete WPATH-aligned training:

> health care providers reviewing adverse benefit determinations denying or limiting access to gender-affirming treatment complete the "WPATH SOC-8 Health Plan Providers Training," which is specifically designed for providers responsible for such reviews, or an equivalent training.[21]

This is notable as WPATH SOC-8 lists a wide range of procedures that should be provided to patients wishing to receive them. These include, in addition to puberty blockers, cross-sex hormones, mastectomy, and male-to-female or female-to-male genital surgeries, procedures such as vaginoplasty with a "retention of penis and/or testicle" (also known as penis-preserving vaginoplasty), removal of genitals entirely to create a "flat front" appearance, and uterine transplantation for male patients. Procedures listed as potentially necessary also include body contouring, liposuction/lipofilling, facelift, blepharoplasty, various implants, hair transplantation, vocal cord surgery, and a wide range of other appearance-modifying surgical procedures.[22]

10.2 The development of SOC-8 and the Adolescent chapter

Unlike most professional medical associations, WPATH does not require its members to be medical professionals. Full professional membership with voting privileges is also available to professionals in such fields as law, family studies, anthropology, and other areas. Reflecting the diverse aims of its broad membership, WPATH treatment

[21] Oregon Department of Consumer and Business Services (2024a). This position was further strengthened in the final ruling in Oregon Department of Consumer and Business Services (2024b).
[22] Coleman et al. (2022, p. S136).

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guidelines are designed to serve multiple purposes, ranging from clinical care to political advocacy.

Published in 2022, SOC-8 marked WPATH's first attempt to develop guidelines that were "evidence-based" and aimed to meet higher methodological standards through reliance on systematic reviews (SRs) of evidence.[23] The previous version, SOC-7, published in 2011 and described in Chapter 4, under which PMT began rapidly to accelerate, did not rely on SRs. Instead, its recommendations were based on "cultural shifts" and other factors.[24]

In pursuit of its goal to develop an evidence-based guideline, WPATH entered into a contractual agreement with the Evidence-Based Practice Center (EPC) at Johns Hopkins University (JHU), tasking JHU experts with conducting SRs and serving as methodological advisors to ensure a trustworthy guideline development process.[25] Given the sharp increase in the numbers of adolescents seeking PMT, and the rapid growth of pediatric gender clinics and PMT providers in the U.S., WPATH recognized the need to develop a robust adolescent section, acknowledging that "the Adolescent chapter is going to be one of the most scrutinized chapters in the entire standards of care."[26]

As the process of guideline development began, WPATH focused on two cornerstone issues for PMT: the evidence regarding the effectiveness of endocrine interventions in treating GD, and the evidence that adolescents have the capacity to consent to such treatments.

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[23] See Sinai (2022): "The World Professional Association for Transgender Health (WPATH) Standards of Care Version 7 (SOC7) are not evidence-based. The WPATH website clearly states that SOC8 is the first version being developed using an evidence-based approach."
[24] The prior version, SOC-7, stated that its recommendations were "based upon significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for transsexual, transgender, and gender nonconforming people beyond hormone therapy and surgery" (Coleman et al., 2012, p. 166).
[25] Coleman et al. (2022, pp. S248-S249); Karen Robinson is named as the EPC lead and listed as a member of the SOC-8 Guideline Steering Committee.
[26] Boe v. Marshall, No. 2:22-cv-00184: 560-18 (2024, p. 42).

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10.2.1 Hope for evidence of effectiveness

At the outset of its collaboration with JHU's EPC team, WPATH leadership expressed confidence that an SR would yield "evidence-based statements" supporting both the benefits of PMT interventions and the capacity of adolescents to consent to them. SOC-8 Adolescent chapter co-chair Scott Leibowitz wrote:

> We are a unique chapter when it comes to the evidence based review because we do feel that there is a justification to do a literature review on what we postulate will be evidence based statements about the interventions (even though we expect the evidence to be graded low). Essentially the literature reviews on some of our statements—as we plan on submitting once I edit them to incorporate the feedback from our workgroup—are important for the following reasons:
>
> - Studies that demonstrate the psychological effectiveness of some of the interventions (blockers, hormones) in adolescence all included cohorts who went through a rather rigorous psychological assessment. We would like to talk this through as a group because it's a very important point.
> - There is also literature on adolescent decision making and capacity to make informed decisions that carry lifelong ramifications. Since our chapter is a new chapter for the standards of care, and it focuses in on a developmental age group/assessment, (as opposed to other chapters that are more intervention specific), we are going to want to justify certain statements with graded evidence in terms of looking at the literature on *decision making in the developmental cohort (adolescence)* in general.[27]

The JHU evidence evaluation team was presented with the expectation that their appraisal would support the "gender-affirming" medical approach WPATH had been advancing for over a decade. The original plan was for SOC-8 recommendations—asserting that treatment effects are beneficial and that adolescents possess sufficient capacity to consent to medical interventions—to be labeled "evidence-based," even if

[27] Boe v. Marshall, No. 2:22-cv-00184: 560-18 (2024, pp. 43-44).

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the quality of the evidence was low.[28] However, the evidence evaluation challenged WPATH's expectations on both fronts: adolescent capacity to consent, and the benefits of PMT overall.

10.2.2 Adolescent capacity to consent

In response to a request from JHU, Annelou de Vries, the leading Dutch developer of PMT and a co-chair of SOC-8's Adolescent chapter section, supplied the JHU team with publications she believed demonstrate adolescent competence to consent to PMT.[29] Upon reviewing these publications, however, the JHU team informed WPATH that they provided, at best, "limited indirect evidence" and were insufficient to support a statement asserting that adolescents possess the capacity to consent.[30]

Following the JHU team's findings, WPATH abandoned its original plan to base its claim about adolescent capacity to consent on evidence. Instead, the Adolescent chapter of SOC-8 features a section on consent that stresses the importance of careful assessment but cites the same studies that JHU had deemed insufficient to answer the question of competence. The section also features a discussion about the "unique situations in which an adolescent minor is consenting for their own treatment without parental permission."[31]

The section fails to acknowledge the dearth of reliable information about whether adolescents in a state of clinical distress can meaningfully consent to drastic interventions—with many known and some unknown risks—in the absence of

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[28] From a WPATH internal email exchange related to SOC-8: "Adolescent medical decision making literature is something that the Johns Hopkins team is able to help out in terms of a literature review and grading" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 116); for discussion of grading recommendations, see Chapter 9.

[29] The primary investigator of the Dutch Protocol and WPATH Adolescent chapter co-lead (de Vries) provided the relevant literature on adolescent consent for JHU evaluation, writing: "some articles on decision making in teens; these are review articles, but show that there is some evidence. I think we need this sort of evidence base on decision making capacity in adolescents, regarding medical affirming treatment" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 106).

[30] The JHU response to WPATH regarding the literature on adolescent consent to PMT stated, "The articles forwarded provide limited indirect evidence for this question. Please let me know if I missed something" (Boe v. Marshall, No. 2:22-cv-00184: 560-18, 2024, p. 106).

[31] Coleman et al. (2022, pp. S61, Section 6.12.c).

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demonstrable physical disease and without credible knowledge of their likely future identity trajectory.

The ethical challenges of obtaining informed consent from adolescents regarding the procedures that are expected to threaten their fertility is illustrated by a candid comment from a WPATH physician, who observed, “it’s always a good theory that you talk about fertility preservation with a 14-year-old, but I know I’m talking to a blank wall,” adding, “they’d be like, ew, kids, babies, gross.”[32]

10.2.3 Treatment effects

In contrast to WPATH’s early abandonment of efforts to evaluate minors' capacity to consent, SRs assessing the treatment effects of puberty blockers (PBs), cross-sex hormones (CSH), and surgeries were completed by the JHU team. As the following sections in this chapter detail, WPATH perceived the JHU evidence appraisals as unfavorable to its goals of promoting broad access to these interventions for minors. In response, WPATH leadership moved to suppress the findings, barring the JHU evidence evaluation team from publishing its results.

The Adolescent chapter does not disclose that the SR regarding the effects of PMT had, in fact, been conducted. Instead, the chapter claims that SRs are not feasible:

> Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible.[33]

Ultimately, SOC-8 recommended that adolescents wishing to undergo PMT be provided with PBs, CSH, and surgery. The recommendations are couched in cautious-sounding language, stating that GD should be “sustained over time,” particularly before administering CSH. However, no clear standard is set; the only guidance offered is the vague and clinically meaningless phrase “several years, leaving critical decisions open to broad and subjective interpretation”:

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[32] Hughes (2024, p. 12).
[33] Coleman et al. (2022, p. S46).

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> Given potential shifts in gender-related experiences and needs during adolescence, it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones or surgeries.[34]

As the following sections describe, the recommendations were deliberately crafted to allow any "willing" medical provider to prescribe hormones or perform surgeries on minors, even those with significant co-occurring mental health conditions.

10.3 The process of creating SOC-8

The creation of trustworthy, evidence-based guidelines requires first assembling a guideline development group (GDG) that is free from conflicts of interest (COI) or, at minimum, where COIs are transparently disclosed and rigorously managed. Only after this foundation is established should SRs proceed, addressing pre-specified guideline questions. Finally, recommendations should be based on SRs of evidence and should consider additional factors, with the aim of improving healthcare quality for individual patients and improving public health and access to care.

Although WPATH originally embarked on an evidence-based guideline development process, internal documents reveal significant deviations from internationally recognized clinical guideline development standards established by organizations such as the National Academy of Medicine[35] (NAM) and the World Health Organization (WHO).[36] These serious deviations from established standards meant that the GDG could not fulfill its promise of producing credible, evidence-based guidelines.

[34] Coleman et al. (2022, p. S60).
[35] Graham et al. (2011), published under its previous name, Institute of Medicine (IOM).
[36] SOC-8's reference to WHO's International Classification of Diseases (ICD) appears to have intended to be WHO's *Handbook for Guideline Development*, 2nd Edition. See Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 204).

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10.3.1 Conflicts of interest management

Managing COIs—both financial[37] and intellectual[38]—is essential for producing trustworthy clinical practice guidelines. Intellectual conflicts may even surpass financial ones in their influence,[39] especially when guidelines rely heavily on expert consensus. The selection of the GDG[40] chair plays a pivotal role in ensuring the integrity of clinical guideline development.[41] WHO recommends selecting a guideline chair who is free of significant conflicts and neutral between differing perspectives.[42] NAM advises using "unconflicted methodologists"[43] to lead recommendation development, working alongside clinical experts as advisors rather than panel members.[44] Both NAM and WHO stress that conflicted members should constitute no more than a minority of any GDG, emphasizing ongoing COI management throughout the entire guideline development process.[45] In 2022, the Endocrine Society adopted NAM's recommendations, prioritizing reduced conflicts even if it limits expert involvement.[46]

When the principal investigator of the JHU EPC team became involved in the SOC-8 process, she observed that they "would expect many, if not most, SOC8 members to have competing interests."[47] SOC-8's final COI statement reads as follows:

> Conflict of interests [sic] were reviewed as part of the selection process for committee members and at the end of the process before publication. No conflicts of interest were deemed significant or consequential.[48]

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[37] The WHO defines financial COI as any "paid work, consulting income or honoraria and travel stipends; support for research, including direct monetary contributions or donations of equipment, laboratory space, etc.;" "that is related to, or could be affected by, the outcome" of the guideline development process (World Health Organization, 2014, p. 63).
[38] NAM and WHO define intellectual COIs relevant to clinical practice guideline development as "academic activities that create the potential for an attachment to a specific point of view that could unduly affect an individual's judgment about a specific recommendation" (Guyatt, 2010, p. 739).
[39] Guyatt et al. (2015, p. 540).
[40] SOC-8's GDG comprised a guidelines steering committee with a chair and two co-chairs, who in turn appointed 26 chapter leads, 77 chapter members, and 16 stakeholders.
[41] Graham et al. (2011, p. 87).
[42] World Health Organization (2014, p. 61).
[43] Graham et al. (2011, pp. 81-82).
[44] World Health Organization (2014, p. 82).
[45] Graham et al. (2011, p. 7).
[46] McCartney et al. (2022).
[47] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 2).
[48] Coleman et al. (2022, p. S177).

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Based in part on correspondence between WPATH and the EPC team during the development of SOC-8, there are serious questions regarding the accuracy of this statement.

SOC-8 GDG members, including Chair Eli Coleman, had unmanaged financial and/or non-financial COIs that were plausibly "significant or consequential." Coleman had both financial and non-financial interests in the topic. He was the lead author of SOC-7[49] and had coauthored academic publications in support of expanded access to medical transition.[50] Using WHO criteria, his professional activities and academic profile, which were closely aligned with advancing medical transition, likely constitute both intellectual and financial COIs.[51]

Additionally, Coleman's academic work was supported with funding from the Tawani Foundation, chaired by Jennifer Pritzker, a philanthropist and advocate for transgender issues.[52] The foundation funded a research center at the University of Minnesota, and Coleman played a significant role in its development. Public statements confirm that the Tawani Foundation also funded the majority of the out-of-pocket costs associated with SOC-8's development.[53]

With Coleman as chair of the GDG, the importance of managing COIs appears to have been consistently misunderstood or undervalued. Coleman admitted under deposition that disclosure statements were not presented until at least six months *after* members had already been selected.[54] In a December 21 (2018) email sent to the SOC-8 education committee, EPC's Karen Robinson stated, "Disclosure, and any necessary

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[49] Coleman et al. (2012).
[50] Eisenberg et al. (2020); Rider et al. (2018).
[51] "Financial and nonfinancial interests can overlap. For example, intellectual interests related to career advancement obviously have a monetary component. Examples of roles or positions that might interfere with the objective assessment of a body of evidence include: prior publication of a study or SR that is part of the evidence base under consideration in the guideline; prior public declaration of a firm opinion or position, as in public testimony during a regulatory or judicial process, or in an editorial in a journal; or professional or personal affiliation with an organization advocating for products or services related to the subject of the guideline" (World Health Organization, 2014, p. 63).
[52] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 239).
[53] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 239).
[54] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, pp. 219-222).

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management of potential conflicts, should take place prior to the selection of guideline members. Unfortunately, this was not done here."[55]

For former WPATH president Marci Bowers, who played an influential role in shaping SOC-8, the idea of appointing an unconflicted professional to lead the project was outright nonsensical.[56] Another SOC-8 member wrote to the EPC to explain that "unlike other medical guidelines, trans health care is a socially and politically charged issue," and strongly recommended that the JHU team therefore rewrite their COI forms for this particular guideline.[57] Part of the justification for different treatment was that COIs were so prevalent within the GDG that it would be "impossible" for the group to be free of them.[58] One submitted COI form, on the question of non-financial interests, recorded that "everyone involved in the SOC process has a non-financial interest."[59]

Although WPATH later claimed that none of the SOC-8 members' COIs were significant or consequential, several members clearly met the internationally recognized definitions of COIs established by the NAM and WHO—the kind of conflicts known to bias clinical practice guidelines and erode their trustworthiness. For instance, SOC-8 chapter leaders Dan Karasic and Loren Schechter were paid expert witnesses in legal cases directly related to medical transition before and during the SOC-8 development process,[60] a role NAM explicitly identifies as a COI.[61] Schechter, co-chair of the surgery chapter and a plastic surgeon who derives part of his livelihood from performing gender

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[55] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 2).
[56] Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024, p. 121).
[57] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 3).
[58] Boe v. Marshall, No. 2:22-cv-00184: 560-16 (2024, p. 3).
[59] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 8).
[60] Schechter provided testimony for Dekker v. Weida, No. 4:22-cv-00325 (N.D. Fla. filed Sept. 7, 2022); Willis v. Flagg, No. 17-cv-02754 (N.D. Ill. filed Apr. 10, 2017); Bruce v. South Dakota, No. 3:17-cv-03023-RAL (D.S.D. filed Oct. 5, 2017); Boyden v. Conlin, No. 17-cv-00264-WMC (W.D. Wis. filed Apr. 6, 2017); Kadel v. Folwell, No. 1:19-cv-00272 (M.D.N.C. filed Mar. 11, 2019); Toomey v. State of Arizona, No. 4:19-cv-00035-RM-LAB (D. Ariz. filed Jan. 23, 2019); and Fain v. Crouch, No. 3:20-cv-00740 (S.D.W. Va. filed Nov. 12, 2020).

Karasic provided testimony for C.P. v. Blue Cross Blue Shield of Illinois, No. 3:20-cv-06145 (W.D. Wash. filed Nov. 24, 2020); Kadel v. Folwell, No. 1:19-cv-00272 (M.D.N.C. filed Mar. 11, 2019); Fain v. Crouch, No. 3:20-cv-00740 (S.D.W. Va. filed Nov. 12, 2020); Brandt v. Rutledge, No. 4:21-cv-00450 (E.D. Ark. filed May 25, 2021); K.C. v. Individual Members of the Indiana Medical Licensing Board, No. 1:23-cv-00595-JPH-KMB (S.D. Ind. filed Apr. 5, 2023); Dekker v. Weida, No. 4:22-cv-00325-RH-MAF (N.D. Fla. filed Sept. 7, 2022); and Doe v. Ladapo, No. 4:23-cv-00114-RH-MAF (N.D. Fla. filed Mar. 23, 2023).
[61] Graham et al. (2011, p. 79).

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transition surgeries, voiced concerns to fellow GDG members about openly acknowledging insufficient evidence, noting the potential impact this would have on two federal court cases in which he was serving as a paid expert witness.[62] Despite this clear overlap of financial interest and guideline content, SOC-8 chair Eli Coleman considered it "ethically justifiable" for members involved in active litigation to advocate for guideline changes that could strengthen their legal positions.[63]

WPATH's process not only permitted significant financial and intellectual COIs among GDG members. It also allowed the creation of substantial panel composition bias—a phenomenon known as "panel stacking." This occurs when GDGs predominantly consist of members sharing similar viewpoints or vested interests, thereby threatening the validity and trustworthiness of clinical guidelines. Experts in evidence-based medicine describe panel stacking as a major threat, emphasizing that it can profoundly reduce the credibility of recommendations, particularly when, as in pediatric gender medicine, the evidence is limited, contentious, or unsystematically reviewed.[64]

Kepp et al. note that "recruitment specifically because of expressed viewpoints and allegiance is a recognized major problem for guideline development." In their own example from an appraisal of a consensus statement on COVID-19 recommendations, the authors characterized a panel with a "35% (or more) prevalence" of advocates of COVID-19 elimination ("Zero-COVID") as "extreme."[65] For SOC-8, WPATH required that all members of the GDG be "WPATH Full Members in good standing."[66] Marci Bowers explicitly stated that it was important for participants to be "advocates" for WPATH's "gender-affirming" approach to be considered for the GDG,[67] further underscoring the GDG's bias.

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[62] Boe v. Marshall, No. 2:22-cv-00184: 700-13 (2024, p. 56).
[63] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 158).
[64] Kepp et al. (2024, p. 5).
[65] Kepp et al. (2024, p. 6).
[66] Coleman et al. (2022, p. 248).
[67] Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024, pp. 119-120). This response came after it was pointed out to Bowers that selecting GDG members based on their "advocacy" for medical treatment was in "tension" with selecting GDG members who could be "impartial arbiters" on the evidence for those treatments.

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Internal documents revealed that WPATH actively monitored SOC-8 members and disciplined those who publicly questioned WPATH's "gender-affirming" approach, creating an environment that discouraged critical dialogue. Psychologist Laura Edwards-Leeper, chair of WPATH's Child and Adolescent Committee and a member of both the child and adolescent SOC-8 committees, co-authored a *Washington Post* opinion piece with Erica Anderson,[68] a psychologist and then-president of WPATH's U.S. chapter, arguing that WPATH "largely seems to be a dangerous echo chamber" resistant to constructive criticism. Edwards-Leeper privately warned WPATH leaders that their intolerance for dissent and attempts to "muzzle clinicians" risked damaging the organization's credibility among professionals, patients, and educated parents.[69] Anderson faced a formal reprimand[70] after criticizing (with Bowers) the quality and consistency of care provided under the SOC framework.[71]

This combination of poorly managed COIs and restrictive membership practices significantly undermines the credibility and scientific integrity of SOC-8 as a clinical practice guideline. The GDG's handling of the SRs of evidence WPATH commissioned for development of SOC-8 further highlights the serious threat to clinical integrity that plagued the guideline development process.

10.3.2 Suppression of evidence

NAM stipulates that trustworthy guidelines must be based on SRs of existing evidence. SOC-8 was promoted as the first to be "evidence-based,"[72] with its chair claiming it followed "the most rigorous protocol in the world to ensure these standards reflect scientific evidence."[73] The Methodology section states that SOC-8 "incorporated the recommendations on clinical practice guideline development set forth by the National

[68] Edwards-Leeper & Anderson (2021).
[69] Boe v. Marshall, No. 2:22-cv-00184: 560-26 (2024, p. 153).
[70] Boe v. Marshall, No. 2:22-cv-00184: 560-26 (2024, pp. 114-115).
[71] Shrier (2021b).
[72] "This version of the Standards of Care is the first to be developed using an evidence-based approach" (Radix, n.d., p. 13).
[73] Coleman (2023).

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Academies of Medicine and the World Health Organization, which addressed transparency, conflict-of-interest policy, committee composition, and group process."[74]

In 2018, as part of its development of a new clinical guideline, WPATH commissioned more than a dozen SRs from the EPC at JHU. SRs were completed and handed over to WPATH for its chapters on assessment, primary care, endocrinology, surgery, reproductive medicine, and voice therapy.[75]

These expert reviews had the potential to advance current understanding of the state of the evidence, but their usefulness cannot be evaluated because WPATH successfully suppressed them. In an email exchange from August 2020, a senior author from EPC, writing to the Agency for Healthcare Research and Quality (AHRQ),[76] stated that their SRs "found little to no evidence about children and adolescents" and that WPATH had been "trying to restrict our [JHU's] ability to publish."[77]

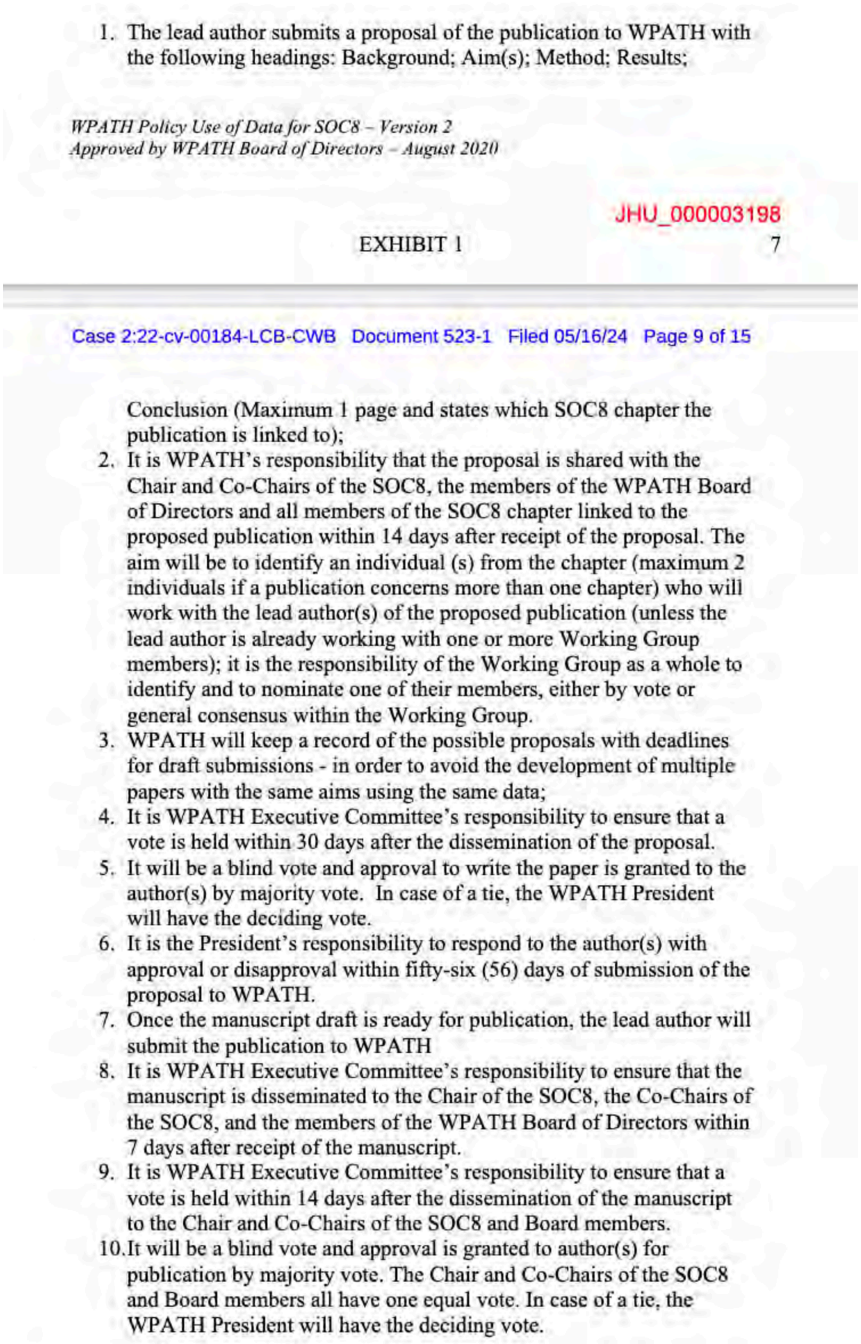
In a memo to all SOC-8 working group members, WPATH leadership reported that they "were caught on the wrong foot" when they learned that JHU wanted to publish reviews that would likely undermine WPATH's "gender-affirming" approach.[78] Despite their initial resistance, the JHU researchers ultimately capitulated to WPATH's new terms, allowing SOC-8's chair, co-chairs, a handpicked chapter member, and WPATH's Board of Directors to pre-approve manuscript content before any independent drafting could occur. Under WPATH's imposed process, researchers were required to submit a proposal form outlining the planned results and conclusions before drafting even began—and again once the manuscript was ready for publication—ensuring that leadership could steer findings to align with predetermined agendas rather than allowing an independent, evidence-driven process.[79]

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[74] Coleman et al. (2022, p. S247).
[75] Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 38).
[76] A unit of the U.S. Department of Health and Human Services.
[77] Boe v. Marshall, No. 2:22-cv-00184: 560-23 (2024, p. 23) The AHRQ official acknowledged the message: "Knowing that there is little/no evidence about children and adolescents is helpful." Nevertheless, two years later HHS released a memo in which it asserted that "[r]esearch demonstrates that gender-affirming care improves the mental health and overall well-being of gender diverse children and adolescents" (OPA: Office of Population Affairs, n.d.).
[78] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, p. 14).
[79] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, p. 8).

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Figure 10.1 WPATH approval process for manuscripts



1. The lead author submits a proposal of the publication to WPATH with the following headings: Background; Aim(s); Method; Results;

WPATH Policy Use of Data for SOC8 – Version 2
Approved by WPATH Board of Directors – August 2020

JHU_000003198

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Conclusion (Maximum 1 page and states which SOC8 chapter the publication is linked to);

2. It is WPATH's responsibility that the proposal is shared with the Chair and Co-Chairs of the SOC8, the members of the WPATH Board of Directors and all members of the SOC8 chapter linked to the proposed publication within 14 days after receipt of the proposal. The aim will be to identify an individual (s) from the chapter (maximum 2 individuals if a publication concerns more than one chapter) who will work with the lead author(s) of the proposed publication (unless the lead author is already working with one or more Working Group members); it is the responsibility of the Working Group as a whole to identify and to nominate one of their members, either by vote or general consensus within the Working Group.
3. WPATH will keep a record of the possible proposals with deadlines for draft submissions - in order to avoid the development of multiple papers with the same aims using the same data;
4. It is WPATH Executive Committee's responsibility to ensure that a vote is held within 30 days after the dissemination of the proposal.
5. It will be a blind vote and approval to write the paper is granted to the author(s) by majority vote. In case of a tie, the WPATH President will have the deciding vote.
6. It is the President's responsibility to respond to the author(s) with approval or disapproval within fifty-six (56) days of submission of the proposal to WPATH.
7. Once the manuscript draft is ready for publication, the lead author will submit the publication to WPATH
8. It is WPATH Executive Committee's responsibility to ensure that the manuscript is disseminated to the Chair of the SOC8, the Co-Chairs of the SOC8, and the members of the WPATH Board of Directors within 7 days after receipt of the manuscript.
9. It is WPATH Executive Committee's responsibility to ensure that a vote is held within 14 days after the dissemination of the manuscript to the Chair and Co-Chairs of the SOC8 and Board members.
10. It will be a blind vote and approval is granted to author(s) for publication by majority vote. The Chair and Co-Chairs of the SOC8 and Board members all have one equal vote. In case of a tie, the WPATH President will have the deciding vote.

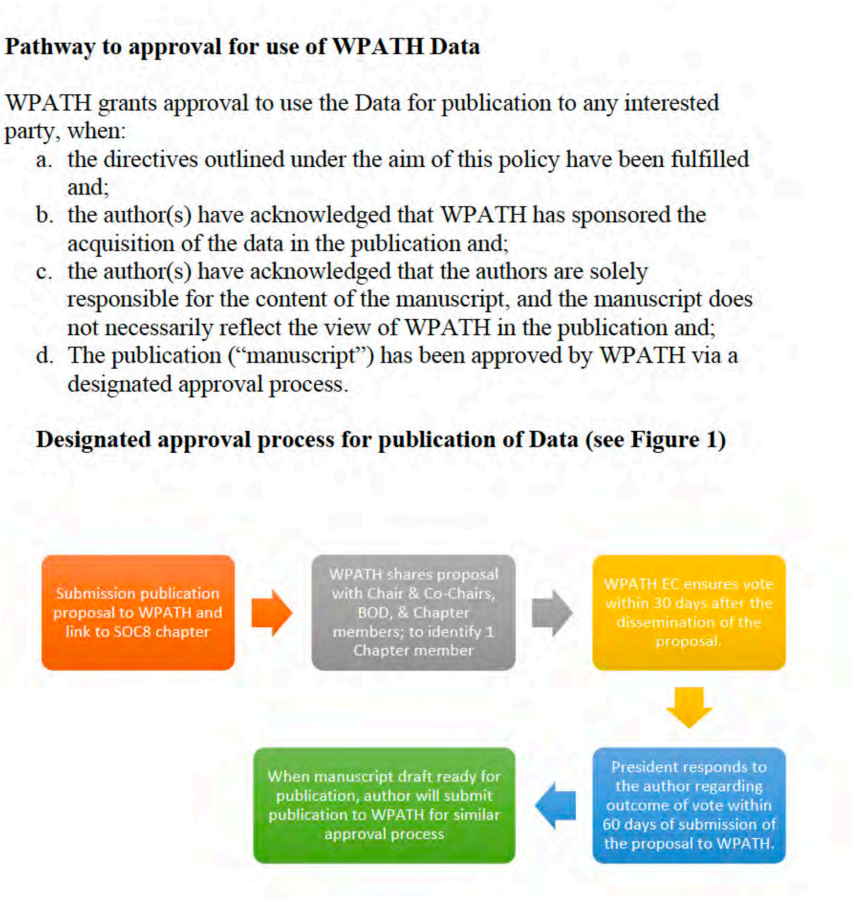
Among the terms required for gaining WPATH approval was ensuring that the SRs' findings supported, or at least did not undermine, WPATH's goal of promoting greater access to medical interventions. Additionally, the SOC-8 chapter's working group leader or an appointed representative or the SOC-8 chair/co-chairs and at least one person

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who identified as transgender were required to oversee and approve the manuscript's design, drafting, and final content.[80]

Despite this close involvement and editorial control, all final documents were required to include a statement to the effect that "the authors are solely responsible for the content of the manuscript, and the manuscript does not necessarily reflect the view of WPATH."[81]

Figure 10.2 Pathway to manuscript approval



WPATH's stated goal was to "ensure that publication does not negatively affect the provision of transgender healthcare in the broadest sense."[82] Following this

[80] Boe v. Marshall, No. 2:22-cv-00184: 523-1 (2024, pp. 5-6).
[81] Boe v. Marshall, No. 2:22-cv-00184: 523-1 Exhibit 1 (n.d., p. 8)
[82] Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 92).

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renegotiation, only one SR was published.[83] Internal WPATH documents reveal that Baker et al. complied with all the mandatory steps of WPATH's updated approval policy—from approving the conclusions before the manuscript was drafted to ensuring extensive WPATH engagement in the process and obtaining the final approvals. The Baker et al. SR was published with the mandatory disclaimer that "WPATH had no role in study design, data collection, analysis, interpretation, or drafting" of the SR, despite the checklist clearly recording that WPATH had engaged in the design, drafting, and final approval of the article.[84]

[83] Baker et al. (2021). Of note, only one other systematic review was published (Wilson et al., 2020), but its publication predates WPATH's updated policy.

[84] Wilson et al. (2020) includes the same statement but was published prior to the new agreement, so it is not possible to determine the degree to which WPATH influenced its drafting and design.

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Figure 10.3 Checklist for Baker et al.[85]

Checklist for JHU SOC8 systematic review papers

Title of Paper: Hormone Therapy, Mental Health, and Quality of Life among Transgender People: A Systematic Review

Supporting Chapter: initial question part of questions from Hormone Chapter

Proposed Authors: Kellan E. Baker, MPH, Lisa M. Wilson, ScM, Ritu Sharma, BSc, Vadim Dukhanin, MD, MHS, Kristen McArthur, BA, Karen A. Robinson, PhD

Acknowledged Authors: None

Yes or No	This paper provides data that advances the knowledge in the field of transgender health in a positive way
Yes or No	This paper will be published in a reputable, academic, peer-reviewed journal
	Journal proposed for first submission The Lancet Diabetes & Endocrinology
Yes or No	Involves the work group leader of the chapter or alternatively a designated representative of that specific SOC8 Chapter in the design, drafting of the article and final approval of the article
	Name of persons involved *chapter members provided original list of questions for reviews*
Yes or No	Involves at least one member of the transgender community in the design, drafting of the article and final approval of the article *chapter members provided original list of questions for reviews*
	Name of person if not open about trans status, if not open about trans status then enter N/A
Yes or No	Adheres to the WPATH language policy

WPATH's policy appears to have effectively blocked the planned[86] and completed[87] research—including critical evidence appraisals—from being developed into publishable manuscripts. As a result, important SRs addressing the safety of PBs, CSH, and surgery for adolescents were suppressed, keeping key findings out of the scientific record and shielding them from professional scrutiny.[88]

[85] Source: Boe v. Marshall, No. 2:22-cv-00184: 560-17 (2024, p. 41).
[86] Robinson, Sharma, Baker, et al. (2019); Robinson, Sharma, Wilson, et al. (2019); Sharma et al. (2018).
[87] In total, only 2 systematic reviews were published, and only one (Baker et al., 2021) followed the policy update.
[88] See Chapter 7 for a more extensive discussion.

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As established in Section 10.3.1, members of the GDG were committed to PMT and believed their positions to be grounded in evidence. Indeed, a central goal for SOC-8 was to deliver an updated version explicitly supported by robust evidence. However, once the GDG began working with methodological experts and applying evidence-based medicine (EBM) standards, it quickly became clear that their understanding of what constituted "strong evidence" was fundamentally at odds with established scientific criteria. Evidence that the GDG previously regarded as strong or compelling was frequently downgraded under EBM standards to low or very low quality, revealing a troubling gap between WPATH members' beliefs about evidence and the actual rigor of the underlying research. This process is clearly articulated by SOC-8 Chair Eli Coleman under points 6 ("Expert Consultation in Guideline Development") and 7 ("Research Agenda") of a 12-point draft following SOC-8's publication:

> As we faced challenges of developing and revising the methodology of SOC 8, we had to rely on Johns Hopkins, which while some degree helpful, was very constraining. We were able to consult with other experts and was [sic] able to learn that there were other ways of developing guidelines that were probably more appropriate for the state of our science. As a result, our methodology evolved and was improved—however, we were not able to be as systematic as we could have been … Now that we have reviewed the evidence, we are painfully aware of the gaps in the literature and the kinds of research that are needed to support our recommendations and strengthened [sic] the level of evidence in support of them.[89]

When confronted with SRs that did not adequately support its positions—particularly given their stated legal and advocacy concerns (see next section)—the GDG chose not to adjust its views but to find an alternative methodology to support its recommendations. As SOC-8 GDG Co-Chair Jon Arcelus explained in an email to other GDG members, "[t]here are many recommendations in the SOC that don't have direct

[89] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, pp. 8-9).

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evidence (most of the direct evidence is in the hormone chapter) but they have background evidence. This is why we have Delphi."[90]

A consensus-building process, Delphi is not a substitute for evidence-based recommendations but rather a method for GDGs to reconcile disagreement in the interpretation of SRs, or in deciding how evidence should inform treatment recommendations.[91] Guidelines that are not based on SRs inadvertently risk promoting suboptimal or even harmful care. This is why guidelines that rely only on consensus are not considered trustworthy.[92]

10.3.3 Redefinition of medical necessity

SOC-8 makes a strong recommendation that PBs, CSH, and surgery be considered "medically necessary" for eligible adolescents:

> We recommend health care systems should provide medically necessary gender affirming psychological, medical and surgical treatments for trans and gender diverse children, adolescents, and adults."[93]

The development of the "medical necessity" statement in SOC-8 starkly illustrates how many WPATH contributors prioritized goals other than ensuring the highest-quality care for adolescents with GD. A good example is WPATH's rewording of patient "wishes" as patient "needs" with the intent to frame them as "medically necessary." At first, the statement described the desired interventions as "wishes":

> There is strong evidence demonstrating the benefits in quality of life and wellbeing of gender affirming treatments, including endocrine and surgical procedures, properly indicated and performed as outlined by the Standards of Care (Version 8), in TGD people *wishing these treatments.*[94]

However, the final SOC-8 statement reads:

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[90] Boe v. Marshall, No. 2:22-cv-00184: 560-37 (2024, p. 101). Delphi is a structured consensus-building method in which a GDG iteratively reviews and rates statements to achieve agreement; SOC-8 utilized a 75% threshold for consensus.
[91] Djulbegovic & Guyatt (2019).
[92] Lima, Tangamornsuksan et al. (2023).
[93] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 32).
[94] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 38).

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> There is strong evidence demonstrating the benefits in quality of life and well-being of gender-affirming treatments, including endocrine and surgical procedures, properly indicated and performed as outlined by the Standards of Care (Version 8), in TGD people *in need of these treatments*.[95]

This consequential textual change was the result of WPATH members recognizing the implications of their word choice for insurance and legal contexts. The change was made based on the following request during the drafting phase:

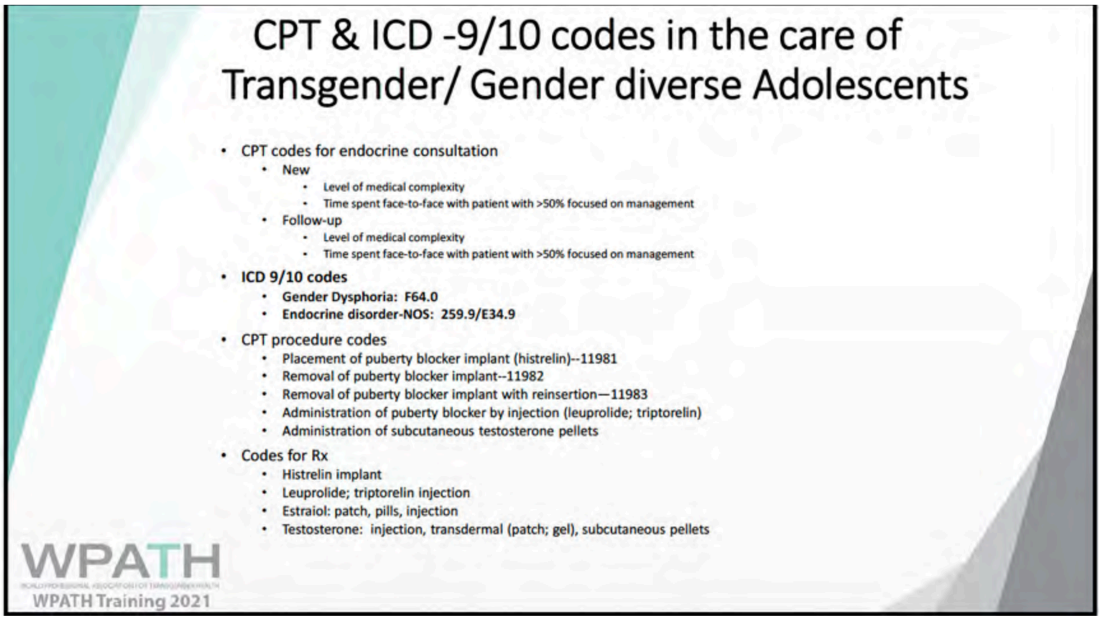
> Thank you, I also very much like this statement and the supporting write-up. There is one word, though, in the middle (on the right side of the page) of the last paragraph on the first page of the document: “wishing.” This word gives me pause, and perhaps I am being too sensitive, but one of the biggest obstacles trans people experience in getting support for coverage of our care is that we are told “you can't always get what you want" and “wishing does not make it so." Wishing makes the needed care seem optional, and we are often told we are imagining that we are not who we are and we should just suck it up. Would it be possible or advisable or prudent to replace “wishing” with “in need of” here? Thanks for your consideration, and for your great work on this.[96]

This was accompanied by WPATH’s explicit instruction to providers to use the “Endocrine Disorder” diagnosis as an alternative for the mental health diagnosis of GD[97]:

[95] Coleman et al. (2022, p. 18, emphasis added).
[96] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 28).
[97] Rosenthal (2021b, Slide 11).

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Figure 10.4 ICD codes for TGD adolescents



Together, these internal WPATH communications reveal that the "medical necessity" framing in SOC-8 was constructed to remove key safeguarding criteria and make patient desires central to treatment decisions. This was confirmed by another GDG member who candidly observed that the guidelines exist to allow any “goodwilling” clinician to meet patients’ wishes—however medically inappropriate they may be.

> I think it is clear as hell that the SOC8 refers to the necessity of treatment (in its broadest sense) of TGD people who pursue treatment (in its broadest sense) for their gender dysphoria (small "d": because it refers to the symptom of distress - which is a very broad category and one that any 'goodwilling' clinician can use for this purpose (or: in the unescapable medical lingo we, as physicians arc stuck with: those who fulfil a diagnosis of Gender Dysphoria and Gender Incongruence as per APA/WHO).[98]

The request to substitute “wish” for “need” and emphasize "medical necessity” was welcomed by WPATH leaders, who responded that the assertion of medical necessity

[98] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 37).

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would influence the “obtuse and unhealthy” U.S. healthcare system by compelling insurance coverage through the courts:

> Thank you for putting this together; you've done a great job with this. Indeed, it is important that such a statement is part of the actual SOC. And, indeed, the original Medical Necessity Statement was specific to the U.S. because this was where we were experiencing the problem with our obtuse and unhealthy system of healthcare "coverage" and we needed a tool for our attorneys to use in defending access to care here. I have long wanted this (and many of our other policy statements) to become part of the SOC because that gives them greater force.[99]

GDG Chair Eli Coleman stated that while WPATH had no definition of “medically necessary,” he understood this to be primarily a term used by insurance companies to determine which conditions or procedures to cover.[100] The SOC-8 legal and political goals are discussed in the next section.

10.3.4 Legal and political considerations

Internal documents reveal that SOC-8 authors manipulated guideline language with the explicit aim of shaping court rulings, legislative actions, and insurance coverage decisions, revealing a clear departure from the principles of unbiased, evidence-driven clinical guideline development. For example, contributors to the “Institutional Environments” chapter disclosed that “social justice lawyers” had advised them against rigorous evidence reviews, stating that such reviews might reveal limited or insufficient evidence, placing them “in an untenable position in terms of affecting policy or winning lawsuits.”[101] As discussed above, a key motivation for including a “medical necessity” statement in the guidelines was described as a strategic move to provide “a tool for our attorneys to use in defending access to care” within the U.S. legal context.[102]

[99] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, pp. 33-34)
[100] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, p. 166).
[101] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 3).
[102] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, pp. 33-34).

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Schechter also expressed concerns about language, cautioning colleagues that terms such as “insufficient evidence” and “limited data” could strengthen legal arguments claiming medical interventions are experimental, and noting his own role as an expert witness in related federal cases.[103] Karasic, chair of the SOC-8 Mental Health chapter, highlighted the critical legal implications of defining treatments for adolescents as “medically necessary,” stating that this determination affects court cases, policy decisions, and insurance coverage.[104] Elsewhere, Karasic emphasized the urgency of addressing this issue clearly in SOC-8 given multiple ongoing lawsuits—some potentially reaching the Supreme Court of the United States—concerning whether medical gender interventions are “medically necessary” or “experimental or cosmetic.”[105]

One internal communication explicitly advised against using specific numerical age guidelines for treatments, stating, “I would avoid absolute numbers [for ages] that can be taken out of context or used in court” because they would disadvantage the people “we are trying to advocate for.”[106] Elsewhere, editorial input was provided specifically to help “Chase” [presumably a reference to Chase Strangio, Deputy Director for Transgender Justice with the ACLU’s LGBT & HIV Project].[107] GDG Chair Coleman urged the group to adopt a stronger defensive stance, stating, “we need a more detailed defense that we can use ... in the many court cases that will be coming up … especially around adolescence.”[108] One contributor even acknowledged prioritizing political advocacy goals explicitly over scientific accuracy, stating that SOC-8 should “land in such a way as to have serious effect in the law and policy settings...even if the wording isn’t quite correct for people who have the background you and I have.”[109]

Further, the U.S. healthcare context was clearly a specific focus of the SOC-8 authors. Karasic (SOC-8 Mental Health chapter chair) wrote:

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[103] Boe v. Marshall, No. 2:22-cv-00184: 700-13 (2024, p. 56).
[104] Boe v. Marshall, No. 2:22-cv-00184: 560-24 (2024, p. 43).
[105] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 44).
[106] Boe v. Marshall, No. 2:22-cv-00184: 560-34 (2024, p. 25).
[107] Boe v. Marshall, No. 2:22-cv-00184: 591-24 (2024, p. 9).
[108] Boe v. Marshall, No. 2:22-cv-00184: 700-8 (2024, p. 40).
[109] Boe v. Marshall, No. 2:22-cv-00184: 560-34 (2024, p. 25).

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> But there are elements of the Medical Necessity statement that are critical to insurance reimbursement and access to care in the U.S., though not so in every country, and these should have a place somewhere in SOC 8. If WPATH SOC 8 fails to adequately support access to trans care in the U.S. by overgeneralizing wording, it may be globally applicable, but it is not globally useful, insofar as the U.S. is part of the globe. There should be room in SOC 8 to address concerns of national health systems, or other non-reimbursement focused systems without making SOC 8 less useful to U.S. trans care … Medical necessity is at the center of dozens of lawsuits in the U.S. right now over state actions to make trans care inaccessible, as well as being at the center of all reimbursement for trans care in the U.S. … it is critical that WPATH SOC 8 gets this right, which I think it does, currently."[110]

Incorporation of legal advocacy goals into guideline language, explicitly for purposes of influencing policy and litigation outcomes, conflicts sharply with accepted international standards emphasizing scientific rigor and impartiality.

Internal documents reveal that WPATH leadership was aware that the guidelines would be criticized due to the "continuing pressure in healthcare to provide evidence-based care." Coleman noted ongoing resistance from "academics and scientists who are naturally skeptical," "parents of youth who are caught in the middle of this controversy," and pressures arising from the "increasing number of regret cases and individuals who are vocal in their retransition process who are quick to blame clinicians for allowing themselves to transition despite an informed consent process."[111]

In response to anticipated criticism of SOC-8, Coleman drafted a "12-point strategic plan to advance gender-affirming care."[112] The plan acknowledged that all members of the GDG were "painfully aware that there are many gaps in research to back up our recommendations," and emphasized the importance of building consensus among

[110] Boe v. Marshall, No. 2:22-cv-00184: 700-10 (2024, p. 65).
[111] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, p. 5).
[112] Boe v. Marshall, No. 2:22-cv-00184: 700-18 (2024, p. 6).

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medical groups in support of SOC-8. Coleman observed that the endorsement of medical organizations "has been an extremely powerful argument" in "legal battles":[113]

> As we are facing so many legal battles over trans health care and rights, the statement that the SOC has so many endorsements has been an extremely powerful argument. We need to be able to get the support of these important organizations and know how to indicate their support accurately or this argument in these court cases could be challenged.[114]

10.4 Elimination of age minimums

The handling of minimum age recommendations for clinical interventions for adolescents in SOC-8 exemplifies what happens when guideline development is compromised by ideological beliefs, COIs, and disregard for established evidence standards.

Initially, SOC-8 included age minimums for certain interventions: 14 years for cross-sex hormones; 15 years for mastectomy; 16 years for breast augmentation and facial surgery; 17 years for metoidioplasty, orchiectomy, vaginoplasty, hysterectomy, and fronto-orbital remodeling; and 18 years for phalloplasty. In July 2022, WPATH faced significant pressure from Admiral Rachel Levine, the U.S. assistant secretary for health, whose office communicated concern that listing specific, minor ages would trigger restrictive legislative actions. Internally, some SOC-8 members expressed discomfort about acceding to pressures from the federal government. "I don't know how I feel about allowing U.S. politics to dictate international professional clinical guidelines that went through Delphi," said one SOC-8 co-chair.[115] Another complained that it "is not appropriate to take any feedback from a nonmedical professional seriously."[116] Despite these reservations, WPATH's apparent investment in securing endorsement from the

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[113] Boe v. Marshall, No. 2:22-cv-00184: 560-40 (2024, pp. 6-8). Of note, although SOC-7 is now outdated, it was SOC-7 that was responsible for establishing the "gender-affirming" medical approach in the U.S. and internationally. The email from the lead author of both SOC-7 and SOC-8, Coleman, discloses that despite the widespread narrative that SOC-7 had been endorsed by all medical organizations, no such endorsements ever occurred. Coleman said he had "no idea how it was ever said that so many medical organizations … endorsed SOC 7" (Boe v. Marshall, No. 2:22-cv-00184: 700-3, 2024, pp. 262-264).
[114] Boe v. Marshall, No. 2:22-cv-00184: 560-40 (2024, p. 8).
[115] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 33).
[116] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 27).

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Biden administration led it to agree to downgrade age guidelines from "recommendations" to "suggestions," thereby circumventing the original consensus process by making these changes without conducting a new round of validation.[117]

The issue of minimum ages resurfaced when the American Academy of Pediatrics (AAP) threatened to publicly oppose SOC-8 unless all age thresholds were eliminated—further exposing how political pressure, rather than scientific evidence or clinical judgment, dictated the final content of the guidelines.[118] Under pressure and facing open opposition from a key ally, WPATH leaders capitulated and agreed to eliminate minimum age criteria for all hormonal and surgical procedures (except phalloplasty). They did so despite acknowledging privately that the individuals within the AAP who were issuing the demand were very junior and lacked the authority or expertise to credibly dictate clinical standards.[119]

In the process of removing minimum ages, WPATH's president wrote that it was "disappointing that politics always trumps common sense and what is best for patients."[120] Another WPATH leader confided that the deletion of age minimums "is a balancing act between what I feel to be true and what we need to say."[121] SOC-8 Co-Chair Jon Arcelus said that removing ages would "make a joke of our methodology."[122]

The rushed, 11th-hour changes—made outside any formal or transparent guideline development process—resulted in SOC-8 initially being published with its original age recommendations still intact. Only after publication did WPATH scramble to issue a correction via an erratum in their official journal, the *International Journal of Transgender Health*, quietly removing age restrictions to align with political demands rather than clinical evidence.[123] The current, published version of SOC-8 states that all

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[117] Boe v. Marshall, No. 2:22-cv-00184: 700-3 (2024, pp. 292-295); Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 33). SOC-8's final round of Delphi processing was in January 2022 (Coleman et al., 2022, p. S251).
[118] Coleman explains that removing ages "led to them [i.e. AAP] formally not opposing the SOC. Yes this is highly confidential" (Boe v. Marshall, No. 2:22-cv-00184: 700-17, 2024, p. 153).
[119] Boe v. Marshall, No. 2:22-cv-00184: 700-16 (2024, p. 201).
[120] Boe v. Marshall, No. 2:22-cv-00184: 700-15 (2024, p. 26).
[121] Boe v. Marshall, No. 2:22-cv-00184: 700-6 (2024, p. 103).
[122] Boe v. Marshall, No. 2:22-cv-00184: 700-16 (2024, p. 110).
[123] Correction (2022).

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recommendations went through the Delphi process. However, Coleman later acknowledged that removal of age minimums did not go through Delphi.[124]

10.5 Continued reliance on SOC-8

It remains concerning that SOC-8 continues to exert substantial influence over U.S. healthcare. WPATH's misconduct during the development of SOC-8 was covered by major news outlets including the *New York Times*,[125] *Economist*,[126] *Boston Globe*,[127] *Fox News,*[128] and *National Review,*[129] as well as by the *BMJ*, a leading medical journal.[130] Despite these reports, with the exception of the American Society of Plastic Surgeons,[131] major American medical associations have not issued public statements addressing the concerns detailed in this chapter.

In an amicus brief submitted to the Supreme Court of the United States for the upcoming case *U.S. v. Skrmetti*,[132] the AAP and 21 other medical organizations describe SOC-8 as an "established, evidence-based clinical guideline." The brief does not address any of the concerns or revelations regarding the guidelines' development outlined in this chapter. Similarly, a group of 11 prominent "adolescent medicine specialists, pediatricians, clinicians, methodologists, professors, and researchers"—including professionals affiliated with the medical schools of Harvard University, Stanford University, and the University of Pennsylvania—asserts in a separate brief that SOC-8 has "all" the National Academy of Medicine's "hallmarks of reliability."[133]

The U.S. Department of Justice (DOJ) intervened in 2022 to challenge Alabama's age limit law in *Boe v. Marshall*, thereby becoming familiar with the subpoenaed documents from WPATH. Nevertheless, in August 2024—two months after the documents were unsealed—the DOJ in a merits brief filed in *U.S. v. Skrmetti* described WPATH as "the

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[124] Boe v. Marshall, No. 2:22-Cv-00184: 700-3 (2024, pp. 294-295).
[125] Ghorayshi (2024b).
[126] The Economist (2024).
[127] Selin Davis (2024b).
[128] Joseph (2024).
[129] Whelan (2024a).
[130] Block (2024a).
[131] Sapir (2024c).
[132] U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024, p. 8).
[133] U.S. v. Skrmetti (No. 23-477), Clinical Practice Guideline Experts, Amicus curiae brief (2024, p. 22).

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leading association of medical professionals treating transgender individuals" and asserted that "[t]he Nation's leading medical and mental health organizations recognize [SOC-8] as reflecting the accepted standard of care for treating gender dysphoria."[134]

[134] U.S. v. Skrmetti (No. 23-477), Brief for the petitioner (2024, p. 3).

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Chapter 11 Collapse of Medical Safeguarding

When children or adolescents develop feelings of severe discomfort with their sexed bodies, parents understandably worry and consult pediatricians or therapists for advice. These frontline clinicians in turn refer them to specialists, believing that this requires special expertise. Both parents and the clinicians they initially consult likely expect that those with expertise in "gender" will conduct a comprehensive evaluation to rule out other, perhaps more common causes of such feelings. They may further assume that puberty blockers (PBs), cross-sex hormones (CSH), and surgery are offered only in rare cases, when less invasive alternatives are ineffective, and after careful consideration of the patient's unique developmental needs as well as the profound uncertainties and risks of the treatments.

This chapter documents how the original Dutch Protocol that underpins pediatric medical transition (PMT) has undergone transformation in the U.S. to become a "child led" process in which the patient's personal "embodiment goals" form the basis for the determination of "medical necessity." Section 11.1 revisits the Dutch Protocol (critically assessed in earlier chapters) and explores how the original safeguards on the practice of pediatric medical transition (PMT) have been systematically dismantled in the U.S. Section 11.2 evaluates the frequent assertion that PMT is "rare," questioning whether this claimed infrequency genuinely indicates rigorous assessment standards. Section 11.3 discusses a deeper shift in PMT objectives, highlighting how the concept and role of "assessment" have fundamentally changed. Section 11.4 introduces whistleblowers with direct experience in PMT who, similarly to their counterparts in the U.K.,[1] have revealed practices they consider unsafe and inconsistent with established clinical standards, providing additional evidence of expedited pathways to medical interventions in leading pediatric gender clinics across the U.S.

11.1 The Dutch Protocol and the relaxation of its criteria in the U.S.

According to WPATH SOC-8, the Dutch studies associated with the Dutch Protocol provide "[t]he most robust longitudinal evidence supporting the benefits of gender-

[1] Barnes (2023).

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affirming medical and surgical treatments in adolescence …"[2] In his testimony before the Florida Boards of Medicine and Osteopathic Medicine, Aron Janssen, vice chair of clinical affairs at Lurie's Pritzker Department of Child and Adolescent Psychiatry, who also serves as chair of the American Academy of Child and Adolescent Psychiatry's Sexual Orientation and Gender Identity Issues Committee, said that "the best longitudinal data we have on transgender youth comes primarily out of the Dutch clinic … The Dutch model of care [is] the prevailing model of care that most of the American clinics have based their care upon."[3] SOC-8 seems to acknowledge the guardrails recommended in the Dutch Protocol, contrasting the "detailed comprehensive diagnostic assessment process" of that Protocol with treatment based on "limited or no assessment." According to WPATH, the latter approach "has no empirical support and therefore carries the risk that the decision to start gender-affirming medical interventions may not be in the long-term best interest of the young person at that time."[4]

11.1.1 U.S. gender clinics' departure from the Dutch Protocol

In 2022, investigative reporters from Reuters interviewed "doctors and other staff at 18 gender clinics across the country" and found that "[n]one described anything like the months-long assessments [the Dutch clinicians] adopted in their research." Seven of the 18 clinics said they were comfortable prescribing hormones on an adolescent's first visit, provided clinicians saw no "red flags."[5]

The Dutch clinicians themselves recognized the divergence of the American model from their approach.[6] Noting the shift in age-of-onset, sex ratio, and mental health profile in the pediatric clinical population, Annelou de Vries wrote in 2020 that "[t]hese youth did not yet participate in the early evaluation studies. This raises the question of whether the positive outcomes of early medical interventions also apply to adolescents who more recently present in overwhelming large numbers for transgender care, including

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[2] WPATH is referring to de Vries et al. (2011) and de Vries et al. (2014), discussed in several earlier chapters.
[3] Florida Boards of Medicine and Osteopathic Medicine Joint Rules/Legislative Committee (2022), 47:45-48:03.
[4] Coleman et al. (2022).
[5] Terhune et al. (2022).
[6] For a study on how different countries have responded to the Dutch Protocol see Kozlowska et al. (2024).

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those that come at an older age, possibly without a childhood history of [gender incongruence]."[7] In 2021, Thomas Steensma complained that "the rest of the world is blindly adopting our research …"[8] Steensma reiterated this position in 2023, explicitly distancing his work from the child-led model prevalent in the United States, stating, "That's not our approach."

Of note, the Dutch Protocol did not recommend surgeries prior to legal adulthood, but according to WPATH guidelines, which are followed in the United States,[9] most surgeries, including most genital surgeries, may be deemed medically necessary for certain adolescents with GD.[10] Accordingly, adolescents with GD do undergo mastectomies[11] and (much less commonly) genital surgeries.[12] In the published research on mastectomies in adolescent females with GD,[13] some participants were as young as 12 years old.[14]

11.2 Is pediatric medical transition "rare"?

To bolster the perception that medical gatekeeping ensures patient safety, advocates of PMT frequently assert that medical interventions are "rarely prescribed" to minors. In 2022, for example, the president of the American Academy of Pediatrics (AAP) asserted in an opinion piece published in *The Wall Street Journal* that "for the vast majority of children," the "gender-affirming" approach recommends the "opposite" of medical interventions.[15] These claims are not supported by the data.

In 2025, a *JAMA Pediatrics* study utilizing insurance data reported that about 0.1% of American 17-year-olds, or one in 1,000, received CSH between 2018 and 2022. The authors concluded that hormonal interventions are therefore "rare" and decried the "politicization of gender-affirming care for transgender youth … driven by a narrative

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[7] de Vries (2020).
[8] Tetelepta (2021a). There is an English translation available: Tetelepta (2021b).
[9] Coleman et al. (2022).
[10] E.g., "A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical *and surgical treatments* (GAMSTs)" (Coleman et al., 2022, S45-S46, emphasis added).
[11] Wright et al. (2023); Ghorayshi (2022); Sapir (2024c).
[12] Milrod & Karasic (2017); Terhune et al. (2022).
[13] Ascha et al. (2022); Olson-Kennedy, Warus, et al. (2018); Tang et al. (2022).
[14] Tang et al. (2022).
[15] Szilagyi (2022a).

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that millions of children are using hormones and that this type of care is too freely given."[16]

Such claims ignore a number of critical facts. First, no serious critic or skeptic of PMT has claimed that "millions of children are using hormones." Second, whether a prevalence of 1 in 1,000 is "rare" is subjective. For context, the prevalence of Type 2 diabetes in less than one in 1,000—a rate that medical authorities have described as "high" and even as "an awakening epidemic."[17] Third, even medical interventions that are objectively "rare" can raise profound ethical concerns. For example, "only" about 600 out of millions of African American men were recruited into the highly unethical Tuskegee syphilis study.

A central question in the debate over the frequency of medical interventions, and by extension whether they are "rare" or "freely given," concerns the appropriate choice of denominator. The authors of the *JAMA* study calculated prevalence using the total population of American adolescents as the denominator. However, in a press release accompanying the study, one of the authors noted that access to hormones was "surprisingly low, given that over 3% of high school youth identify as transgender"—implicitly invoking a different denominator.

Another denominator, which yields an even higher estimated frequency, is the number of adolescents diagnosed with GD and/or referred to a gender clinic, where they ostensibly undergo an "assessment" to determine whether medical interventions are indicated. Data on the rate of medicalization among adolescents diagnosed with GD and/or referred to a gender clinic are lacking.

Reports from individual clinics suggest that medicalization is the norm, rather than the exception. For example, pediatric endocrinologist Daniel Shumer of the Comprehensive Gender Services Program (CGSP) at University of Michigan Health estimated that "65 percent" of pediatric patients referred to his clinic end up receiving CSH.[18] According to data collected by Jamie Reed, a case worker at the Washington University School of

[16] Hughes et al. (2025).
[17] Lawrence et al. (2021); Kingsbury & Greene (2025) and the research articles cited therein.
[18] Doe v. Horne, No. 4:23-cv-00185-JGZ: 265 (2025, p. 52).

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Medicine Pediatric Transgender Center at St. Louis Children's Hospital, 67 percent of the clinic's patients were prescribed endocrine interventions during her four-year tenure at the clinic.[19] Finally, WPATH has itself implied that medical interventions are appropriate for "most adolescents" who seek them. In its response to the release of the Cass Review in the U.K., WPATH issued a statement criticizing the Review as being "rooted in the false premise that non-medical alternatives to care will result in less adolescent distress for most adolescents…"[20]

11.3 Shift in objectives and the new meaning of "assessment"

The AAP and other American medical associations argue that transition-related medical decisions for minors are made in consultation with parents and only after a "robust diagnostic assessment."[21] Under the original Dutch Protocol, assessments were intended to predict lifelong transsexuality, with pubertal suppression conceptualized as part of the diagnostic process (buying "time to think"). By contrast, the "gender-affirming" model, as it has evolved in the United States, prioritizes the autonomy of children and adolescents, allowing their current "embodiment goals" to direct treatment decisions.[22]

A systematic review of recommendations for the management of GD in children and adolescents found an absence of "[d]etailed guidance" and "no consensus about the aim or clinical approach"[23] of assessment. Understanding the realities of clinical care for youth with GD in the U.S. requires appreciating the shift in the meaning of assessment, which reflects a deeper change in the goals of PMT. According to the Dutch approach, the goal was to predict lifelong "transsexualism." Mental health professionals were to ascertain whether a GD diagnosis was appropriate and if so, whether it was likely to persist through adulthood. Although advocates of this approach generally regard a

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[19] Broyles & Trakas (n.d.).
[20] Block (2024c). The original statement from WPATH/USPATH (2024, April 12) was deleted from WPATH's website (404 Not Found | WPATH, n.d.). The April 12 WPATH/USPATH statement was covered by the NPR station WBUR (Scheimer et al., 2024). WPATH subsequently changed the statement, removing the referenced passage (see World Professional Association for Transgender Health & United States Professional Association for Transgender Health, 2024a; 2024b).
[21] U.S. v. Skrmetti (No. 23-477), American Academy of Pediatrics and Additional National and State Medical and Mental Health Organizations, Amicus curiae brief (2024).
[22] Block (2023d).
[23] Taylor, Hall, Heathcote et al. (2024b, s80).

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diagnosis of GD as a necessary condition for medical interventions, there is considerable disagreement about whether it is sufficient.

More recently, advocates of early intervention have argued that "trans kids know who they are"[24] and that the goal of treatment is to help them achieve their personal "embodiment goals."[25] If an adolescent's self-conception or embodiment goals later change, this is not considered a failure of treatment but part of a "gender journey."[26] In 2023, Jason Rafferty, the lead author of the AAP's 2018 policy statement, "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents," explained that PMT is about "affirming and validating the child's sense of identity from day one through to the end." If a child says, "I'm X, we operate under the assumption that what they're telling us is their truth, that the child's sense of reality and feeling of who they are is the navigational beacon to sort of orient treatment around." If patients later detransition, this does not mean that the treatments were inappropriate, even if the interventions' effects are partly or fully irreversible: "They're not treatment failures if that's what's affirming," Rafferty said.[27]

Of note, the more cautious approach, which seeks diagnostic and prognostic clarity and aims at improvements in mental health, has been found to be unsupported by evidence. No test can reliably predict the natural course of an adolescent's identity development. The U.K.'s Cass Review found that a gender dysphoria diagnosis "is not predictive that the individual will go on to have longstanding trans identity."[28] Clinicians who adopt the earlier diagnostic-oriented model might perceive their approach as more cautious relative to colleagues practicing the newer "affirming" model; however, research on outcomes from both approaches has been rated unreliable.

One indicator of the changing definition of "assessment" is that leading gender clinicians—who until recently characterized PBs as a "fully reversible" and temporary "pause button" intended to give patients "time to think"—now acknowledge that these

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[24] See Note 33 in Chapter 2.
[25] Ashley et al. (2023); Boskey et al. (2025, p. 2); Brennan et al. (2025, p. 5); Mosier-Mills et al. (2024).
[26] "Clinicians should see detransition as one of many possible steps in a person's gender journey" (Ashley et al., 2025, p. 7).
[27] Block (2023d).
[28] Cass (2024, p. 146).

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drugs function as the first step in a broader medical transition protocol and must be considered in conjunction with cross-sex hormones. For example, in an amicus brief submitted to the Supreme Court of the United States, a leading advocate for PMT, Meredithe NcNamara of the Yale School of Medicine, and colleagues, fault the University of York systematic reviews, commissioned for the Cass Review, for failing to conceptualize PBs and CSH as a single "consistent, well-organized standard of care." According to McNamara et al., if, as research suggests, "the vast majority of adolescents with gender dysphoria who receive puberty blockers progress to cross-sex hormone therapy," that is not because PBs interfere with the natural process of GD resolution but "because [the adolescents] are indeed transgender and because their diagnosis of gender dysphoria is accurate."[29] This explanation for the observed high persistence of GD lacks empirical support due to the absence of controlled prospective studies and raises concerns about motivated reasoning. Many of the brief's authors are actively engaged in the practice of PMT and therefore have intellectual and financial conflicts of interest.[30]

11.3.1 Ambiguity in SOC-8

On the surface, WPATH SOC-8 might appear to recommend a cautious approach toward assessment. Mental health providers are to conduct a "comprehensive biopsychosocial assessment" prior to initiating medical interventions in order "to understand the adolescent's strengths, vulnerabilities, diagnostic profile, and unique needs to individualize their care."[31] At the same time, however, WPATH recommends that clinicians use the *International Classification of Diseases* (ICD-11) diagnosis of "Gender Incongruence of Adolescence and Adulthood," which, unlike the DSM-5 diagnosis of "Gender Dysphoria," requires only "marked and persistent incongruence between an individual's experienced gender and the assigned sex." Because SOC-8 defines transgender in a similar way ("people whose gender identities and/or gender

[29] U.S. v. Skrmetti (No. 23-477), Expert Researchers and Physicians, Amicus curiae brief (2024, pp. 16-17).
[30] The lead author, McNamara, has positioned herself in media and court appearances as a provider of PMT to minors. However, in a deposition McNamara revealed that she does not in fact administer PMT to minors with GD. See Sapir (2024b).
[31] Coleman et al. (2022, Chapter 6).

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expressions are not what is typically expected for the sex to which they were assigned at birth") and provides no meaningful distinction between this meaning of transgender and gender non-conformity, SOC-8 effectively recognizes transgender identification as a medical condition justifying medical interventions.[32]

It is widely recognized that a fundamental tension exists between WPATH's desire to treat transgender identity (gender incongruence) as a normal and healthy variation of human development and its insistence that gender incongruence requires "medically necessary" treatment. This tension was explicitly acknowledged in medical literature supporting PMT contemporaneous with the preparation and publication of the fifth edition of the DSM. For example, in 2013, Jack Drescher, a prominent clinician-advocate of PMT, noted the significant difficulty in reconciling the "contradictory narratives" of "reducing stigma (which underlies the call for removal of the gender diagnoses [from the DSM]) and maintaining access to care (which requires the existence of a diagnosis in order to obtain needed medical treatment covered by third party payers)."[33]

In the lead-up to SOC-8's publication, *The New York Times* reported on disagreements among proponents of PMT concerning the proposed assessment recommendations for adolescents. One clinician told the *Times* it was "harmful and destructive and abusive and unethical and immoral" to require that a candidate for medical transition have longstanding GD since childhood—a key element of the Dutch Protocol. Another described the assessment recommendations as a "comprehensive inquisition of [an adolescent's] gender." The International Transgender Health Group criticized WPATH's draft chapter for its "harmful assertion of psychogatekeeping" and for "undermin[ing] patient autonomy." Asked whether it was appropriate to assess "the basis of a kid's gender identity," physician Colt St. Amand, a coauthor of SOC-8, told the *Times* that this "just reeks of some old kind of conversion-therapy-type things … People are who they say they are, and they may develop and change, and all are normal and OK." St. Amand was "less concerned with certainty around identity, and more concerned with

[32] See Chapter 13; The acronym "T/GNC" [transgender and gender-nonconforming] is commonly used in literature supportive of PMT.
[33] Drescher (2014, pp. 11-12).

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hearing the person's embodiment goals. Do you want to have a deep voice? Do you want to have breasts? You know, what do you want for your body?"[34]

11.3.2 SOC-8 guardrails abandoned

Although WPATH's guidelines do not necessarily discourage mental healthcare, they likewise do not require it as a precondition for PMT. Some guideline authors opposed even minimal requirements for mental health support, arguing that such provisions were analogous to "conversion therapy."[35] SOC-8's only formal recommendation is for a "comprehensive biopsychosocial assessment," although WPATH emphasizes that its guideline is "flexible," thereby leaving room for considerable variation in clinical practice.[36]

In 2024, leaked discussions among WPATH members illustrated the extent to which the organization's own members' practice is not always consistent with SOC-8 recommendations. Some WPATH members candidly acknowledged foregoing even minimal psychological evaluations and moving quickly toward hormonal interventions. The candid nature of these exchanges suggests that non-adherence to the guidelines is not a source of professional shame, and not an isolated phenomenon.[37] The flexibility embedded in SOC-8 has facilitated significant gaps between the guidelines' theoretical standards and the practical reality in clinical settings.

Further, this flexibility has effectively provided leaders in the field of PMT with a basis to argue that assessment should not serve the purpose of differential diagnosis or medical "gatekeeping" but rather should function primarily to inform patients and their caregivers about the nature and effects of medical interventions. In 2020, a Canadian conference presentation reported that among pediatric gender clinics surveyed, half did not require any mental health assessment prior to initiation of hormonal interventions.[38] As one group of clinicians recently stated:

[34] Bazelon (2022b).
[35] Bazelon (2022a).
[36] Coleman et al. (2022, p. S6).
[37] Hughes (2024).
[38] Lawson et al. (2020).

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> When a family comes to a mental health provider requesting a letter for a biopsychosocial assessment for pubertal suppression, work begins by explaining, in developmentally appropriate language, that this is not an assessment of whether they 'are actually transgender,' as many patients worry; rather this assessment is meant to help them understand the intricacies of pubertal suppression, so that they can make the best decision for themselves. The primary goal is to provide information, while identifying all potential avenues of support (social, educational, medical, and legal) related to gender.[39]

Jack Turban, the lead author of this statement and Director of the Gender Psychiatry Program at the University of California San Francisco, has said that differential diagnosis is pointless and may even be harmful. He disputes the notion that mental health assessment can reduce the risk of later regret, claiming that "there's not data [sic] that … any of these assessments make that [outcome] less likely."[40] According to Turban, children and adolescents "are just going to figure out the answers and then tell you what you want to hear. And you've set up this argumentative relationship with your patient or client."

Robert Garofalo of Lurie Children's Hospital in Chicago agrees that determining the causes of a child's feelings of alienation from their body through assessment is unnecessary.

> Sometimes parents will come in and be like, "I want to make sure that my young person, my child, is really trans … Can you help me with that?" And I'll turn to the child and be like, "yeah, so, you know, what gender identity do you have?" … You know, there's no form, there's no scale, there's no psychological battery of tests that needs to be done. Really, any young person can answer that question for themselves … Parents … think that they're going to come in and have this evaluation that is gonna help determine their child's gender identity, when really

[39] Turban et al. (2025, pp. 12-13).
[40] GenderGP (2021).

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> … our work sometimes is just getting them to recognize that anyone's gender identity … is a normal variation …[41]

Amy Tishelman, formerly of the Gender Multispecialty Service at Boston Children's Hospital, expressed discontent with the new model of assessment in an interview with *The Boston Globe*. "I've never been happy with that way of characterizing it. I feel like an assessment should encompass more than just, 'Should a person get medical intervention, or shouldn't they?'"[42] In contrast, physician A.J. Eckert, former medical director at Anchor Health Initiative in Connecticut, avowed: "If you are trans, I believe you." For Eckert, minors "are best equipped to make decisions about [their] own body." Eckert further clarified that while medical interventions at Anchor Health are not provided before puberty, psychological therapy is not mandatory because "being trans is not a pathology."[43]

11.3.3 Collapse of assessment times

The erosion of medical safeguarding practices within American gender clinics is evident in the significant reductions in patient assessment durations at prominent institutions.

11.3.3.1 Boston Children's Hospital

GeMS at Boston Children's Hospital is the nation's first pediatric gender clinic and is highly regarded internationally. Whereas in 2013 GeMS allocated a minimum of 20 hours for mental health assessments per patient, court records indicate that by 2021 the clinic had reduced these evaluations to approximately two hours per patient.[44] Laura Edwards-Leeper, the clinic's founding psychologist, characterized this change as "shocking." Amy Tishelman, a former GeMS psychologist and SOC-8 developer, described it as "reckless."[45] Tishelman's tenure ended following disagreements with colleagues, culminating in litigation. Current co-director Kerry McGregor defended the reduction in assessment times, stating that two-hour assessments were initiated around

[41] Figliolia (2025).
[42] Damiano (2024b).
[43] Edwards-Leeper & Anderson (2021); the quote from Eckert is in Eckert (2020).
[44] Alder (2024).
[45] Ryan (2024a).

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2017–2018 and are “appropriate” given the expanding patient load.[46] Endocrinologist and GeMS director Jeremi Carswell remarked in 2021 that puberty blockers were being prescribed “a lot like candy.”[47]

11.3.3.2 Children’s Hospital Los Angeles

Johanna Olson-Kennedy, medical director of the Center for Trans Youth Health and Development at Children’s Hospital Los Angeles, has acknowledged that she approves some of her minor patients for endocrine interventions after “a couple of hours” of assessment.[48] In December 2024, Olson-Kennedy and the hospital were named as defendants in a lawsuit filed by a former patient whom Olson-Kennedy allegedly approved for PBs at age 12 following a single consultation with no involvement of a mental health professional. The lawsuit further alleges that Olson-Kennedy told the parents of the patient that the patient faced suicide risk without medical interventions, despite no prior suicidal history. Subsequently, the patient was put on testosterone at 13, underwent a double mastectomy at 14, and was recommended for hysterectomy at 17.[49]

11.3.3.3 Lurie Children’s Hospital

In a webinar hosted by AMAZE, a producer of sex education content for students, Robert Garofalo of Lurie Children’s in Chicago explained how his clinic handles parents who have doubts about the safety of medical interventions.

> Most of the young people who come in are wanting to figure out how fast they can get on hormones and what is the safest process to do that … 80% of the young people who come are often really activist [sic] in their mindset and come dragging their parents to the medical visit … The counterweight to that is the parents who are often coming in with questions about how can this be done safely, is this really the right decision, and so it’s really a bit of a puzzle to put the pieces together to make sure that you are meeting the patient’s needs but also

[46] Damiano (2024a).
[47] Lindquist (2022).
[48] Deposition of J. Olson-Kennedy in LB v Premera Blue Cross NO. 2:23:Cv-00953-TSZ (2024, p. 63).
[49] Complaint, Breen v. Olson-Kennedy, No. 24STCV32096 (2024).

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> moving the parents along … in a way that continues to get them educated so that they feel comfortable with the decisions they're about to make, because the truth is that these young people need their parents to be well and to do this well, and so it's our job as pediatricians to make sure that the entire family unit in some ways hopefully moves forward in an ideal situation in a way that feels supportive and nurturing. So, it's usually the young person who comes in knowing exactly what they want and us trying to navigate a process to ensure that's done safely and allaying parents' fears.

Garofalo went on to elaborate on his understanding of what shared decision-making means:

> If the medical provider thinks they have the answer [to whether medical interventions are appropriate] then they're the wrong medical provider. The answer lies within the young person and the family. Your job as a healthcare provider is to help them along that path, to find the answers and the solutions that feel authentic and healthy for them.[50]

11.3.3.4 Seattle Children's Hospital

In a response to Tordoff et al. (2022), a study conducted at Seattle Children's Gender Clinic,[51] one commentator pointed out that the control group, which received only psychotherapy, might have shown comparatively worse mental health due to selection bias: "patients with coexisting mental concerns may have been potentially discouraged from accepting the treatments until their coexisting conditions were addressed."[52] Lead author Diana Tordoff responded to the comment by pointing out that "youth who reported moderate to severe depression, anxiety, or suicidal thoughts were not precluded access to PB/GAH [puberty blockers and gender-affirming hormones], especially since initiating PB/GAH is known to improve or mitigate these symptoms."[53] Eighteen-year-olds "were provided care using an informed consent model and were not

[50] Figliolia (2025).
[51] Tordoff et al. (2022); see Section 6.2.2 for further discussion.
[52] Tordoff et al. (2022) [online comment; March 7, 2022].
[53] Tordoff et al. (2022) [online comment; March 13, 2022].

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required to complete a mental health assessment." Tordoff also noted that Seattle Children's practices were consistent with the (then draft) SOC-8 guidelines.[54]

11.3.3.5 UCSF Benioff

In 2018, the organization Gender Spectrum hosted a panel with Ilana Sherer, a pediatrician and gender clinician, and Diane Ehrensaft, a clinical psychologist at UCSF Benioff and one of the principal architects of the "gender-affirming" approach in the United States. Sherer said that she sees "lots and lots of kids" who "don't have [gender] dysphoria, that really don't have mental health issues, and so to say to them 'you have to go get a letter from a mental health provider' feels challenging to me." But since a letter of support is required for medical interventions, Sherer went on to explain that "what we've started to do in our clinics is have someone like Diane [Ehrensaft] ... go in and do a brief assessment, and give their rubber—I know you [addressing Ehrensaft] said you don't rubber-stamp, but basically in my mind that's what it feels like—and so then we can move on and say 'OK, now we can talk about what you're actually here for.'"[55]

11.3.3.6 Planned Parenthood

Specialized gender clinics are not the only institutions prescribing hormonal interventions to adolescents. According to a 2024 investigative report published in *The Free Press*, Planned Parenthood is "the country's leading provider" of hormones for young people. Approximately 40% of the more than 40,000 patients for whom Planned Parenthood prescribed hormones in 2023 were between the ages of 18 and 22. Some branches, however, "offer hormones starting at age 16 with parental approval." In recent years, Planned Parenthood clinics have adopted an expedited access policy on an "informed consent" basis. Nicole Chaisson, medical director of Planned Parenthood North Central States, told *The Free Press* that "Gatekeeping is not necessary. People are the experts of their own body and of their own journey, and as long as they can

[54] Tordoff et al. (2022) [online comment; March 13, 2022].
[55] Sherer (2018).

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make decisions, they should be the agent of their own healthcare." Chaisson said it was appropriate for teenagers to "leave the clinic with their prescription" after a single visit.[56]

Jamie Reed, the former case manager at the Washington University pediatric gender clinic in St. Louis, had previously worked at Planned Parenthood. Reed testified in a deposition that the St. Louis gender clinic would refer minor patients to Planned Parenthood "when we did not have consent from legal guardians" because Planned Parenthood would get "these kid's scripts [prescriptions] when they did not meet" diagnostic criteria. Although Planned Parenthood requires consent from an adult caregiver to prescribe hormones to minors, Reed said that Planned Parenthood "would not verify who the adult is that is bringing [the minor patient] to the building."[57]

11.4 The whistleblowers

In public statements, advocates and practitioners of PMT routinely imply that assessment functions as a form of medical gatekeeping, suggesting that PBs, CSH, and surgeries are offered cautiously and only to patients who genuinely require such interventions. Meredithe McNamara has argued that it is a "misconception" that "a child's disclosure of gender dysphoria leads to impulsive, irreversible decisions." Rather, "decisions on whether, when, and how to pursue medical interventions are slow-moving, rigorous, and individualized."[58] In his testimony before the Florida Boards of Medicine and Osteopathic Medicine in 2022, Aron Janssen, of Lurie Children's, said that treatments follow a "careful and thorough assessment of a patient's mental health including co-occurring conditions, history of trauma, substance use, among many other factors."[59]

In recent years, however, whistleblowers with firsthand experience working in gender clinic environments have come forward with compelling counterexamples. Their testimonies have often been dismissed, ignored, marginalized, or disparaged by colleagues. Several have also faced retaliation because of their disclosures.

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[56] Block (2024d).
[57] Noe v. Parson, No. 23AC-CC04530 (2024, p. 172).
[58] McNamara (2024).
[59] Florida Boards of Medicine and Osteopathic Medicine Joint Rules/Legislative Committee (2022), a 43:57.

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11.4.1 Laura Edwards-Leeper and Erica Anderson

In 2021, Laura Edwards-Leeper, the founding psychologist of the first pediatric gender clinic in the United States, and Erica Anderson, a clinical psychologist and former president of the U.S. Professional Association for Transgender Health (USPATH), became the first prominent whistleblowers in the United States. In an opinion piece for *The Washington Post,* Edwards-Leeper and Anderson warned that adolescents were "being rushed into" medical interventions without sufficient psychological assessment or deliberation. "A flood of referrals to mental health providers and gender medical clinics, combined with a political climate that sees the treatment of each individual patient as a litmus test of social tolerance, is spurring many providers into sloppy, dangerous care,"[60] they wrote.

Following publication in *The Washington Post*, USPATH sought to impose a moratorium on Anderson's ability to speak to the press while WPATH was finalizing its SOC-8. Anderson resigned from the organization in protest.[61]

In an interview with journalist Abigail Shrier, Anderson cautioned that the current PMT approach involved "sloppy healthcare work," which could result in young people making decisions they would later regret. Marci Bowers, a gynecologist and surgeon who, like Anderson, identifies as transgender, echoed these concerns in the same interview. Bowers observed that although medical interventions initially seemed promising, in practice they had not yielded better—or even equivalent—outcomes compared to earlier approaches. Bowers specifically voiced concern about the long-term implications of these interventions on reproductive capacity, sexual health, and the ability of patients to experience intimacy.[62]

Despite criticizing the "gender-affirming" approach now dominant in their field, Anderson and Edwards-Leeper continue to believe that at least some children and adolescents benefit from medical transition. Bowers issued a detailed letter of apology to WPATH

[60] Edwards-Leeper & Anderson (2021).
[61] Selin Davis (2022).
[62] Shrier (2021b).

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leadership[63] and remained with the organization, serving as its president from 2022 to 2024.

11.4.2 Jamie Reed

In 2022, Christopher Lewis and Sarah Garwood, then co-directors of the Washington University School of Medicine Pediatric Transgender Center at St. Louis Children's Hospital, testified before the Missouri House Judiciary Committee that "[m]edical interventions are done with a thorough and multidisciplinary team approach, which includes mental health assessment and requires consent from all custodial parents or caregivers."[64] Opening with the unfounded assertion that PMT is "literally lifesaving" (see 4.3.4 for discussion of suicide risk), Lewis, the Center's endocrinologist, emphasized that "[f]or pubertal transgender adolescents, medical services are started only after meeting strict eligibility criteria… [This] includes mental health professionals who have adequately documented and explored various aspects of gender and mental health exploration [sic], psychosocial medical concerns and conditions, and ability to understand their decisions and provide assent."[65]

These assertions were later disputed by Jamie Reed, who worked for four years at the Center as a case manager responsible for patient intake and oversight. In deposition testimony, Reed stated that Lewis had indicated at an early stage that he "[didn't] care" if patients met criteria for gender dysphoria. It was "not a requirement for [him] to prescribe hormones."[66] An investigation by *The New York Times* provided additional details about the clinic's practices and corroborated most aspects of Reed's testimony. According to the investigation, one patient, who subsequently detransitioned, received a prescription for testosterone following a single visit, without prior assessment by any mental health professional. When WPATH SOC-8 was published in September 2022, Lewis texted Karen Hamon, the Center's nurse, saying: "Right now I have no idea how to meet what would be the most intensive interpretations of the SOC."[67]

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[63] Boe v. Marshall, No. 2:22-cv-00184: 700-5 (2024, pp. 67-71).
[64] Lewis & Garwood (2022, 9:14:55).
[65] Lewis & Garwood (2022, 9:16:40).
[66] Noe v. Parson, No. 23AC-CC04530 (2024, p. 244).
[67] Ghorayshi (2023b).

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According to Reed, the Center responded to a 5-fold increase in its patient caseload by offering mental health providers a letter-of-support template for them to sign, in the hope that this would speed up the process of approval for endocrine treatments. It "was just copy paste," Reed testified in a deposition. Reed said that when she brought her concerns to Lewis, he "didn't care and was going to pass it [the letter] anyway".[68]

Concerned that the Center was not tracking patient outcomes, Reed and Hamon created a "red flag list," a private Excel spreadsheet in which they documented cases of patients with complex mental health presentations. As reported by the *Times*, the list included "a patient on testosterone [who] stopped taking schizophrenia medication without consulting a doctor and another [who] had visual and olfactory hallucinations. Another had been in an inpatient psychiatric unit for five months."[69] Reed also described an adolescent female from an "unstable family" who was in "an uncertain living situation and had a history of drug use" and was put on hormones at age 16, followed by a double mastectomy at 18. Three months later she regretted the surgery and informed the clinic, "I want my breasts back."[70] According to the *Times*, the patient contacted the surgeon at Washington University twice about her wish for breast reconstruction, but did not receive a response.[71]

Reed recalled a 17-year-old girl who was given testosterone and reported "bleeding from the vagina." The girl was advised to use a heavy pad to absorb the blood. "In less than an hour she had soaked through an extra heavy pad, her jeans, and a towel she had wrapped around her waist. The nurse at the center told her to go to the emergency room right away." The Center "found out later this girl had had intercourse, and because testosterone thins the vaginal tissues, her vaginal canal had ripped open. She had to be sedated and given surgery to repair the damage."[72]

Reed reported that when she raised concerns regarding inadequate mental health assessment and safeguarding with the Center's physicians, her objections were

[68] Noe v. Parson, No. 23AC-CC04530 (2024, p. 165).
[69] Ghorayshi (2023b).
[70] Reed (2023a).
[71] Ghorayshi (2023b).
[72] Reed (2023a).

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repeatedly dismissed and she was advised to “Get on board, or get out.” Individuals who expressed doubts frequently faced “being called a transphobe.”[73] A similar phenomenon of intimidation was documented at the Tavistock’s Gender Identity Development Service in the U.K.[74]

Reed, who is lesbian, profoundly regrets her past involvement in PMT, and has since become a leading advocate for restrictions on practices she regards as harmful, especially for youth with emergent same-sex attraction who are overrepresented among patients.[75] The Center stopped providing PMT following the enactment of Missouri's Senate Bill 49 (SB 49).[76] Lewis, the Center’s endocrinologist, accepted a job in Colorado, where he currently practices PMT at Children's Hospital Colorado.[77]

11.4.3 Tamara Pietzke

In February 2024, Tamara Pietzke, a licensed clinical social worker and therapist at MultiCare Health System in Tacoma, Washington, disclosed harmful practices occurring in her clinical environment.[78] Pietzke described patients with significant comorbid mental health conditions and complicated life histories, who, despite these vulnerabilities, were approved for hormonal interventions.

One patient, a 13-year-old adolescent female, had diagnoses of depression, anxiety, post-traumatic stress disorder, and intermittent explosive disorder. She had experienced childhood abuse, neglect, and sexual violence, and, according to Pietzke, reported that “horror and porn movies … were the only ones available in her house.” The patient also told Pietzke that her mother practiced bestiality. She communicated in therapy sessions by displaying extremely sadistic and graphic pornographic videos to Pietzke on her phone. The patient also was reported to have autism spectrum disorder, a factor that may have contributed to her communication difficulties. Pietzke noted that the girl would “age-regress” by “watching *Teletubbies* and sucking on a pacifier.”[79] A restraining order

[73] Reed (2023a).
[74] Barnes (2023); Cass (2024).
[75] Reed (2023b).
[76] Washington University (2023).
[77] University of Colorado Anschutz Medical Campus (n.d.).
[78] Pietzke (2024a).
[79] Pietzke (2024a).

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was also in place against the patient's mother, who had previously attempted to harm the girl's sister in her presence. The girls were being raised by their mother's former boyfriend.

In addition to these obvious red flags, Pietzke noted that her 13-year-old patient never asked for testosterone and failed to demonstrate an understanding of the hormone when the subject was raised. Nevertheless, the gender clinic at Mary Bridge Children's Hospital, part of MultiCare, approved the teenager for testosterone on her first visit. The clinic requested that Pietzke sign a letter of support clearing the patient of any mental health contraindications. Pietzke refused, and the case was referred to the hospital's risk management team. Instead of siding with Pietzke, however, the risk management team reassigned the adolescent to another therapist. Pietzke wrote to Amber Rolfe, MultiCare's in-house "gender-affirming care" expert, explaining her concerns and even citing Sections 6.3 and 6.12 from the Adolescent chapter of WPATH SOC-8 in support of her decision.

Rolfe disagreed with Pietzke's clinical judgment and citations from SOC-8, insisting that nothing in the patient's history, behavior, or concurrent diagnoses was a contraindication for hormone treatment.[80] "There is not valid, evidenced based, peer reviewed research that would indicate that gender dysphoria arises from anything other than gender (including trauma, autism, other mental health conditions, etc.)," Rolfe wrote to Pietzke.[81] "At it's [sic] core the diagnosis centers on an incongruence of gender identity and assigned gender at birth." Rolfe also suggested that Pietzke examine her biases and consider transferring the client "to someone who is comfortable with providing gender affirming care."[82] Pietzke resigned from MultiCare shortly thereafter and went public with her story.

11.4.4 Eithan Haim

Eithan Haim, a surgeon formerly affiliated with Texas Children's Hospital (TCH), became a whistleblower after discovering that TCH was performing medical transition

[80] Sapir (2024a).
[81] Rolfe (2023).
[82] Rolfe (2023).

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procedures on minors despite publicly announcing a cessation of such procedures.[83] In 2022, prompted by a Texas Attorney General's opinion describing PMT as potentially abusive, TCH declared it would pause hormone interventions for transgender-identifying youth.[84] Despite this declaration, Haim became aware of ongoing practices that he asserted contradicted these claims; three days following the public statement, an 11-year-old patient received a puberty blocking implant, and similar interventions continued throughout the subsequent year involving dozens of other patients.[85] In May 2023, Haim anonymously provided de-identified hospital records and related documents to journalist Christopher Rufo, which resulted in a public exposé. The released data suggested that TCH had misled the public about halting its PMT program.[86]

Haim was charged with four felony counts under the Health Insurance Portability and Accountability Act (HIPAA). Prosecutors argued that Haim was not authorized to access patient data and that he did so with intent to maliciously harm the hospital.[87] The charges carried penalties of up to 10 years' imprisonment. Haim pleaded not guilty, denying his access to patient records was inappropriate, and asserting his disclosures were whistleblower actions aimed at safeguarding children rather than malicious acts.[88] The allegations were unusual, as HIPAA violations are typically addressed through civil rather than criminal procedure. The choice to pursue criminal charges raised suspicion that the federal government's actions were retaliatory in nature.[89]

The DOJ's indictment against Haim had to be amended multiple times after it was revealed that the government was mistaken about Haim's involvement with TCH. A second indictment had to be revised again because Haim was charged with actions as crimes that are not criminal under the law. The third indictment, which was shorn of most of the initial factual allegations, was for unauthorized access to patient records with intent to cause harm to doctors and the hospital, not patients. In January 2025,

[83] Haim (2024).
[84] Campion (2022).
[85] Haim (2024).
[86] Alder (2025).
[87] Trombly (2024).
[88] Alder (2025).
[89] Trombly (2024).

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after months of legal contention and growing public criticism of the prosecution as "lawfare," federal prosecutors dismissed all charges against Haim with prejudice, effectively exonerating him.[90]

In November 2024, Haim's lawyers informed the DOJ that the lead prosecutor in the case, Tina Ansari, and her family, had "substantial financial and political ties" to Texas Children's Hospital and Baylor College of Medicine, resulting in a potential conflict of interest.[91] Shortly thereafter, Ansari withdrew from the case.[92]

[90] House Judiciary Committee (U.S. Congress) (2025).
[91] Patrick (2024).
[92] Whelan (2024b).

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Chapter 12 Medical Association Response

This chapter examines how, despite growing recognition of its problems, the 8th version of the World Professional Association for Transgender Health (WPATH) *Standards of Care* (SOC-8) continues to have substantial influence on the medical field. This can be better understood by examining the critical role that major medical and mental health associations (MMHAs) play within the U.S. healthcare system (Section 12.1). Section 12.2 explores the reasons why MMHAs have not properly responded to updated evidence, nor to serious ethical concerns; Section 12.3 is a summary conclusion.

12.1 The role of major medical and mental health associations

Given the decentralized and fragmented nature of the U.S. healthcare system, MMHAs play a central role in shaping clinical practice guidelines, healthcare policy, and medical practices. They educate clinicians on emerging research, develop authoritative clinical practice guidelines, publish peer-reviewed journals, facilitate interdisciplinary collaboration, and engage in professional advocacy on behalf of their members. Typically, MMHAs limit full professional membership to practitioners actively engaged in clinical medicine or the mental health disciplines and enforce professional codes of conduct under which members may face sanctions or loss of privileges for noncompliance. MMHAs derive their authority in large part from their perceived adherence to rigorous professional standards and to science.

However, despite their scientific orientation, MMHAs are not immune to institutional biases, including groupthink and the disproportionate influence of vocal, specialized subcommittees. These specialized groups may receive broad deference from the larger organization, especially when their initiatives are framed in the language of civil or human rights. Consequently, MMHAs can inadvertently become echo chambers where dissent is suppressed, confirmation biases go unchecked, and professional deference is exploited. This dynamic of institutional capture is hardly unique to MMHAs: it occurs whenever support for a particular viewpoint is concentrated within a small, motivated subgroup, while opposing views are diffuse, less attentive, and less organized. As a result of this dynamic, the general public may inaccurately perceive the wider membership of individual MMHAs as uniformly aligned with the professed position of

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their professional association. It is easy to overlook the fact that fundamentally, these organizations operate as trade associations, with a primary role of protecting their members' autonomy and professional interests. Although individual clinicians generally are motivated by altruism, it should not be assumed that the collective actions of an organization always reflect the values or intentions of its individual members.[1]

Historical examples demonstrate that despite their crucial role in safeguarding patients' interests, MMHAs have at times resisted necessary medical reforms, even when confronted with strong evidence of their urgency. For instance, the American Academy of Pediatrics (AAP) delayed rescinding its 2000 guidelines discouraging early peanut exposure for two years after evidence emerged linking the policy to increased rates of peanut allergies.[2] Similarly, professional organizations resisted evidence-based recommendations to limit arthroscopic knee surgeries, lobbying against healthcare reforms despite clear evidence of limited efficacy.[3] MMHAs may impede or even oppose evidence-based medicine when the professional or financial interests of their members are threatened by medical practice reversal.

The reliance of MMHAs on WPATH is exemplified by the Endocrine Society (ES) clinical practice guideline for the treatment of gender dysphoria (GD). As discussed in Chapter 9, the close alignment of these groups' guidelines suggests a lack of robust, independently derived frameworks for care, potentially limiting critical appraisal and alternative perspectives within the field. Notably, Joshua Safer, who is leading the 2024 revision of ES guidelines, is himself closely associated with WPATH and is a prominent advocate for pediatric medical transition (PMT).[4] His leadership role raises concerns about compliance with the National Academy of Medicine's standards for trustworthy guideline development, in particular with regard to conflict of interest management (see 10.3.1).[5]

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[1] For a discussion of this phenomenon and its consequences for medical policy, see Patashnik et al. (2017).
[2] See Section 1.2.2.
[3] Patashnik et al. (2017, Chapter 2).
[4] Sapir (2024d).
[5] Graham et al. (2011, p. 87).

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MMHAs have been reluctant to transparently address the weak evidence base underlying PMT. For example, the American Psychiatric Association's (APA) textbook *Gender-Affirming Psychiatric Care*[6] has faced internal criticism for failing to acknowledge the scientific debate and the policy shifts occurring internationally.[7] A petition with over 7,000 signatures, many from medical and mental health professionals, has called for the withdrawal or correction of the textbook,[8] yet APA leadership has not issued a substantive response.[9] Similarly, the American Academy of Child and Adolescent Psychiatry (AACAP) has rejected multiple proposals addressing important evidence and dissenting perspectives that were submitted to its conferences.[10] The AAP likewise has repeatedly declined to platform critical perspectives at its events.[11] This pattern of organizational defensiveness fosters environments in which clinicians feel compelled to self-censor.

The AAP has rejected multiple internal requests to conduct systematic reviews of the evidence underpinning PMT.[12] Although AAP leadership ultimately agreed in principle to a systematic review, it simultaneously reaffirmed the existing policy[13]—a move that evidence-based medicine experts have criticized as methodologically unsound and premature, as it presupposes the outcome of a review intended to impartially evaluate the evidence.[14] To date, there is no evidence the AAP has begun the review.

After the National Health Service (NHS)-commissioned Cass Review was published in April 2024, several affiliates of the American Psychological Association (APA) prohibited its very discussion on their professional listservs. When a San Francisco-area psychologist posted information about the Cass Review on a listserv of Division 39 of the APA, the listserv moderator blocked the post, citing a 2020 "Letter of Apology to

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[6] Goetz & Keuroghlian (2023).
[7] Satel (2024).
[8] Foundation Against Intolerance & Racism (2024).
[9] Posner (2024).
[10] Sibarium (2023).
[11] Shrier (2021a).
[12] Block (2023c).
[13] Wyckoff (2023). AAP policy statements automatically expire after 5 years unless readopted, revised, or revoked.
[14] Ghorayshi (2023a).

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LGBTQ+ Communities" that forbids "speech that is injurious to LGBTQ+ members."[15] The Pennsylvania Psychological Association (PPA), a state affiliate of the APA, sent an email to all its members informing them that the Cass Review was "no longer welcomed for discussion" on its professional listserv. The PPA explained that the Review "fail[s] to meet" the PPA's "professional standards," and that "LGBTQIA+" members and their "allies" might feel "targeted, harmed, and hurt by this literature being repeatedly shared."[16] A clinical psychologist who describes herself as "a liberal feminist" and who has "marched in Pride marches" told the *BMJ* that she was "reprimanded" by the Illinois Psychological Association after posting about the Cass Review on a therapist listserv.[17]

12.2 Factors contributing to neglect of evidence and open debate

Hilary Cass, past president of the Royal College of Paediatrics and Child Health and leader of the U.K.'s comprehensive review of pediatric gender medicine services, has stated that American physicians are "out of date" in their approach to pediatric gender medicine.[18] Several factors may help explain the reluctance of American MMHAs to engage fully with the shifting perspectives on evidence and ethics in this area of practice.

First, in managing unusual or complex conditions, primary care providers and generalist clinicians often rely on the expertise of specialists to inform their clinical decisions.[19] When the former also hold leadership positions in medical organizations and are tasked with shaping policies for the treatment of youth with GD, they often defer to specialized committees—such as committees devoted to LGBT issues—whose members they regard as the organization's content experts. These committees typically are composed of professionals whose careers are closely tied to supporting or delivering medical transition, limiting their ability to impartially evaluate the evidence due to significant intellectual and financial conflicts of interest. While reliance on specialist committees

[15] Selin Davis (2024a).
[16] Ryan (2024c).
[17] Block (2024b).
[18] Ghorayshi (2024a).
[19] Tzartzas et al. (2019).

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poses fewer risks in well-established subspecialties with decades of robust research,[20] pediatric gender medicine remains a new, highly controversial field characterized by a limited and low-certainty evidence base.

Second, the framing of PMT as a civil rights matter[21] may have contributed to premature and uncritical support at both the individual and institutional levels. Most medical professionals are broadly supportive of civil rights.[22] U.S. specialty committees often frame PMT as a morally righteous or progressive cause, leading many professionals reflexively to adopt supportive positions. Given that transgender identification is relatively common among youth—estimated at 2–5%, though precise figures remain uncertain—many clinicians and policymakers also may have personal connections, such as friends or loved ones who identify as transgender. These personal ties, combined with a genuine desire to be compassionate and supportive, may understandably make it more difficult for professionals to critically and objectively evaluate the evidence base or ethical considerations underlying PMT.

Third, by the time the weak evidence and growing international retreat from the practice became difficult to ignore, several major U.S. MMHAs had been actively promoting PMT and denouncing its critics.[23] As a result, some organizations responded to international developments defensively rather than reflectively, viewing the shifts as a potential challenge to their institutional credibility.[24] The only notable exception to this pattern appears to be the American Society of Plastic Surgeons which, following the publication

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[20] It should be noted, however, that with respect to developing reliable clinical practice guidelines the role of clinicians with intellectual conflicts of interest should be minimal: see Graham et al. (2011); McCartney et al. (2022).
[21] In 2016 psychologist Diane Ehrensaft, leading proponent of the "gender-affirming" approach, explicitly conceptualized her work as having “finally created a civil rights movement” (Ehrensaft, 2016, p. 355). Some medical guidelines in this field also call for specific political activism on the part of clinicians; e.g., the AAP policy statement (Rafferty et al., 2018). The editorial board of *The Washington Post*, recognizing the failure of pediatric gender specialists to self-regulate in the U.S., recently called for “new research of maximum possible rigor, overseen by scientists *who are not gender medicine practitioners*” (Washington Post Editorial Board, 2024, emphasis added).
[22] Levine & Abbruzzese (2023).
[23] Szilagyi (2022b).
[24] E.g. Endocrine Society (2024); Hoffman (2024).

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of the Cass Review, publicly adopted a more cautious stance regarding the use of surgical interventions for treating pediatric GD.[25]

Experts within pediatric gender medicine hold sharply divergent views about best practices.[26] However, the absence of professional consensus is often obscured, as dissenting voices are seldom included on specialty committees responsible for policy development. Researchers who study detransition, investigate social influences underlying epidemiologic changes in GD presentations, express concerns about PMT, or advocate for a more cautious approach to pediatric GD frequently encounter hostility and a lack of support from major publishers, medical societies, and academic institutions.[27] Organizations advocating for higher evidentiary standards, journalists reporting on the controversies, and academics writing about issues related to sex and gender have also faced hostility and attempts at public shaming.[28] Activist organizations have contributed significantly to this dynamic, often targeting individuals and groups that question or critically examine prevailing practices in gender medicine.[29]

When MMHAs update their treatment guidelines and position statements, experts who question the evidence supporting PMT are excluded from guideline development

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[25] American Society of Plastic Surgeons (2024).

[26] As the Cass Review found, "clinicians who have spent many years working in gender clinics have drawn very different conclusions from their clinical experience about the best way to support young people with gender-related distress. Some feel [they should] access a medical pathway at an early stage. Others feel that we are medicalising children and young people whose multiple other difficulties are manifesting through gender confusion and gender-related distress" (Cass, 2024a, p. 13). Examples of divergent clinical opinions can be found by comparing two papers on the role of mental health assessments: Levine (2024); Turban et al. (2025). Differing treatment approaches are also described in Levine et al. (2022a) and two follow-up articles: Drescher (2023); Levine et al. (2022b).

[27] For some examples, see Barnes (2023); Bazelon (2022a); Brown University (2019); Byrne & Gorin (2025); Edwards-Leeper & Anderson (2021); Gecsoyler (2024); Jenkins & Panozzo (2024); Keenan & Lovett (2025); LGBTQIA+ Coalition (2022); Pietzke (2024a, 2024b); Reed (2023a); Schenck (2022); Society for Evidence-Based Gender Medicine (2023d); Turley (2024).

[28] 100 signatories (2023); GLAAD (2023a, 2023b); Hansford (2024); Hooven (2023); Singal (2023a, 2023b); Weale (2025).

[29] In addition to the examples above, a recent article recounted therapists' experiences of attending a training workshop where the representative of the political activist group Southern Poverty Law Center (SPLC) spoke about efforts to "hunt" therapists who practice exploratory therapy, with the goal of leveling complaints leading to licensure revocations. Another therapist reported having been formally investigated by her graduate school for sharing information about new pediatric gender medicine evidence from Europe, an investigation which remains on her permanent record (Jenkins & Panozzo, 2024). SPLC also chose to wield the emotional power of the "hate group" label on several groups that have engaged in evidence-based evaluation of PMT or the development of alternative approaches.

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committees.[30] Efforts to exclude dissenting perspectives from conferences and publications have been documented.[31] In addition, there is growing evidence of self-censorship among clinicians and researchers, driven by concerns about professional repercussions and reputational risks.[32] Some proponents of PMT explicitly endorse the use of silencing tactics and reputational attacks:

> The point of activism is sometimes 'silencing,' if by that one means destroying the credibility of professionals that activists deem dangerous.[33]

Medical professionals' years of training and social status leave them acutely aware of and sensitive to reputational risks. Fear of online attacks and social disapproval within professional medical societies may have contributed to widespread self-censorship among clinicians, mirroring similar trends observed across academia.[34] This dynamic is further reinforced when PMT is framed as a civil rights issue or a struggle against discrimination and oppression. Under this framing, critics—even those raising evidence-based concerns—are labeled "anti-trans" or intolerant by reputable, influential sources.[35] As Hilary Cass observed in the introduction to the Cass Review,

> There are few other areas of healthcare where professionals are so afraid to openly discuss their views, where people are vilified on social media, and where name-calling echoes the worst bullying behaviour. This must stop. Polarisation and stifling of debate do nothing to help the young people caught in the middle of a stormy social discourse, and in the long run will also hamper the research that is essential to finding the best way of supporting them to thrive.[36]

The American healthcare system relies heavily on MMHAs to create, organize, and disseminate knowledge and to referee scholarly dialogue through journals and

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[30] Marci Bowers, president of WPATH when its 2022 guidelines were published, acknowledged that it was "absolutely" important for someone to be an "advocate" of the "gender-affirming" approach to be considered for the committee. See Boe v. Marshall, No. 2:22-cv-00184: 564-8 (2024). Furthermore, most members of the guideline development committee had conflicts of interest, which were poorly managed.
[31] Curlin (2024); Kaliebe & Johnson (2024); Kaltiala (2023); Mason (2021); Sapir (2025).
[32] Clark et al. (2024); Pfaus (2023).
[33] Nichols (2008).
[34] Clark et al. (2024); Curlin (2024); Pfaus (2023).
[35] E.g., Endocrine Society (2024); Szilagyi (2022b).
[36] Cass (2024, p. 13).

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conferences. Regardless of the underlying causes, major MMHAs have issued advocacy-driven recommendations prematurely, without adequate scientific support.[37] This contributed to a degradation of the norms of open inquiry and constructive disagreement—norms that are essential for the credibility of MMHAs and their capacity to issue trustworthy, evidence-based guidance.

12.3 Conclusion

The significant influence MMHAs exert over professional opinion, clinical practice, and healthcare policy extends broadly across the healthcare landscape. In the area of pediatric gender medicine, prominent MMHAs have aligned their clinical guidelines and policy statements with WPATH SOC-8. This reliance on WPATH guidelines effectively imported into MMHAs many of the methodological and ethical deficiencies documented in WPATH's guideline development process. Consequently, problems originating within WPATH have not remained isolated but have instead propagated through influential MMHAs, contributing to a broader erosion of clinical standards, scientific rigor, and open academic discourse.

Today, MMHAs wield considerable influence over both public and professional perceptions of medical practices through statements frequently cited in the media. These shape broader societal attitudes toward both the medical field generally and the practices within that field specifically. The implicit social contract underlying MMHAs' self-regulatory privileges rests on the expectation that these organizations will prioritize the best interests of patients and society. However, MMHAs' handling of issues related to PMT illustrates how institutional biases, reliance on external guidance from advocacy-oriented groups, and internal political dynamics can undermine their regulatory effectiveness and scientific credibility.

[37] See also Chapters 6-8.

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PART 4

ETHICS REVIEW

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Chapter 13 Ethical Considerations

This chapter discusses central ethical issues in pediatric medical transition (PMT), which involves the use of puberty blockers (PBs), cross-sex hormones (CSH), and surgery to suppress or alter the development of sex- and age-typical sex characteristics in physically healthy children or adolescents.[1] These interventions are used as treatment for the conditions of "Gender dysphoria" (GD) in the *Diagnostic and Statistical Manual* (DSM-5-TR) or "Gender incongruence of adolescence or adulthood" in the *International Classification of Diseases* (ICD-11).[2] In assessing the effects of PBs, CSH, and surgery, researchers typically focus on conventional psychiatric outcomes such as depression, anxiety, and suicidality; recently, some have added novel outcome measures such as "chest dysphoria," "appearance congruence," and "gender euphoria."[3]

However, some clinician-researchers have called into question what they call the "logic of improvement," according to which PMT is justified only if it enables "a progression from 'doing worse' to 'doing better,' ultimately leading to an overall improvement in the individual's functioning and well-being."[4] Acknowledging that the evidence that PMT has this effect is weak, these clinicians argue that conventional outcome measures should be supplemented with—if not replaced by—patient-determined outcomes.[5] In the same vein, other advocates of PMT claim that focusing on clinical improvement is "pathologizing" and question the need for any clinical indication beyond the adolescent's "embodiment goals"[6] or mere desire for the intervention.[7] The guiding question of this chapter is whether the provision of hormonal or surgical interventions for these shifting and sometimes contradictory purposes is consistent with well-established principles of

[1] Patients may reach Tanner Stage 2 of puberty by age 8 or 9. An 8- or 9-year-old person is uncontroversially a child. However, for the sake of brevity the remainder of this chapter will use "adolescents" rather than "children and adolescents" in most cases to refer to this patient population.
[2] American Psychiatric Association (2022); World Health Organization (2022b).
[3] See, respectively, Olson-Kennedy, Warus et al. (2018); Chen et al. (2023); Blacklock et al. (2025).
[4] Oosthoek et al. (2024, p. 10).
[5] Oosthoek et al. (2024, p. 17).
[6] Ashley (2019, pp. 480-482).
[7] Chu (2024).

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medical ethics. Despite the high stakes—medical, social, political, and legal—this urgent question has received relatively little critical attention from bioethicists.

After a brief note on consent (Section 13.1), Section 13.2 summarizes how the medical profession's shift away from medical paternalism toward shared decision-making has strengthened patient protections against unwanted medical interventions via the mechanism of informed consent. This move toward greater respect for patient autonomy, however, does not negate clinicians' professional and ethical obligation to protect and promote their patients' health.

Section 13.2.3 turns to the pediatric context, where the latter obligation is especially strict due to the distinctive vulnerability of children and adolescents as well as their underdeveloped decision-making capacity. The best available evidence indicates an unfavorable risk/benefit profile for the prescription of hormonal and surgical interventions for adolescents with GD. The prescription of these interventions also raises justice-related concerns for members of this medically and socially vulnerable population.

Section 13.3 examines an alternative justification for PMT, one grounded in a purported right to access the medical resources needed to satisfy the patient's preferences for body modification. The shift to this alternative justification, which follows researchers' decades-long inability to demonstrate clear medical benefit, suggests that advocates of PMT have significantly altered the criteria for success.[8] The chapter then turns to a brief discussion of patient regret in Section 13.4 before concluding with some remarks on research ethics in Section 13.5.

13.1 Consent

Some disagreements in this field center on the question of whether adolescents have medical decision-making competence (MDC)—that is, whether they can provide

[8] "Clinicians remarked that there is no agreed fixed point of reference on which to judge the success of an intervention, let alone a societal consensus on the appropriate response" (Cass, 2024a, Appendix 3, p. 9).

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informed consent or assent to transition-related medical interventions.[9] Some proponents of these interventions believe they can.[10] In support of this position, some point to research showing that many adolescent patients have MDC as assessed using a quantitative semi-structured interview tool.[11] They also note that there are other invasive, life-shaping interventions to which adolescents and their guardians commonly and unproblematically assent or consent. For example, an adolescent may assent to treatment of leukemia, even when the treatment may cause future infertility. An adolescent also may assent to amputation of a limb that is diseased or damaged beyond repair. There are many similar situations in which assent by the adolescent, and legal consent by the parents, is given to an intervention necessary to preserve the adolescent's overall health but which also causes foreseen serious adverse side effects.

Some critics of PMT, on the other hand, maintain that patients—some of whom are only 8 or 9 years old when they reach Tanner Stage 2 of puberty and thereby become candidates for PBs[12]—are too immature[13] to adequately understand the full range of consequences of medical transition. These young people cannot deliberate about the relevant considerations in a manner that is appropriately attentive to the seriousness and complexity of the decision. Critics point out that even proponents of PMT recognize that children and adolescents lack the cognitive and social maturity to deliberate well about their future fertility.[14]

Moreover, critics assert—reasonably[15]—that providers of PMT often fail properly to inform patients and their guardians about the uncertainty of the clinical evidence for medical benefit and that they overstate the probability and magnitude of the harms of

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[9] "Consent" and "assent" here are technical terms. In the U.S. minors cannot provide *legal consent* for medical treatment (there are limited exceptions, e.g. for emancipated minors or for a narrow range of interventions such as treatment for sexually transmitted infections). Guardians provide legal consent while minors provide *assent*, or agreement to the intervention.
[10] Giordano et al. (2021); Mosier-Mills et al. (2024).
[11] Vrouenraets et al. (2021); See also Marino et al. (2024).
[12] See Chapter 7.
[13] Diekema (2020).
[14] Vrouenraets et al. (2022).
[15] See Chapter 11.

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non-medicalization.[16] Finally, as noted in Chapter 2, clinicians providing PMT routinely employ euphemistic and morally loaded language, which can mislead or unduly influence patients and their guardians. The concern, then, is that this combination of high pressure, low information, and reflexive "affirmation" undermines the possibility of genuinely informed consent or assent.

Informed consent is critically important, but before it is even a consideration, the intervention must be otherwise ethically permissible. For example, before asking whether patients can consent to any proposed intervention, from antibiotics to lobotomy, a clinician must determine whether the intervention has a favorable risk/benefit profile as a treatment for the patient's condition. Thus, while informed consent plays a central role in medical ethics and clinical practice and informs discussions about the distinctive challenges that attend decision-making in pediatrics, this Review's ethical analysis of PMT focuses primarily on the necessarily prior step. Namely: do these interventions have favorable risk/benefit profiles?

13.2 From paternalism to shared decision-making and patient-centered care

Over the course of the 20th century, advances in the biomedical sciences, expansion of healthcare delivery systems, increasing professionalization in medicine, and a series of medical scandals and seminal legal cases led to greater sensitivity among clinicians and researchers to the rights of patients and participants in medical research. Judges, regulators, lawmakers, and ethicists introduced constraints on the power of clinicians to impose their values, preferences, and perspectives on patients.[17] The "paternalistic model" in medicine, according to which "doctor knows best," gave way to a more egalitarian model of "shared decision-making" that emphasizes respect for the autonomy and authority of competent patients and research participants. There is now universal consensus that respect for patient autonomy requires clinicians to provide patients with information relevant to their medical options and to act on competent

[16] Reluctant parents have reported being asked by their child's clinicians whether they (the parents) preferred having "a dead son or a living daughter." In an interview, Dr. Johanna Olson-Kennedy stated, "We often ask parents, Would you rather have a dead son than a live daughter?" (ABC News, 2011).
[17] Faden et al. (1986).

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patients only with patients' consent. As the American Medical Association's *Code of Medical Ethics* puts it, patients have the right "[t]o make decisions about the care the physician recommends and to have those decisions respected. A patient who has decision-making capacity may accept or refuse any recommended medical intervention."[18] Patients are protected from unwanted medical interventions not only by professional and ethical norms but by the law. As Justice Cardozo famously wrote, "a surgeon who performs an operation without his patient's consent, commits an assault, for which he is liable in damages."[19]

13.2.1 Respect for autonomy vs *caveat emptor*

Crucially, the shift from medical paternalism to shared decision-making does not absolve clinicians of their ethical and professional obligation to protect and promote the health and well-being of their patients. Beneficence "undergirds all medical and health care professions and their institutional settings."[20] As mentioned in Chapter 1, clinicians have ancient but enduring ethical duties to avoid harming their patients and to promote their health and welfare: "The health and well-being of my patient will be my first consideration."[21]

The principle of respect for patient autonomy does not justify subjecting patients to interventions that pose medically unnecessary risks of harm, or which are otherwise nonbeneficial, even when patients prefer, request, or demand those interventions. An ethical analysis of PMT published by Finnish health authorities provides a succinct explanation:

> In healthcare, self-determination primarily manifests as the right to refuse treatments within the available service spectrum. This principle must be balanced against the freedom of individuals to express their own gender identity. Nevertheless, autonomy in healthcare does not imply unrestricted freedom to select treatments based purely on personal preference; rather, patient autonomy

[18] American Medical Association (2016).
[19] Schloendorff v. Society of New York Hospital (1914).
[20] Beauchamp & Childress (2019, p. 217)
[21] Parsa-Parsi (2017, p. 1971).

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> involves the choice among treatments *that are medically justified* and included within the recognized service options.[22]

The well-established moral and legal right of competent patients to refuse any medical intervention does not entail a corollary right to receive nonbeneficial interventions. The Institute of Medicine's Committee on Quality of Health Care in America warns clinicians against providing interventions based on this illicit inference, stating, "When a patient seeks inappropriate health care services, the challenge for clinicians is to find ways of reducing this conflict … If a conflict cannot be resolved through counseling, the clinician should refuse to provide nonbeneficial services."[23]

In refusing requests for nonbeneficial interventions, clinicians do not force anything upon their patients. They do not threaten, deceive, or mislead them. Nor do they withhold relevant information about risks, benefits, and available alternatives. In other words, withholding nonbeneficial interventions does not entail acting on patients without their informed consent. Conflating the right of patients to refuse medical intervention or to choose among the beneficial options offered by their clinicians with the wholly separate "right" to determine which interventions must be offered transforms the ethos of beneficent respect in medicine to the crude, responsibility-abdicating ethos of medical consumerism: *caveat emptor.*

> Using patient autonomy to justify acquiescence to patients' requests for nonbeneficial services violates professional integrity. Professional integrity requires physicians to adhere to standards of intellectual and moral excellence. Physicians achieve intellectual excellence by submitting clinical judgment to disciplined, evidence-based reasoning. Physicians achieve moral excellence by protecting patients' health-related interests as a primary concern, keeping self-

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[22] Saarni & Uusitalo (2020, p. 41, emphasis added). Original text: "Itsemääräämisoikeus terveydenhuollossa toteutuu ensisijaisesti oikeutena kieltäytyä palveluvalikoimaan kuuluvista hoitotoimista. Tämä on tasapainotettava sen näkökulman kanssa, että ihmiset saavat itse vapaasti ilmaista omaa sukupuolista identiteettiään. Autonomialla ei terveydenhuollossa kuitenkaan tarkoiteta vapaata oikeutta valita hoitoja omien preferenssien perusteella, vaan potilas voi valita palveluvalikoiman ja lääketieteellisesti perusteltujen hoitomuotojen sisällä."

[23] Committee on Quality of Health Care in America, Institute of Medicine (2001, p. 77). See also the "Physicians Charter" mentioned in Section 1.3.

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> interests systematically secondary. Commitment to professional integrity requires that physicians challenge requests for nonbeneficial interventions.[24]

13.2.2 Nonmaleficence, beneficence, and autonomy in pediatrics

Uncontroversially, then, the norms of medicine require clinicians to protect and promote the health and well-being of their patients. This means they must abstain from providing nonbeneficial interventions even when such interventions are requested by competent patients. In the domain of pediatrics, these norms limit the authority not only of patients (who in any case lack full decision-making capacity) but of parents as well. The American Academy of Pediatrics' (AAP) Committee on Bioethics puts it as follows:

> Pediatric health care providers have legal and ethical duties to provide a standard of care that meets the pediatric patient's needs and not necessarily what the parents desire or request. Parental decision-making should primarily be understood as parents' responsibility to support the interests of their child and to preserve family relationships, rather than being focused on their rights to express their own autonomous choices. It is important to note that parental authority regarding medical decision-making for their minor child or young adult who lacks the capacity for medical decision-making is constrained compared with the more robust autonomy in medical decision-making enjoyed by competent adults making decisions regarding their own care.[25]

The "constraint" on patient and parental authority is grounded in the medical best interests of the child:

> In pediatrics, the duties to protect and promote health-related interests of the child and adolescent by the physician are also grounded in the fiduciary relationship (to act in the best interest of the patient and subordinating one's own interests) between the physician and patient, but these duties may conflict with the parent's or patient's wishes …[26]

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[24] Brett & McCullough (2012, p. 149).
[25] Committee on Bioethics et al. (2016, p. e5). First published in 2016, this report was reaffirmed by the AAP in 2023.
[26] Committee on Bioethics et al. (2016, p. e2).

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In its influential policy statement, "Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents," the AAP states that in navigating disagreements between parents and children clinicians should "maintain their primary responsibility to the welfare of the child."[27] Thus, while the statement recommends that "transgender and gender-diverse" youth have access to PMT, this recommendation is contingent not on the autonomy rights of patients or their guardians,[28] but rather on these interventions' purported contribution to patient health and well-being. [29] This affirms the longstanding, consensus view of medicine's fundamental aim as protecting and promoting the health and well-being of patients.

13.2.3 Risk/benefit in pediatric medical transition

To discharge their duties of nonmaleficence and beneficence, clinicians must ensure, insofar as reasonably possible, that any interventions they offer to patients have clinically favorable risk/benefit profiles relative to the set of available alternatives, which includes doing nothing.[30] As described in Chapter 5, systematic reviews (SRs) of the

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[27] Rafferty et al. (2018, p. 8).
[28] Bester (2024).
[29] It is worth noting, however, that while the AAP and WPATH support PMT, they do not promote intervening over a patient's objections. Neither group holds that a patient with gender dysphoria/incongruence who refuses puberty blockers, cross-sex hormones, or surgery should be strongly encouraged or, if necessary, forced to receive them. This distinguishes medical transition from other interventions claimed to offer great, potentially lifesaving benefit. In gender medicine and perhaps nowhere else, whether transition-related medical interventions are deemed medically necessary seems to hinge largely on whether the patient desires them. See Chapter 11 for more on this issue.
[30] An intervention has a clinically favorable risk/benefit profile when the expected medical benefits outweigh the expected medical harms. Expected benefits and harms are determined by their probabilities and magnitudes. This is a standard method for guiding action and policy, including in medicine, though the precise manner in which it is carried out can vary and depends on many variables, including risk tolerance, the way "benefit" and "harm" are defined and measured, the way probabilities are assigned, and the way uncertainty/ignorance is accounted for. Of course, it would not be difficult to adopt expected utility theory, defining "benefit" and "harm" and assigning values to the relevant variables, in a way that would render a verdict markedly different from the negative one reached in this Review. That said, the claims made here about the probability and magnitude of harms and benefits are grounded in the best available evidence. Sometimes, the probabilities are known with a high degree of certainty. For example, the probability that mastectomy will lead to an inability to breastfeed is 1.0 or close to it. Puberty blockers and cross-sex hormones threaten sexual function, though the precise magnitude of the problem and its distribution in the treated patient population is unknown. Where precise or even rough values are not available due to the absence of quality research, the analysis in this Review assumes plausible, if rough, estimates. As for the nature of medical benefits and harms and their relative weights, the Review's working assumptions cohere with common moral intuition, standard medical judgment as revealed in medical diagnostic criteria, and the outcomes of interest to clinicians and researchers, as well as the law. For example, the analysis would conclude that a minor improvement in depressive symptoms does count

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evidence for benefit of hormonal or surgical intervention in the treatment of GD in adolescents have concluded that this evidence is of low or very low certainty. This means that the true effects of the interventions may or are likely to be substantially different from the effects reported in the studies.[31] In other words, the best available evidence indicates that PBs, CSH, and surgery have not been shown to improve mental health outcomes.

At the same time, there is increasing recognition of the risks and harms associated with PMT, which are supported by clinical research or grounded in established biological theory.[32] While the value or disvalue of some outcomes, such as hirsutism in females, may be determined primarily by the preferences or tastes of patients, other possible outcomes, such as impaired cognitive function, greater susceptibility to hormone-sensitive cancers, cardiac disease, reduced bone density, sexual dysfunction, infection, and infertility[33] are objectively detrimental to health. Such medical harms, or plausible

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as a benefit but that such a benefit, even if assured, does not outweigh moderate or even low but non-negligible risks of infertility or serious sexual dysfunction, loss of breastfeeding function, or lifelong medical dependency, which the Review considers harms.

[31] Balshem et al. (2011).

[32] See Chapter 5 and Chapter 7.

[33] It may be objected that infertility is not necessarily a harm. One version of this objection is that for some young patients, perhaps those who have very clearly expressed that they do not want and will never want genetically-related children, infertility is not a harm since it is consistent with their chosen life plan. The response to this objection is that the medical profession does not ordinarily permit voluntary permanent contraception (sterilization) in children or adolescents and always takes the risk of infertility seriously in assessing the risk/benefit profile of any intervention that plausibly may impact reproductive health. That is to say that as a matter of well-established sociological fact, infertility is recognized by the medical profession as a harm (Geis et al., 2024). The second version of the objection relies on the claim that some patients are willing to accept infertility as a consequence of medical transition, even if they do not intend infertility. These patients prefer to remain fertile, all else being equal, but because all else is not equal they accept interventions that will undermine their fertility. The response to this objection is that such preferences reveal that these patients view infertility as a harm. The real question in the latter case is whether there is good reason to believe that the benefits of medical intervention outweigh this harm, and the answer to this question will depend on the evidence regarding benefits. Finally, research suggests that many transgender-identified people do want children and that some who medically transition experience decisional regret over their infertility. This suggests they also view infertility as a harm even if they do not regret their transition. See Asseler et al. (2024); Stolk et al. (2023).

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risks thereof,[34] should not be imposed on children or adolescents in the absence of a reasonable expectation of proportionate medical benefit.[35]

Although a favorable risk/benefit profile is necessary to justify an intervention, it is not sufficient.[36] The intervention must be favorable relative not only to doing nothing but also to other known alternatives. With respect to PMT, a relevant alternative is some combination of psychotherapeutic interventions.[37] Like the evidence for hormonal and surgical interventions, evidence regarding alternative approaches to GD is sparse and inconclusive,[38] though as Chapter 14 reveals there is good reason to believe that psychotherapy can be an effective intervention. Regarding the potential harms of psychotherapy for adolescents with GD, a systematic review of the evidence found no evidence of negative or adverse effects in any of the studies examined.[39]

One possible objection is that although the evidence supporting hormonal and surgical interventions is of low or very low certainty, this does not prove that the interventions are ineffective. For all we know, the interventions may be *more* effective than researchers have reported. The methodological weaknesses of the studies do not prove inefficacy—they tell us only that we cannot infer much of anything about beneficial effects. The same limitations apply to evidence on harms—after all, because there are no well-designed randomized controlled trials (RCTs) of PMT, it follows that there are no well-designed RCTs demonstrating sexual dysfunction, infertility, bone density loss, impaired cognitive function, susceptibility to hormone-sensitive cancers, and other potential harms. Some argue that in the face of uncertain evidence both for benefit and for harm, patients themselves (and their families), with expert clinicians providing relevant clinical

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[34] Sweden's National Board of Health and Welfare concluded that "the risks of puberty blockers and gender-affirming treatment are likely to outweigh the expected benefits of these treatments" (Socialstyrelsen, 2022a, p. 3).
[35] The "should not" here is a moral "should not." It does not entail any conclusions about what the law should permit or require. The relationship between ethics and the law is complex and is not taken up in this Review.
[36] If considerations not directly related to health are included in the risk/benefit analysis, there may be cases where an intervention that is marginally less effective in promoting health may be recommended (e.g. when the marginally more effective treatment is much more expensive). And of course, to say that the clinicians should offer the more favorable intervention is not to say that patients do not have the right (in most cases) to refuse it.
[37] See Chapter 14.
[38] Cass (2024a, pp. 153-154).
[39] Heathcote et al. (2024, pp. s19-s32, Suppl. 2).

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information, should decide how to proceed.[40] Medical decisions under uncertainty, the reasoning goes, should be made by those with the greatest personal stake in the outcome. In pediatrics, this means children and adolescents, supported (usually) by their families.

This objection properly expresses concern for patient health and well-being as well as respect for the developing decision-making capacity of children and adolescents (and the greater capacity of their guardians). But it fails, for two reasons.

First, the objection understates the cumulative case for evidence of harm. We can be certain in the ordinary sense of "certain" that these interventions cause harm, even if we do not have "high certainty" evidence in the technical sense employed in evidence-based medicine (EBM).[41] We do not need results from RCTs to be certain that removing an adolescent's breasts will eliminate or substantially impair capacity for breastfeeding. Nor do we need RCTs to establish that PBs and CSH stunt growth of the penis, increasing the risks associated with future surgery.[42] And apart from any systematic reviews of published studies, basic human physiology indicates that blocking puberty at Tanner Stage 2 and following with CSH will negatively impact fertility. That advocates of PMT recommend fertility counselling before undergoing these interventions is evidence that they, too, anticipate the risk of infertility and regard it as a harm. Other forms of evidence, such as indirect evidence from research on adults, also contribute to the case that these interventions cause harm.[43] Finally, research on PMT has focused largely on potential benefits to mental health, with less attention given to potential physical harms, compounding the problem of publication bias.[44]

Second, even granting that the uncertainty of the evidence makes it impossible to assign precise values to the probabilities or magnitudes of various potential outcomes, it does not follow that clinicians are dependent on their patients to guide clinical decision-

[40] Antommaria (2024).
[41] Smith & Pell (2003)
[42] Terhune et al. (2022).
[43] See Chapter 7.
[44] See Chapter 6 for discussion of publication bias.

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making.[45] Rather, the obligation to avoid serious harm justifies a precautionary approach, particularly in the absence of evidence for a proportionately serious threat to the patient's health without the intervention. In their seminal textbook on medical ethics, Beauchamp and Childress write:

> Depending on what is valued and what is at risk, it may be ethically justifiable and even obligatory to take steps, in the absence of conclusive scientific evidence, to avoid a hazard where the harm would be both serious and irreversible—that is, a catastrophe. Triggering conditions for these measures include plausible evidence of potential major harm where it is not possible to adequately characterize and quantify risk because of scientific uncertainty and ignorance. The process of developing precautionary norms should not be viewed as an alternative to risk analysis and scientific research. It should instead be viewed as a way to supplement risk appraisals when the available scientific evidence does not permit firm characterizations of the probability or magnitude of plausible risks.[46]

It seems clear that the triggering conditions for adopting a precautionary approach to the use of hormonal and surgical interventions for the treatment of pediatric GD have been met. When precautionary considerations are added to the cumulative case for harm, the ethical argument against PMT becomes compelling.

> The importance of avoiding harm is emphasized by the fact that many treatments (e.g., surgery, hormone therapy) can lead to relatively common and potentially serious long-term adverse effects. This necessitates particularly strong justification (i.e., clear evidence of benefits and the decision-maker's competence) before administering such treatments or accepting these risks. In practice, physically modifying healthy bodies is generally associated with potential harms or risks. Empirical evidence concerning the long-term benefit-to-harm ratio of these interventions is often limited. In other words, avoiding harm

[45] One would hope this would come as a relief to clinicians and especially to pediatricians, though some seem happy to let children lead the way. See Chapter 11.
[46] Beauchamp & Childress (2019, p. 250)

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> prompts considerations similar to those raised by competence: when evidence of benefit is uncertain, but risks are probable, the ethical imperative to minimize harm is further underscored.[47]

The unfavorable risk/benefit profile distinguishes PMT from many other off-label uses of drugs and medical devices. Advocates for PMT point to the prevalence of off-label prescribing in pediatrics,[48] but the legitimacy of some off-label uses does not license the prescription of any pharmaceutical to any patient for any reason. The favorable risk/benefit threshold, or, more minimally, the precautionary threshold, must be met irrespective of whether the intervention is approved by FDA. Off-label use of an intervention is sometimes justifiable based on studies of the intervention in a different patient population or for a different indication. Such use may be warranted when there is a reasonable expectation of benefit, when there are no superior alternatives, and when the prognosis, absent medical intervention, is predicted to be worse for the patient than the negative effects of the off-label drug.

This is decidedly not the situation with PMT. The natural history of pediatric GD is poorly understood[49] and decades of research has shown that early-onset GD usually resolves without medical intervention.[50] There is no compelling evidence that the same will not prove true in the case of adolescent-onset symptoms, and limited evidence suggesting it will.[51] And in any case, it is widely acknowledged that clinicians are unable to distinguish patients whose GD will persist from those whose GD will resolve.[52] Further,

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[47] Saarni & Uusitalo (2020, p. 41); our translation. Original text: “Haittojen välttämisen tärkeyttä korostaa se, että monista hoidoista voi seurata varsin yleisiä ja vakaviakin pitkän tähtäimen haittoja (esim. kirurgia, hormonihoidot), jolloin hoitojen antamiselle (eli näiden riskien ottamiselle) pitää olla erityisen hyvät perusteet (eli näyttö hyödyistä sekä päätöksentekijän kompetenssista). Käytännössä terveiden kehojen fyysiseen muokkaukseen voidaan katsoa useimmissa tapauksissa liittyvän haittoja tai riskejä. Empiirinen näyttö hoitojen pitkän tähtäimen hyöty/haitta-suhteesta on useissa tapauksissa vähäistä. Toisin sanoen haitan välttäminen johtaa siis samankaltaiseen pohdintaan kuin kompetenssikysymys: jos näyttö hyödyistä on epävarmaa mutta haitat todennäköisiä, haittojen minimoinnin tärkeys eettisenä periaatteena korostuu.”

[48] Meng et al. (2022).

[49] See Chapter 4.

[50] Ristori & Steensma (2016); Singh et al. (2021).

[51] Bachmann et al. (2024); Byrne (2024a); Rawee et al. (2024); Sun et al. (2023)

[52] “Although a diagnosis of gender dysphoria has been seen as necessary for initiating medical treatment, it is not reliably predictive of whether that young person will have longstanding gender incongruence in the future, or whether medical intervention will be the best option for them.” (Cass, 2024a, p. 29). The

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there are concerns about the role medicalization itself may play in contributing to the persistence of the conditions being treated,[53] and less invasive and less risky interventions are available.[54] Lastly, medical intervention has known and plausible harms,[55] and decades of research conducted by leading academic institutions have failed to produce reliable evidence of medical benefit.[56]

13.2.4 Justice

According to the Belmont Report, published in 1978 in the wake of the U.S. Public Health Service's Untreated Syphilis Study at Tuskegee, "An injustice occurs when some benefit to which a person is entitled is denied without good reason or when some burden is imposed unduly."[57] While the Belmont report set out ethical principles to guide human subjects research, the principle of justice applies also to clinical medicine. Advocates for PMT sometimes claim it is unjust to withhold PBs, CSH, or surgeries from youth with GD.[58] They cite research finding that this patient population has significant healthcare needs and also suffers from social marginalization and stigma.[59] These patients indeed are vulnerable along multiple axes, and it would be an injustice to deny them safe and effective medical care. It would also be unjust, however, to subject them to serious hormonal and surgical interventions that lack a favorable risk/benefit profile. In fact, it seems particularly unjust to subject youth struggling with complex psychiatric, neurodevelopmental, and psychosocial challenges to the harms associated with these interventions. The justice principle has been rightly invoked but wrongly applied.

In both her Interim and Final Reports, Cass notes concerns brought to her by patients and families about "diagnostic overshadowing."[60] Diagnostic overshadowing is a form of

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recent German clinical guidelines note that its own review found no studies that could supply empirical criteria to determine whether GD or gender incongruence would persist into or beyond adolescence (German Society for Child and Adolescent Psychiatry, Psychosomatics and Psychotherapy (DGKJP), 2025, p. 188).

[53] Jorgensen (2023a).
[54] See Chapter 14.
[55] See Chapter 7.
[56] See Chapter 5.
[57] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (2010).
[58] Kimberly et al. (2018); Maung (2024).
[59] Hatzenbuehler & Pachankis (2016); Rider et al. (2018).
[60] Cass (2022a, p. 46; 2024b, p. 200).

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bias that leads clinicians to misattribute symptoms of one condition to a different previously diagnosed condition. This can happen, for example, when clinicians mistakenly attribute patients' complaints of physical discomfort to the patient's previously diagnosed psychiatric condition, a mistake that may lead to misdiagnosis and inadequate treatment.[61] Diagnostic overshadowing is especially salient in mental health care contexts, where a patient with psychiatric problems, neurodevelopmental challenges, or cognitive disabilities may be treated one-dimensionally as a "case" of some psychiatric diagnosis rather than holistically as a person susceptible to a range of health problems unrelated to that diagnosis.

In the context of PMT, the concern is that the diagnosis of GD tends to obscure causes of distress and crowd out other mental health care needs, particularly when patients are referred to specialty gender clinics. The gender clinic model of care becomes Maslow's hammer to which every problem appears as a nail. The risk of diagnostic overshadowing increases insofar as (1) clinicians fail to provide comprehensive psychiatric evaluations;[62] (2) clinicians face pressure from colleagues, patients, and parents to "affirm" patients prematurely, that is, prior to providing them sufficient time to develop and mature;[63] and (3) co-occurring mental health challenges or problem behaviors are reflexively assumed to be minority stress-mediated sequelae of the patient's GD diagnosis.[64] To neglect the mental health care needs of members of an already vulnerable population of youth with complex psychiatric, neurodevelopmental, and psychosocial challenges is to deny them a benefit to which they are entitled, and to expose them to medically unnecessary risk of harm is to impose a burden unduly.

There are additional problems related to justice. Compared to their age-matched peers, same-sex attracted youth are significantly overrepresented among patients presenting to gender clinics.[65] As noted in Chapter 3, this phenomenon has been observed from the beginning. Of the 70 patients recruited by de Vries and colleagues in the

[61] Hallyburton (2022); Jones et al. (2008); Reiss et al. (1982).
[62] Damiano (2024a).
[63] Edwards-Leeper & Anderson (2021).
[64] Papers claiming minority stress explains various health problems of transgender-identified adolescents include Delozier et al. (2020); Dolotina & Turban (2022); Hunter et al. (2021).
[65] Drescher & Yarbrough (2024); Singh et al. (2021); Wood et al. (2013).

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Netherlands from 2000 to 2008, 62 reported being exclusively same-sex attracted, six reported being bisexual, and one reported being exclusively opposite-sex attracted.[66] That is, the original Dutch Protocol patient cohort was comprised almost entirely of gay, lesbian, and bisexual patients[67]—one of whom died as a result of surgical complications from vaginoplasty following pubertal blockade and cross-sex hormones.[68] Reports of negative attitudes towards homosexuality, which may be internalized, are not uncommon in this field.[69] One of the earliest clinical reports on adolescent transition describes a family concerned that their son's gender nonconformity was a sign of homosexuality.

> It is of interest to note that [the patient's family] were all reassured to discover that George was not a *homosexual*. The diagnosis of 'transexual' provided an explanation for his feminine behavior and was, especially for the parents, psychologically relieving.[70]

Given the medical profession's history of pathologizing and medicalizing same-sex attraction,[71] serious justice-related concerns are raised by the overrepresentation of gay, lesbian, and bisexual adolescents among patients receiving unproven interventions that adversely impact fertility and sexual function.

13.3 Alternative clinical rationales

Clinical research on pediatric medical transition has focused primarily on its effects on psychiatric morbidity and to a lesser extent on psychosocial function. The original Dutch

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[66] de Vries et al. (2011, Table 1). The remaining one patient reported "don't know yet."
[67] Biggs (2023b).
[68] Biggs (2023b); de Vries et al. (2014); Negenborn et al. (2017) Bachmann et al. (2024); Sun et al. (2023).
[69] Barnes (2023); Sansfaçon et al. (2023); Littman (2021).
[70] Newman (1970). Given clinician reports of his self-reported sexual behavior and desires, it is almost certain that George was gay.
[71] Hodge (1950); Murphy (1992); Shidlo et al. (2001). From Hodge: "Male aged 37 years, who came voluntarily, being concerned by his definite homosexual bias which, though it had not since puberty found overt expression, was nevertheless a source of great worry and unhappiness … He appeared after close investigation to be a homosexual deviant of very long standing—an 'innate' pattern rather than one of traumatic 'level fixation'—and he failed to respond to psychotherapy. Treatment by oestrone has been followed by loss of sexual libido and he reports considerable 'mental relief.'" (p. 135) See also Chapter 3 for the influential case of George/Christine Jorgensen and the subsequent wave of lesbian and gay people who sought medical transition.

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Protocol required patients to have "Gender Identity Disorder" (GID), as GD was then called. The diagnostic criteria for GID and its DSM-5 successor GD include clinically significant distress and/or functional impairment.[72] While the diagnostic criteria for GD closely mirror the previous criteria for GID, the DSM-5 more explicitly emphasizes that cross-sex identity, by itself, does not constitute a pathology. The attendant distress, if present, is what is pathological. As such, medical interventions target the patient's distress or impairment, not the underlying identification.

That patients must have a mental health disorder to access medical resources has long troubled some patients and advocacy groups.[73,74] Some clinical protocols require patients to undergo assessment to determine if they meet (*inter alia*) the distress or impairment criterion—it is not enough that a patient attests to cross-sex identification or incongruence. These criteria thereby create an impediment[75] for people who do not suffer distress or impairment but who nevertheless wish to medically alter their bodies. To access the interventions they want, these patients may need to exaggerate or feign symptoms or else shop for clinicians willing to rubber stamp a diagnosis.[76]

One possible solution to this challenge is simply to eliminate any requirement for a medical diagnosis. Doing this would remove the obstacle of assessment from the path of patients seeking medical interventions. The problem with this solution for the DSM and the ICD working groups was that removing the diagnoses altogether would make reimbursement for medical intervention difficult or impossible. The tension between

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[72] Because GID and GD are DSM diagnoses and the DSM is a manual of mental disorders, this is not surprising. However, it does constrain the options available to clinician-researchers insofar as reimbursement requires a DSM diagnosis, i.e. the categorization of the patient as suffering from a mental disorder.

[73] Drescher (2017).

[74] Objections to medical "gatekeeping" and tensions between patients and clinicians regarding the pathologization of cross-sex identification predate the Dutch Protocol and the medicalization of pediatric gender distress by decades. Adults, wishing for hormones and surgeries to satisfy their longing to modify their bodies and to be perceived as members of the other sex, have butted heads with psychiatrists, psychologists, endocrinologists, and surgeons since the early 20th century when the first "sex change" procedures took place. Disciplinary turf wars between experts, with each field vying for authority over diagnosis and treatment, contributed to the ongoing professional uncertainty over the fundamental aims of medical intervention and the appropriate balance of power between patients and clinicians. See Meyerowitz (2009); Shuster (2021).

[75] Jacobsen (2024).

[76] For accounts of patients feigning symptoms and manufacturing histories in order to convince clinicians of their medical need, see Ashley (2019); Pimenoff & Pfäfflin (2011); Shuster (2021).

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ensuring reimbursement and thereby access, on the one hand, and satisfying the demands of patients and activist groups for depathologization, on the other, required compromises on the part of DSM and ICD developers.[77] The DSM developers depathologized incongruence and pathologized distress. The ICD-11 developers had more options because unlike the DSM, which is devoted exclusively to mental disorders, the ICD catalogues all diseases and health conditions. Having considered the various possibilities,[78] the ICD-11 working group decided to move the diagnosis out of the mental health chapter, where it was believed to contribute to stigma, and into a new chapter, "Conditions Related to Sexual Health," where it would be less stigmatizing but still useful for purposes of reimbursement.

Consequently, present DSM and ICD diagnoses comprise different frameworks shaped by historical contingencies—including, crucially, payment considerations.[79] According to the DSM-5, experiencing gender incongruence itself is not pathological, while associated distress or impairment are, rendering GD a mental disorder. Meanwhile, according to the ICD-11, gender incongruence (that is, being transgender according to contemporary understandings of what it is to be transgender) itself is pathological, but not a mental health disorder. ICD-11's diagnosis, Gender Incongruence of Adolescence or Adulthood, includes no requirement of distress or impairment for medicalization. Thus, DSM-5 and ICD-11 differ on whether hormonal and surgical interventions are treatments for a mental health problem or rather some other kind of pathology, on whether transgender identity itself is pathological, and on whether a patient must be distressed or impaired to receive reimbursable medical intervention. Despite these differences and inconsistencies, both diagnoses are employed to justify and reimburse the provision of hormonal and surgical interventions to adolescents.

The more permissive approach to medicalization is defended by some clinicians,[80] bioethicists, and activists.[81] For example, bioethicist Florence Ashley argues that the

[77] Drescher (2015).
[78] Drescher et al. (2012).
[79] See Drescher (2015); Drescher & Yarbrough (2024).
[80] See Chapter 11.
[81] Chu (2024).

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provision of hormonal and surgical interventions to adolescents is justified by the interventions' capacity to satisfy patients' "gender embodiment goals":

> Adolescent medical transition aims at preventing or altering the development of sexual characteristics to achieve the individual's gender embodiment goals. Given its purpose, the effectiveness of adolescent medical transition is defined by its ability to achieve the sought physiological outcomes—a standard undisputedly met.[82]

While the Dutch Protocol was designed to alleviate adolescents' psychiatric distress and improve psychosocial functioning, Ashley's approach drops the requirement of clinical improvement—achieving the patient's embodiment goals is enough.[83] Elsewhere, Ashley explains that some people seek hormonal or surgical interventions not because they are suffering from a pathology but rather because these treatments can deliver certain desired experiences such as "gender euphoria" and "creative transfiguration." Gender euphoria is a "distinct enjoyment or satisfaction caused by the correspondence between the person's gender identity and gendered features associated with a gender other than the one assigned at birth."[84,85] Creative transfiguration, Ashley writes, "is more difficult to capture in words. Foregrounding creativity and aspirational aesthetics, creative transfiguration sees the body as a gendered art piece that can be made ours through transition-related interventions."[86]

Because contemporary gender medicine countenances a multiplicity of "genders," this newer emphasis on embodiment goals moves beyond the "sex change" framework of previous decades, in which male patients acquired female-typical characteristics to "live as women" and female patients acquired male-typical characteristics to "live as men"

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[82] Ashley (2022a, p. 127).
[83] See Gorin (2024). It is notable that de Vries, the lead author of the two seminal papers (de Vries et al 2011 and 2014) that established the Dutch Protocol, has more recently questioned the "logic of improvement" that undergirds that original clinical rationale and has favorably cited the approach advocated by Ashley (Oosthoek et al., 2024).
[84] Ashley & Ells (2018, p. 24). The definition of gender euphoria offered by Ashley and Ellis entails that no one who does not experience incongruence can experience gender euphoria. According to other writers, however, gender euphoria is "quite common… among trans and cis folks alike." (Kukla, 2024, p. 288).
[85] Researchers recently have developed a scale intended to measure gender euphoria (Blacklock et al., 2025).
[86] Ashley (2019, p. 481).

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(see Chapter 3). Nothing in the newer "gender affirming" approach limits the number of bodily variations clinicians may be asked to create. Some girls or women want just a bit of stubble while others want full beards and flat chests; some boys or men want softer skin and breasts but wish to keep their penises intact. Expanding clinical offerings reflect these expanding embodiment goals. Surgeons provide penis-preserving vaginoplasty for patients who want both male and female genitals and offer "nullification" procedures for patients who identify as nonbinary and want no external genitals at all. There are at least as many physical combinations for patients to acquire as there are "gender identities"—indeed more, since presumably each gender identity can be embodied in different ways.[87]

While the ICD-11 does not mention "gender euphoria" or "gendered art pieces," the diagnostic criteria for Gender Incongruence of Adolescence or Adulthood implicitly formalize the "embodiment goals" approach to medical transition. The diagnosis is explained as follows:

> Gender Incongruence of Adolescence and Adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.[88]

According to Jack Drescher, a member of the World Health Organization's (WHO) Working Group on the Classification of Sexual Disorders and Sexual Health, which was tasked with making recommendations for the ICD's eleventh edition, to qualify for the diagnosis of Gender Incongruence of Adolescence or Adulthood, a patient need satisfy only two of the following four criteria:

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[87] James et al. (2015).
[88] World Health Organization (2022b).

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1. Strong dislike or disagreement with primary or secondary sexual characteristics due to incongruence with the experienced gender.

2. Strong desire to get rid of some of those sexual characteristics due to the incongruence with the experienced gender.

3. Strong desire to have the primary or secondary sexual characteristics of the experienced gender.

4. Strong desire to be treated and accepted as a person of the felt gender.[89]

It is hard to see how either of the first two criteria could be used to diagnose gender incongruence. ICD-11 says that gender incongruence is "characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex …"[90] Criteria (1) and (2) themselves include incongruence and so the diagnosis, when met by the first two criteria, suggests that a person has gender incongruence because they have attitudes or desires due to incongruence.[91]

Setting problems of circularity aside, an adolescent can be diagnosed with gender incongruence by satisfying (3) and (4),[92] which amount to having certain strong embodiment goals. A male who strongly desires to have (some? all?) the sex characteristics of a female and to be treated or accepted as such, or a female who strongly desires to have (some? all?) the sex characteristics of a male and to be treated or accepted as such, qualifies for the diagnosis. According to the ICD-11, a patient with such desires has a "condition related to sexual health" and, therefore, clinicians have a rationale for providing, and being reimbursed for, hormonal or surgical interventions.

It is noteworthy that the ICD-11 employs identical diagnostic criteria for adolescents and adults, despite the clear physiological and psychological developmental differences

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[89] Drescher & Yarbrough (2024, p. 2508).
[90] World Health Organization (2022a).
[91] The problem of circularity is also discussed in Chapter 2. It is also unclear what it could mean to be in a state of "disagreement" with one's sex characteristics. Perhaps the authors mean that one finds one's sex characteristics disagreeable, that is, unpleasant. This makes sense, as long as the unpleasantness does not rise to the level of distress, which would transform gender incongruence into something like gender dysphoria and thereby undermine the rationale for moving the gender incongruence diagnosis out of the mental disorder chapter of ICD-11.
[92] Whether the criteria must be met for a specific period of time is unclear. ICD-11 does not specify a time requirement; Drescher and Yarbrough say "several months" (Drescher & Yarbrough, 2024, p. 2508).

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between these populations and their respective capacities for decision-making and self-understanding. Neither DSM-5-TR nor ICD-11 provide any explanation for why children or adolescents might desire to modify their sex traits or to be treated or accepted as someone other than a member of their sex, and counseling approaches that might explore possible explanations with patients often are labeled "conversion therapy" by advocates of the "gender-affirming" approach.[93] As far as the DSM-5-TR and ICD-11 diagnoses are concerned, it makes no difference that a patient of 10 or 13 or 17 might wish to modify their body and be perceived and treated as someone other than a member of their sex for any number of reasons. These may include discomfort with one's homosexuality, a history of sexual trauma, pubertal distress, the rejection of perceived sex-based roles, and/or psychiatric comorbidities. For the ICD-11, desire alone is sufficient to justify a medical diagnosis and, within the "gender-affirming care" framework, set the adolescent on a course of PMT.

If using hormonal and surgical interventions to reduce psychiatric morbidity associated with gender dysphoria lacks a favorable risk/benefit profile, using these interventions merely to satisfy adolescents' embodiment goals veers from clinical error into clinical recklessness.

13.4 Regret

Patient regret has begun to receive significant attention in discussions of PMT. Proponents of PMT claim that regret is extremely rare.[94] Some also claim that since mental health assessments have not been shown to reduce regret rates, they should not be required prior to prescribing.[95] The tacit assumption is that absence of regret is an indication of medical benefit or at least of absence of harm. Other researchers point out that research on regret, like most research in PMT, is severely lacking and that we do not know the true prevalence of regret.[96] Whether implicitly or explicitly, proponents and critics alike consider the question of regret as central to the ethics of PMT.

[93] Ashley (2023). See Chapter 14.
[94] Crabtree et al. (2024); Kidd & Sequeira (2024); McNamara et al. (2024); Turban et al. (2021).
[95] Ashley et al. (2023); Wu & Keuroghlian (2023). See also Chapter 11.
[96] Cohn (2023); Jorgensen (2023b); MacKinnon, Expósito-Campos et al. (2023).

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That some patients report profound regret after undergoing invasive, life-changing medical interventions is clearly of importance. However, regret alone (just like satisfaction alone) is not a valid indicator of whether an intervention is medically justified. Not only is regret a complex phenomenon itself,[97] but its relation to ethical considerations in medicine, and to benefit and harm in particular, is tenuous. Patients sometimes come to regret consenting to interventions that were in fact well-justified, that is, interventions that did offer a favorable risk/benefit profile at the time the intervention was proposed. Patients may come to regret such interventions because they suffer harmful complications that were unlikely to occur but did occur in their case. Or they may come to regret the interventions for other reasons. For example, a woman may undergo a spine surgery for which there is compelling evidence of net benefit to her health and yet come to regret the surgery because the modest relief of pain seems to her retrospectively to have not been worth the cost or hassle involved in recovering from the surgery. Or perhaps the improvement in her health allowed her to take some course of action that turned out to make her life worse, all things considered. That she comes to regret the surgery does not mean that it was clinically or ethically unjustified, nor that her clinician violated medical ethics.

Conversely, humans have a remarkable capacity to incorporate suffering and loss into their life stories. A man may be paralyzed as the result of a spine surgery that did not prospectively offer a favorable risk/benefit profile, and which should never have been attempted by the surgeon. Yet months or years later the man may report that he does not regret undergoing the surgery, because the injury and debility it caused led him to focus more attention on the love and care of his family and friends. Or perhaps, as able-bodied, he was isolated and lonely but now, due to his greater physical dependency, he finds a supportive community within which he develops a new identity that imbues his life with structure and purpose. Or maybe as a result of his injury he simply comes to appreciate more deeply the gift of life in its fragility. That this man does not regret the surgery does not imply that his decision to consent to it was prudent, nor that the surgeon was justified in offering the surgery.

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[97] Landman (1987).

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The implications for PMT are complex. The provision of hormonal or surgical interventions to physically healthy adolescents cannot be vindicated by purportedly low rates of regret. Some patients who have suffered objective medical harm and then detransitioned nevertheless do not regret having been medicalized.[98] Nor can the interventions be condemned based on the fact that some adolescents who have undergone them do report regret. The central question for PMT is not: "Do these medically transitioned patients have regret?" A more fundamental question is, "Does medical transition provide health benefits proportionate to its harms?" The best available evidence, along with a risk/benefit analysis and precautionary approach ethically appropriate to pediatrics, shows that the answer to the latter question is almost certainly "no."

13.5 Research Ethics

Multiple SRs, commissioned by leading international health authorities and conducted by independent academic researchers, have concluded that the evidence underpinning the expected benefits of PMT is of low or very low certainty.[99] A natural response among researchers to the absence of higher quality evidence is to conduct more and better research. Whether and how such research should be conducted, however, is a matter of significant ethical controversy.

One controversy concerns RCTs, the "gold standard" for clinical research.[100] Some proponents of PMT claim that RCTs on the effects of PBs or CSH would be infeasible and unethical.[101] With respect to feasibility, because the effects of PMT interventions are so apparent, it is not possible to blind researchers and participants in an RCT for which the control group receives only psychotherapeutic support. Some worry that many adolescents would refuse to participate in a study that does not guarantee they receive hormonal interventions, or that they would drop out if randomized to the control group. These challenges may be harder to overcome in the current climate in which adolescents have been led to believe that hormonal and surgical interventions are well-

[98] For some real examples, see Sansfaçon et al. (2023).
[99] See Chapter 5.
[100] Hariton et al. (2018).
[101] Ashley et al. (2024, 407-418).

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supported by the evidence and even life-saving.[102] However, randomization does not require blinding, and until an RCT is attempted, speculation about how potential participants will respond is just that—speculation.

With respect to research ethics, one objection to conducting RCTs is that such research would violate the principle of equipoise. In their textbook, *Principles of Biomedical Ethics*, Beauchamp and Childress explain that "[t]he community of reasonable physicians is … in a state of 'clinical equipoise'" when "[n]o one knows, prior to conducting the research, whether it is more advantageous to be in the control group or in the experimental group … In this model, no patient, then, will receive something known to be less effective or to have a higher risk than an available alternative."[103]

Advocates for PMT allege that it would violate the principle of equipoise to conduct an RCT of PMT in which the control group receives only psychological counseling, "given the numerous studies associating adolescent gender-affirming interventions with improved mental health."[104] This allegation is unfounded, however, because it mischaracterizes the state of the science. Indeed, if equipoise were violated, it plausibly would be in the other direction, given the more certain evidence of harm. In the end, while their reasons differ, there may be a point of agreement between proponents of PMT and some of its critics concerning the impermissibility of conducting RCTs for hormonal or surgical interventions for pediatric GD.

It is not clear that hormonal or surgical interventions for GD can ethically be offered in a trial, irrespective of trial design. Currently, researchers in the U.K. are planning a PB trial. At the time of this Review's writing, the trial has not yet received official ethics approval, and details regarding the trial's design, which outcomes will be studied, what the inclusion and exclusion criteria will be, and so on, have not been published. Some critics of PMT already are raising concerns about the proposed study. They worry about prescribing PBs even in research settings given the recognized inability of clinicians to distinguish between patients whose GD will persist into adulthood from those whose GD

[102] Clayton, A. (2023).
[103] Beauchamp & Childress (2019), p. 365; See also Freedman (1987).
[104] Ashley et al. (2024, p. 408).

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will resolve on its own,[105] and the high likelihood that any patient who begins PBs will go on to CSH and possibly surgery.[106] Since most adolescents who take PBs go on to CSH, and since it is CSH and surgery that provide the sought-after physical characteristics in PMT, it is unclear whether PBs are a stand-alone treatment and should be studied as such.

Other critics point out that safer types of research—for example, research into various psychotherapeutic approaches—have yet to be explored with this population of patients. They also point out that U.S. gender clinics have yet to collect longitudinal data on existing patients.

There are other important ethical problems to consider. The Nuremberg Code is a foundational and internationally accepted statement of norms guiding human subjects research and it includes the following:

> The experiment should be so designed and based on the results of animal experimentation and a knowledge of the natural history of the disease or other problem under study, that the anticipated results justify the performance of the experiment.[107]

This suggests that, insofar as PMT poses risks that can be explored through animal studies, such studies should be conducted before these treatments are further tested on humans. Animal studies could help clarify how hormonal interventions affect fertility, brain development,[108] bone development (including future risk of fracture), and cardiovascular outcomes. Such studies also could help clarify to what extent and under what conditions fertility can be recovered after suppression by hormonal interventions.

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[105] Feinmann (2025).
[106] E.g. Brik et al. (2020); Carmichael et al. (2021); Karakılıç Özturan et al. (2023a); van der Loos, Klink et al. (2023); Wiepjes et al. (2018).
[107] BMJ (1996).
[108] Chen and colleagues, for example, write, “studies in rodents show ovarian hormones, acting during puberty, program cognitive flexibility by exerting long-lasting effects on excitatory-inhibitory balance in the pre-frontal cortex . . . [and] testosterone, acting during puberty, programs the ability to adapt behavior as a function of social experience” (Chen et al., 2020, Table 2).

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The World Medical Association's Declaration of Helsinki is another foundational and internationally accepted statement of guidance for human subjects research. It includes the following:

> All medical research involving human participants must be preceded by careful assessment of predictable risks and burdens to the individuals and groups involved in the research in comparison with foreseeable benefits to them and to other individuals or groups affected by the condition under investigation. Measures to minimize the risks and burdens must be implemented. The risks and burdens must be continuously monitored, assessed, and documented by the researcher.
>
> Physicians and other researchers may not engage in research involving human participants unless they are confident that the risks and burdens have been adequately assessed and can be satisfactorily managed.[109]

It is not ethical to subject adolescents to hormonal and surgical interventions used in PMT, even in a research trial, until and unless the state of the evidence suggests a favorable risk/benefit profile for the studied intervention, *and* the researchers have well-grounded confidence that the foreseeable "risks and burdens have been adequately assessed and can be satisfactorily managed." As explained in this Review, the state of the science does not support a favorable risk/benefit profile, nor does it give researchers a basis for confidence that the risks of PMT can be satisfactorily managed.

Finally, the Belmont Report, authorized by the National Research Act of 1974 and published in 1979 by the United States National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, is a landmark statement of ethical principles to guide human subjects research in the United States. The Belmont Report affirms that research on humans should not be conducted until and unless that research is "justified on the basis of a favorable risk/benefit assessment" arrived at through "systematic, nonarbitrary analysis of risks and benefits." It continues:

[109] World Medical Association (2025).

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> Thus, there should first be a determination of the validity of the presuppositions of the research; then the nature, probability and magnitude of risk should be distinguished with as much clarity as possible … It should also be determined whether an investigator's estimates of the probability of harm or benefits are reasonable, as judged by known facts or other available studies … [and] When research involves significant risk of serious impairment, review committees should be extraordinarily insistent on the justification of the risk (looking usually to the likelihood of benefit to the subject …).[110]

As demonstrated throughout this Review, the presuppositions that guide PMT have not been shown to be valid; the nature, probability and magnitude of risks associated with PMT have not been distinguished with sufficient clarity; PMT proponents' estimates of the probability of harm and benefit have not been shown to be reasonable, as judged by known facts and available studies; and the risks of serious impairment that PMT involves have not been shown to be justified. For these reasons, administering PMT to adolescents, even in a research context, is in tension with well-established ethical norms for human subjects research.

[110] National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research (2010).

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PART 5

PSYCHOTHERAPY

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Chapter 14 Psychotherapy

This chapter reviews psychotherapy (talk therapy) for gender dysphoria (GD).[1] First, the chapter describes relevant trends in society at large and in the medical profession; specifically, trends in youth mental health (Section 14.1) and in diagnostic and social labels (Section 14.2). Section 14.3 discusses the role of mental health assessment in the care of youth with GD. Section 14.4 briefly recounts the re-emergence of psychotherapy as the primary treatment for this patient population in Europe, and Section 14.5 discusses psychotherapy and its specific application to GD.

14.1 Youth mental health

Puberty is the biological, developmental process during which a child becomes a sexually mature adult.[2] Puberty overlaps significantly with adolescence, the period between childhood and adulthood.[3] During puberty, hormonal fluctuations can affect mood and behavior.[4] The onset of puberty often coincides with heightened sensitivity to social dynamics and self-image along with increasing vulnerability to stress and anxiety. Emotional regulation can become challenging as adolescents navigate the complexities of identity formation and peer relationships. Cognitive development accelerates, allowing deeper abstract thinking and self-reflection, which can contribute to existential questioning and emotional instability.[5] Adolescence also involves learning to function independently, as part of identity formation and individuation from the family of origin. Rebellion and resistance to parents and other caregivers or authority figures frequently occur during this process. Adolescents often struggle with long-term planning and are more susceptible to risk taking, as drives for stimulation and affiliation increase but the prefrontal cortex, responsible for executive functions, is still maturing.[6]

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[1] Gender Dysphoria is a formal diagnosis in the fifth edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5): see Appendix 2. In this chapter and throughout the Review the term "gender dysphoria" is used to refer to sex-related distress or discomfort, not the formal diagnosis (see Chapter 1, Note 1).
[2] See Chapter 7.
[3] According to the American Academy of Pediatrics (AAP), adolescence spans ages 12-21 (Hardin et al., 2017). See also National Academies of Sciences, Engineering, and Medicine (2019, pp. 22-23).
[4] Viner (2015).
[5] E.g., Reena (2015); Steinberg (2005).
[6] Steinberg (2009).

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14.1.1 Trends in youth mental health

In 2021, the American Academy of Pediatrics (AAP), the American Academy of Child and Adolescent Psychiatry (AACAP), and the Children's Hospital Association declared a "National State of Emergency in Children's Mental Health."[7] In December of that year, U.S. Surgeon General Admiral Vivek Murthy issued an Advisory on Protecting Youth Mental Health, highlighting rising rates of depression, anxiety, hopelessness, and self-harm among youth—trends that worsened during the COVID-19 pandemic. The Lancet Psychiatry Commission on youth mental health noted a similar worldwide trend.[8]

In the U.S., there has been a significant increase in mental illness among teens and young adults since 2010.[9] Data reveal sharply increased rates of diagnosed depression and anxiety; some studies indicate that these rates have more than doubled.[10] Increases also have been documented in rates of suicidal ideation and behavior and self-harm,[11] emergency room visits and hospitalizations for self-harm,[12] and death by suicide.[13] Young people today experience weaker social connections and greater feelings of loneliness. Since 2010, adolescents have had fewer in-person social

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[7] American Academy of Child and Adolescent Psychiatry et al. (2021).
[8] McGorry et al. (2024).
[9] Twenge (2020).
[10] Data from a large national database showed that rates of major depressive episodes among adolescents aged 12 to 17 increased by 52% from 2005 to 2017 (from 8.7% to 13.2%) and by 63% among young adults aged 18 to 25 from 2009 to 2017 (from 8.1% to 13.2%) (Twenge et al., 2019). The "Anxious Generation" website, using Centers for Disease Control and Prevention (CDC) data, shows that rates of major depressive disorder from 2010 to 2022 more than doubled for both boys and girls, with major depression in boys increasing by 161% and in girls by 145%. Mental illness for college students increased, with a 134% increase in anxiety and 106% increase in depression over that same period (Rausch & Haidt, 2023). A cohort study of approximately 1.7 million individuals aged 5 to 22 years in Southern California revealed that from 2017 to 2021 the overall incidence of depression increased by approximately 60%, and anxiety by 31% (Xiang et al., 2024). A survey of a Midwestern school district found from 2012 to 2018 there was a 29% increase in youth screening positive for past-month anxiety (Parodi et al., 2022). See also Goodwin et al. (2020); Keyes & Platt (2024).
[11] See CDC trends report, 2013-2023 (Centers for Disease Control and Prevention, 2023).
[12] See Gutiérrez-Sacristán et al. (2022) for information about increase in psychiatric hospitalizations during the COVID-19 pandemic, for example. See also McGorry et al. (2024).
[13] Suicide death rates for children and young adults aged 10 to 24 years increased 62% from 2007 (6.8 per 100,000 individuals) to 2021 (11.0 per 100,000 individuals) (Curtin et al., 2023). Youth suicides began to rise in the 2000s, with a sharper upward trend starting around 2012; see Farah et al. (2023); Miron et al. (2019); Twenge (2020).

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interactions with peers compared to previous generations.[14] The deterioration in youth mental health has no one simple explanation. Researchers and theorists have identified several potential factors, including overprotective parenting,[15] the decline in free play,[16] and the ubiquity of smartphones and social media.[17] In 2023, the Surgeon General released an Advisory of Social Media and Youth Mental Health, which called attention to the potential risks associated with social media use for children and adolescents.[18]

14.2 Diagnostic and social labels

The rise in reported mental health problems may be partly attributable to overdiagnosis. Some argue that the rise in mental health awareness campaigns aimed at reducing stigma and increasing understanding may have led some young people to interpret normal behaviors and typical developmental challenges as a mental health disorder.[19] Being labeled with a mental health diagnosis can influence how young people see themselves, affect their belief in the possibility of change, and shape how others perceive them. The very act of classifying psychiatric conditions changes the behavior of patients and clinicians. Although diagnostic labels are important for research—where categorizing people or experiences is often necessary—they can oversimplify the

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[14] Twenge et al. (2021); Twenge (2023). Based on CDC data, adolescents have, over time, reported increased feelings of meaninglessness, as well as less willingness to engage in risk-taking behaviors. This includes behavior such as drug and alcohol consumption, but also encompasses developmental experiences such as working or learning to drive a vehicle (Haidt, 2024).
[15] Wang et al. (2024); Winnicott (1965); Zhang & Ji (2024).
[16] According to the AAP: "Children need to develop a variety of skill sets to optimize their development and manage toxic stress. Research demonstrates that developmentally appropriate play with parents and peers is a singular opportunity to promote the social-emotional, cognitive, language, and self-regulation skills that build executive function and a prosocial brain" (Yogman et al., 2018).
[17]Increased use of technologies, including social media, caused a displacement of other activities, such in-person socializing, schoolwork, sleep, sports, reading, and other hobbies. Heavy use of smart phones and social media is ubiquitous among teenagers today (Rothwell, 2023; Twenge et al., 2022; Twenge & Campbell, 2019; Vogels et al., 2022), and common among pre-teens (Rideout et al., 2022). Social media in particular may result in worsening mood and negative self-image in adolescent girls (Choukas-Bradley, 2024; Rodgers & Rousseau, 2022; Scott et al., 2023), and in some cases may play an etiologic role in increasing presentations of specific psychiatric and neurologic issues (Giedinghagen, 2023; Haltigan et al., 2023; Hull & Parnes, 2021; Padín et al., 2021; Pringsheim et al., 2021; Weigle & Shafi, 2024). Social media has introduced a new sociomedical phenomenon in which individuals may find a sense of belonging online through identification with an illness or condition, which may place them at risk of inappropriate or unnecessary medical care (Corzine & Roy, 2024). For a meta-analysis that found reasons for skepticism about the evidence for the effects of social media on mental health, see Ferguson (2025).
[18] Office of the Surgeon General (2023).
[19] Foulkes & Andrews (2023).

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richness and complexity of human experiences for the benefit of a standardized clinical language. To some extent, skillful clinicians can compensate for this reductionism,[20] but they cannot prevent diagnostic labels from escaping the clinic and being used in unintended ways in the wider culture.[21]

Overdiagnosis can lead to overtreatment; unnecessary tests, procedures or medical interventions may cause harm rather than helping. Loosening the diagnostic criteria for a condition will likely increase overdiagnosis and the risk of iatrogenic harm, so definitions should be formulated responsibly:

> … any changes [to diagnoses] should use a systematic, transparent approach where benefits and harms are explicit, especially when they lead to an increase in the prevalence of disease, and broadening of definitions should require evidence of clinical benefit.[22]

Although the term "gender identity" was used in the 1960s,[23] it did not appear in the *Diagnostic and Statistical Manual of Mental Disorders* until 1980 (third edition, DSM-III). "Gender Identity Disorders" was a subcategory of "Psychosexual Disorders," further divided into "Transsexualism" (for late adolescents and adults) and "Gender Identity Disorder of Childhood."[24] In the DSM-IV, published in 1994,[25] "Transsexualism" vanished, and "Gender Identity Disorder" (GID), covering both adults and children, appeared under "Sexual and Gender Identity Disorders." The DSM-5, published in 2013,[26] replaced "Gender Identity Disorder" with "Gender Dysphoria" and designated it as a separate category. This last change "focused the diagnosis on the gender identity-related distress that some transgender people experience (and for which they may seek

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[20] Johnstone (2018).
[21] Hacking (1998); Shorter (1993). See also Brossard (2019); Elliott (2000); Haslam (2016); Lindholm & Wickström (2020); Smids & Vasterman (2025).
[22] Kale & Korenstein (2018, p. 8). The field of psychiatry is no stranger to the phenomenon of misdiagnosis, overdiagnosis and overtreatment; see, for example, Harris & Carey (2008), Havens et al. (2022), and Moreno et al. (2007) for discussion of controversies related to overdiagnosis of pediatric bipolar disorder.
[23] See Chapter 2.
[24] American Psychiatric Association (1980).
[25] American Psychiatric Association (1994).
[26] American Psychiatric Association (2013).

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psychiatric, medical, and surgical treatments) rather than on transgender individuals or identities themselves."[27]

The intention of the DSM's linguistic evolution—from "Transsexualism," to "GID," to "GD"—was to reduce stigma. A parallel linguistic evolution in society at large has resulted in the increasing adoption of labels such as "nonbinary," "genderqueer," "queer," "gender-fluid," "two-spirit," and "transgender."[28] The individuals who identify with these labels—unlike historical or contemporary "transsexuals"[29]—are not a patient group of any kind. "Transgender," "nonbinary," and similar words are not medical terms: they apply to a diverse group of individuals, many of whom are neither dysphoric nor desire any medical or surgical interventions. If there is a common experience, it is "incongruence" between "experienced gender" or "gender identity" and "assigned sex." As the 2022 Text Revision of the DSM-5 explains, "not all individuals will experience distress from incongruence."[30]

As discussed in Chapter 4, social influences have plausibly contributed to the dramatic increase in adolescents presenting to pediatric gender medicine (PGM) clinics over the past decade.[31] Adolescents' need for belonging and acceptance[32] can be met by online communities and spaces centered around identity. The growing use of identity labels such as "transgender" and "nonbinary" among adolescents is an important topic for social science research. In the current U.S. healthcare environment, self-labeling of this kind increases the likelihood that a young person will seek input from a gender clinic,

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[27] Drescher (2017). According to a systematic review of cross-sex hormones and mental health outcomes commissioned by the World Professional Association for Transgender Health (WPATH), "[the diagnostic changes] clarify that the target of gender-affirming medical interventions is not the person's gender identity itself but rather the clinically significant distress that can accompany a misalignment between gender identity and sex assigned at birth" (Baker et al., 2021, p. 2). For the diagnostic criteria, see Appendix 2.
[28] See James et al. (2015), and also Section 13.4 of the previous chapter, on "gendered art pieces."
[29] Some individuals who have medically and surgically transitioned still claim this label: e.g., "I do consider myself more as a Transsexual person, which to me is somebody who wanted to switch genders. I always wanted to be a man, I identify as a man, that's what I am, I don't identify as a Transperson at all" (LOTL staff, 2014). See also American Psychological Association (2023), and Chapter 3.
[30] American Psychiatric Association (2022). See also Chapters 2 and 11.
[31] See also the discussion of rapid-onset gender dysphoria (ROGD) in the same chapter.
[32] Especially in girls, e.g., Archer (2019); Prinstein et al. (2005); Rose & Rudolph (2006).

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where medical transition may be recommended as early as the first appointment (see Chapter 12).[33]

14.3 Controversies regarding assessment and the role of the psychotherapist

In the Dutch research that underpins the contemporary pediatric medical transition (PMT) approach, the psychotherapist occupied an essential role. The original Dutch approach involved an intensive assessment process.[34] Adolescents who began medical transition were required by the protocol to continue to receive regular mental health care.[35]

When discussing contemporary applications of PMT in the U.S., providers often describe a similar approach: multidisciplinary, slow, careful, and methodical.[36] For healthcare providers, the term "multidisciplinary" may connote the lengthy, intensive deliberations that occur at "tumor boards"[37] or during organ transplantation assessments. In inpatient psychiatric units, it is considered preferable to have a multidisciplinary approach, for example involving nursing staff, psychologists, occupational therapists and social workers.[38]

However, in PGM, multidisciplinary teams (MDTs) often do not function like the collaborative model just described. They are more similar to the common healthcare scenario in which a patient sees a cardiologist for cardiac clearance before undergoing

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[33] Discussion of labels is also salient to the treatment of the prepubertal patient cohort with GD. As discussed in Chapter 2, the relatively recent practice of calling gender dysphoric youth "transgender children" may increase the likelihood these patients will be placed on a medicalized pathway.
[34] As described in Delemarre-van de Waal & Cohen-Kettenis (2006), "[In] the first diagnostic phase, information must be obtained from both the adolescent and the parents on various aspects of general and psychosexual development of the adolescent, the adolescent's current functioning and functioning of the family. Standardized psychological assessment is a part of the procedure. The patient is always seen by two members of the gender team. If a child and adolescent psychologist makes the diagnosis, the child is also seen by a child and adolescent psychiatrist and vice versa" (p. S132).
[35] Delemarre-van de Waal & Cohen-Kettenis (2006). Mental health visits were required every 3 months.
[36] E.g., from ABC News: "[Kellan] Baker [the executive director of the Whitman-Walker Institute, an LGBTQ research organization and care provider] said the decision to pursue gender-affirming care is often a lengthy process that includes teams of medical care providers and mental health professionals who work with families to talk about their child's experience, their needs, their choices, and more…'We're talking months of appointments with a mental health specialist. We're talking lots of conversations between providers, parents, and kids,' Baker said" (Alfonseca & Geho, 2024).
[37] Okasako & Bernstein (2022).
[38] Russ (2021).

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an orthopedic procedure. Under some models, the mental health professional (MHP) seeing the minor with GD writes a note or may just fill in a pre-written template; this is taken to an endocrinologist, who prescribes, or a surgeon, who operates.[39] Further, individuals who comprise the MDTs may all subscribe to the PMT model of care, which prioritizes administration of endocrine and surgical interventions to patients who desire them.[40] This is different from traditional MDTs where various specialties approach problem-solving from different perspectives, enhancing the accuracy of the diagnosis and identification of effective treatments.[41]

The MDT model in the context of PMT has created considerable uncertainty about whether the MHP or the physician providing the medical (and/or surgical) interventions bears the ultimate responsibility for the decision. This may have resulted in "diffusion of responsibility," a phenomenon in which "individuals can underperform in circumstances of shared accountability."[42] With respect to the U.K.'s National Health Service (NHS), the Cass Review's interim report provided some clarity by stipulating that the pediatric endocrinologist, as the physician providing the intervention, should be responsible for assessing the patient and formulating a full differential diagnosis. In other words, according to the interim report, receipt of a therapist's letter should not be sufficient for the prescription of hormonal intervention.[43]

In the U.S., no such clarity exists regarding which MDT professionals are ultimately responsible for medical interventions. Endocrinologists and surgeons may believe that the medical necessity of any intervention has been determined by the MHPs who made the diagnosis.[44] Whether the MHP "letter of approval" for hormones or surgery

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[39] See description of the university-based multidisciplinary clinic in Reed (2023a). See description of two-hour long assessments at Boston Children's Hospital in Damiano (2024a).
[40] To further mitigate the potential biases of established MDT teams who subscribe to the PMT model, the National Health Service (NHS) in England issued a new clinical policy for cross-sex hormones in 2024. It calls for independent oversight, specifying that new national MDTs must include "clinicians *not directly involved* in the formation of the individual's care plan," who must agree "on the suitability of the individual receiving [CSH]" (National Health Service England, 2024c).
[41] Morabito et al. (2024).
[42] Marcotte et al. (2020, p. 802).
[43] Cass (2022a).
[44] See, for example, the role of endocrinologists as described in Karakılıç Özturan et al. (2023b). The field of pediatric gender medicine is unusual in this respect: "It [is] not the norm for doctors to prescribe powerful medication to people—especially children—they themselves [did] not diagnos[e]" (Barnes, 2023, p. 337).

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constitutes a formal treatment indication will likely be determined by ongoing lawsuits brought by young people against the clinicians who treated them. In practice, these MHP approval letters may primarily serve to ease the ethical concerns of the physicians.[45]

Some prominent PMT advocates assert that children and adolescents should not receive *any* mental health assessment prior to initiation of hormonal interventions or surgeries.[46] As a principal investigator of NIH-funded research on PMT, Johanna Olson-Kennedy, a U.S. pediatrician and president-elect of the U.S. Professional Association for Transgender Healthcare (USPATH), likened the initiation of PMT to treating diabetes, asserting: "I don't send someone to a therapist when I'm going to start them on insulin."[47]

14.4 Psychotherapy for GD: Re-emergence in Europe

Three European countries—Sweden, Finland, and England—have conducted independent systematic reviews of evidence commissioned by their public health authorities.[48] All three concluded that the risks of medicalization may outweigh the benefits for children and adolescents with GD at the population level, and subsequently sharply restricted access to medical gender transition interventions for minors.[49] All three countries now suggest traditional mental health approaches and have begun efforts to de-exceptionalize GD. Psychotherapy is now the recommended first-line treatment, as it is for all psychological distress based on the conventions of "conservative management."[50]

Per England's National Health Service (NHS):

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[45] Levine (2024, p. 4).
[46] As described in McDeavitt (2025, p. 1298), "The argument for doing away with mental health assessments is often articulated alongside the opinion that the presence of a DSM-5 diagnosis of gender dysphoria (or indeed any type of psychological distress) should not have to be required in order for an adolescent to be initiated on PBs/GAH." See Mosier-Mills et al. (2024), for example, and similar arguments in Ashley (2022a, 2022b, 2023).
[47] Singal (2018).
[48] Ludvigsson et al. (2023); National Institute for Health and Care Excellence (2020b, 2020a); Pasternack et al. (2019); Taylor, Mitchell, Hall, Heathcote et al. (2024); Taylor, Mitchell, Hall, Langton et al. (2024).
[49] See Chapter 4.
[50] Adhiyaman & Ambalavanan (2021).

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> The primary intervention for children and young people … is psychosocial (including psychoeducation) and psychological support and intervention; the main objective is to alleviate distress associated with gender dysphoria and promote the individual's global functioning and wellbeing.[51]

Per Finland's Council for Choices in Health Care in Finland (COHERE):

> The first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders.[52]

Per Sweden's National Guidelines:

> The psychosocial care of young people with gender dysphoria needs to be adapted to the needs of the individual adolescent. Psychosocial support that helps adolescents deal with natal puberty without medication needs to be the first option when choosing care measures. For those suffering from mental health problems, measures such as supportive counseling, psychotherapy, child psychiatric treatment, and suicide prevention need to be offered and adapted to the nature and severity of the mental health problem and the young person's overall situation.[53]

14.5 Psychotherapy and its application to gender dysphoria

Psychotherapy is the least invasive intervention for addressing psychological distress, regardless of its etiology, and it has been recognized as the international standard of care for a wide range of mental health diagnoses. However, the evidence for psychotherapy for GD is of very low certainty. As noted in Chapter 5, there are multiple reasons for the paucity of data, and "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[54]

[51] National Health Service England (2022, p. 2).
[52] Council for Choices in Healthcare Finland (2020b, p. 5).
[53] Socialstyrelsen (2022b, p. 45).
[54] Cass (2024a, p. 155).

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14.5.1 Psychotherapy for conditions frequently co-occurring with gender dysphoria

The etiology of GD in youth remains understudied. However, patients presenting to PGM clinics today have a range of neurodevelopmental disorders and mental health conditions, including comorbid depression, anxiety, eating disorders, self-harm, and suicidality.[55] Some studies suggest that in more than 70% of cases, other DSM diagnoses appeared before the GD.[56] Etiologically, the relationship between the GD and the high rate of co-occurring mental health conditions in this population is unclear. [57] As explained by psychologist Kenneth Zucker,

> it may be that the gender dysphoria has emerged as secondary to another, more "primary" mental health diagnosis, such as autism spectrum disorder or borderline personality disorder, or as a result of a severe trauma (e.g., sexual abuse). Another explanation is that gender dysphoria is inherently distressing, i.e., the marked incongruence between one's felt gender and somatic sex—even within psychosocial milieus that are largely "affirming/supportive"—which leads to clinically significant symptoms such as anxiety or depression.[58]

Regardless of its etiology, psychotherapy as an effective intervention for depression, the most common mood disorder, has been studied extensively and is supported by high-quality evidence. For example, cognitive behavioral therapy (CBT), an (often) manualized therapy that helps patients recognize the reciprocal relationships between

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[55] See Section 4.3.

[56] Becerra-Culqui et al. (2018); Kaltiala-Heino et al. (2015); Kozlowska et al. (2021).

[57] Littman (2021), a study that analyzed online survey data from a convenience sample of detransitioners, found that 40.6% of females and 25.8% of males reported that their "feelings of being transgender actually were the result of a mental health condition." 44.9% of females and 16.1% of males reported that "feelings of being transgender actually were the result of trauma" (p. 3364). The Cass Review reported that "Clinicians have described … how in patients with [body dysmorphic disorder, or BDD], the intense focus on appearance is most commonly on facial features, but that some experience distress about genitalia or breasts. In this situation it can be difficult to determine whether the distress is due to BDD or gender dysphoria. However, at the end of a treatment package for BDD some young people say they no longer feel ill at ease with their birth-registered gender, while some may have less distress about their genitalia or breasts but still have marked gender incongruence and proceed to a social or medical gender transition" (Cass, 2024a, p. 92).

[58] Zucker (2019). In addition to these two possibilities, a third theory is that "co-occurring mental health issues are simply secondary to factors such as family rejection or social ostracism within the peer group vis-à-vis the gender dysphoria" (p. 3). This "minority stress model" is discussed later in the present chapter.

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thoughts, feelings, physiology, and behaviors, has evidence for benefit across age groups.[59] Psychodynamic psychotherapy (PDT) focuses on relational interactions, the role of formative life events, and unconscious processes, with the aim of facilitating emotional expression and interpersonal effectiveness.[60] Research indicates that PDT is effective in adults with depression, and there is also evidence of benefit for younger populations.[61] Another approach for adolescent depression with evidence for benefit is family-based treatment (FBT).[62]

Anxiety disorders also are highly prevalent in children and adolescents. The AACAP clinical practice guidelines strongly recommend that children and adolescents (ages 6-18) be offered CBT to address social anxiety, generalized anxiety, separation anxiety, specific phobias, or panic disorder.[63] PDT is less-well studied for anxiety, but may also be effective.[64]

For suicidality and self-harm in adolescents, evidence suggests that dialectical behavioral therapy (DBT), an approach that combines CBT with mindfulness and

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[59] "Manualized" therapeutic approaches follow specific, standardized guidelines. CBT is the most well-studied. A recent meta-analysis of CBT for depression, including more than 50,000 patients across all age groups and 409 randomized controlled trials (RCTs), found that "CBT is effective in the treatment of depression with a moderate to large effect size, and that its effect is still significant up to 12 months (Cuijpers et al., 2023, p. 114). Other forms of psychotherapy were also found to be significantly beneficial. With respect to studies specifically focused on children and adolescents, evidence suggests CBT had modest positive effects on depressive symptoms (Espada et al., 2023).

[60] Opland & Torrico (2025).

[61] A systematic review of PDT for adults, which used the GRADE framework for evidence assessment, found "high quality evidence for depressive disorders and somatic symptom disorders, and moderate quality evidence for anxiety and personality disorders, that PDT achieves clinically meaningful effects in target symptoms and functioning compared to controls and is associated with low risk of harms and reasonable costs" (Leichsenring et al., 2023, p. 286). Midgley et al. (2021) is a narrative review of studies on PDT for children and adolescents (including some RCTs), finding "evidence of effectiveness for psychodynamic therapy in treating a wide range of mental health difficulties in children and adolescents" (p. 1).

[62] For example, attachment-based family therapy is an evidence-based approach to treating adolescent mood disorders, including depression, using a combination of separate (adolescent-only and parents-only) and joint family sessions (Diamond et al., 2021).

[63] This recommendation was based on a commissioned Agency for Healthcare Research and Quality (AHRQ)/Mayo Clinic systematic review and meta-analysis that included 60 RCTs and almost 7,000 pediatric patients. It found moderate-strength evidence that CBT improves primary anxiety symptoms and global functioning (Walter et al., 2020).

[64] Leichsenring et al. (2015); Midgley et al. (2021).

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interpersonal skills training,[65] is an effective treatment.[66] Guidance published by the Substance Abuse and Mental Health Services Administration (SAMHSA) in 2020 found strong evidence that DBT was associated with reductions in suicidality (ideation, non-suicidal self-injury, and suicide attempts).[67] Another evidence-supported intervention, attachment-based family therapy, supports adolescents and parents as they rebuild trust and safety within their relational patterns, gradually reducing the risk of self-harm and suicidality.[68]

Eating disorders also frequently co-occur with GD.[69] CBT has shown some effectiveness as treatment for eating disorders in adults,[70] and CBT, DBT, and family-based treatment or family therapy for eating disorders (FT-ED) have shown effectiveness in adolescents.[71] Such approaches initially target the presenting issue by helping parents and caregivers support their children more effectively, while issues related to identity development are addressed as the condition improves. These family-based treatments are considered first-line interventions for treating adolescent eating disorders, particularly anorexia nervosa and bulimia nervosa.

Body dissatisfaction, which is common in adolescence, is treated with specific evidence-informed protocols. A combination of CBT and selective serotonin reuptake inhibitors (SSRIs) is recommended by the National Institute of Health and Care Excellence (NICE) in the U.K. for body dysmorphic disorder. It also recommends that parents and caregivers actively participate in the treatment process.[72]

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[65] DBT originated as a treatment for adults with borderline personality disorder with chronic suicidality. Its focus is on helping patients achieve mindfulness, interpersonal effectiveness, emotional regulation, and distress tolerance (Substance Abuse and Mental Health Services Administration, 2020).
[66] This is in direct contrast to hormonal interventions, which have *not* been shown to reduce suicidality or suicide in minors with GD. See Section 4.3.4 and Chapter 5.
[67] This SAMHSA guidance considered evidence to be "strong" if positive impact was demonstrated by two or more RCTs (or other controlled trials). Nine studies (of varying methodologies) of DBT for suicidality in adolescents were included in this evidence review; two were RCTs (Substance Abuse and Mental Health Services Administration, 2020).
[68] Diamond et al. (2010).
[69] From a theoretical standpoint, eating disorders and GD both have been conceptualized as arising, in some cases, out of a subconscious desire to avoid the development of adult sex characteristics, perhaps in part due to maladaptive coping strategies or to avoid sexual objectification (Nadrowski, 2023).
[70] Öst et al. (2024).
[71] Datta et al. (2023); Lock et al. (2010); Vogel et al. (2021).
[72] National Institute for Health and Care Excellence (2005).

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When discussing the broader issue of the high prevalence of GD in patients presenting with conditions like eating disorders, body dysmorphic disorder, and functional tic-like behaviors, the Cass Review noted that "[t]he distressing symptoms that occur in these 'body and mind' conditions are real, and like pain or discomfort that arises from other causes can be addressed and helped with psychological interventions. It is very important that gender-questioning young people are able to access these evidence-based treatments."[73] The Cass Review also observed,

> Some therapies, which are well proven for associated mental health problems, already have a strong evidence base. Where it is clear that children/young people have such problems, they should receive the appropriate therapies in the same way as any other young person.[74]

14.5.2 Psychotherapy for gender dysphoria

The overview of systematic reviews (Chapter 5 and Appendix 4) found a dearth of evidence for psychotherapeutic interventions for youth with GD. As summarized in the Cass Review,

> there is a lack of evidence about alternative approaches for managing gender-related distress, and it is difficult to obtain information about routine clinical practice or pathways of care for children and young people who do not receive medical interventions. An explicit clinical pathway must be developed for non-medical interventions, as well as a research strategy for evaluating their effectiveness.[75]

Although several studies suggest that psychotherapy for GD may effectively resolve the condition noninvasively,[76] the quality of the evidence is very low certainty.[77] At the same time, the overview identified two SRs deemed as trustworthy (i.e., at low risk of bias),

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[73] Cass (2024a, p. 93)
[74] Cass (2024a, p. 155).
[75] Cass (2024a, p. 157).
[76] Churcher Clarke & Spiliadis (2019); Cohen-Kettenis & Kuiper (1984); Costa et al. (2015); Smith et al. (2001); Spiliadis (2019).
[77] See Chapter 5.

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and noted that "neither systematic review suggested that there is indication of harm from psychotherapy." One of the SRs concluded:

> Most analyses of mental health, psychological and/or psychosocial outcomes showed either benefit or no change, with none indicating any negative/ adverse effects of the interventions offered.[78]

Although there is no reliable evidence to suggest that psychotherapy for GD is harmful, some proponents of PMT have alleged that it is a form of "conversion therapy." This allegation is addressed in the following section; the final section surveys psychotherapeutic approaches to GD.

14.5.2.1 The charge of "conversion therapy"

Although psychotherapy for GD is described by its practitioners as "neutral" and "unbiased,"[79] some advocates for PMT maintain that such "exploratory" approaches are equivalent to conversion practices.[80]

"Conversion therapy"—sometimes called "reparative therapy"—originally referred to efforts to change the sexual orientation of gay and lesbian people. In 1973, homosexuality was officially de-pathologized by the American Psychiatric Association (APA) when it was declassified as a mental disorder (via its removal from the DSM).[81] While proponents of PMT have characterized exploratory psychotherapeutic approaches for GD as a form of "conversion therapy," others have claimed that PMT

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[78] Heathcote et al. (2024, p. s19).
[79] D'Angelo et al. (2021, p. 12).
[80] E.g. Ashley (2022b, 2023); see also the quotation by Colt St. Amand conflating psychological assessments for minors seeking medical or surgical transition with conversion therapy in Bazelon (2022a). Turban, Beckwith et al. (2020), a widely-cited peer-reviewed analysis of data from the 2015 U.S. Transgender Survey (USTS) concluded that individuals who recalled having been exposed to "gender identity conversion efforts" in the past were more likely to have experienced recent psychological distress and lifetime history of suicidal thoughts, but D'Angelo et al. (2021, p. 12) pointed out that this analysis was based on a "simplistic 'affirmation' versus 'conversion' binary … The notion that all therapy interventions for GD can be categorically classified into this simplistic binary betrays a misunderstanding of the complexity of psychotherapy. At best, this blunt classification overlooks a wide range of ethical and essential forms of agenda-free psychotherapy that do not fit into such a binary; at worst, it effectively mis-categorizes ethical psychotherapies that do not fit the "affirmation" descriptor as conversion therapies" (p. 7). For methodological concerns about the USTS itself, see Chapter 4, Note 117.
[81] Drescher (2010, p. 434); McNally (2011, pp. 21-24). The first edition (1952) of the DSM classified same-sex attraction as a type of "sociopathic personality disturbance" (American Psychiatric Association, 1952, pp. 38-39).

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itself deserves that label. This latter group contends that altering a person's body in response to distress rooted in internalized social disapproval is no more appropriate than attempting to change someone's sexual orientation for similar reasons.[82] Public and academic debates over what constitutes "conversion" in the context of youth with GD have been hindered by the politicization of the issue.[83]

Critics of exploratory psychotherapy for GD claim that therapists are trying to "promote gender identities that are aligned with the person's sex assigned at birth."[84,85] A less theoretically-laden description would be that some therapists are trying to help children and adolescents come to terms with their bodies.[86] Discomfort with the sexed body or with societal sex-based expectations is common during puberty and adolescence. For this and other reasons, characterizing as "conversion therapy" any approach focused on reducing a minor's distress about their body or social role is a problematic and potentially harmful rhetorical device.[87] There is evidence that the specter of being

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[82] See Bannerman (2019) and Hamedani (2014). A recent bioethics article argues that "a society that marginalizes youth who do not conform to gender norms must, as a matter of justice, change its ways. The burden of enacting this change is all of ours to bear. It should not be borne by the bodies of our youth" (Gorin, 2024, p. 43).

[83] Defenses of psychotherapy for GD have roundly rejected the label of "conversion therapy": e.g., "Psychotherapy resides outside the affirmation-conversion binary and aims to address the distress of gender-dysphoric youth rather than to correct a sense of misalignment. Psychotherapy does not attempt to force change or impose any predetermined notion … A core ethical principle of psychotherapy is that therapists must respect patient autonomy and self-determination and refrain from any attempt to influence the patient … A genuine psychotherapeutic process starts from a position of not knowing and seeks to open things up. Anything else is a misuse of psychotherapy" (D'Angelo, 2023, p. 3).

[84] The full quotation is: "Trans conversion practices refer to sustained efforts to promote gender identities that are aligned with the person's sex assigned at birth and/or to discourage behaviours associated with a gender other than the person's sex assigned at birth" (Ashley, 2022b, p. 26). This seems to more broadly characterize conversion therapy as an attempt to encourage conformity with sex stereotypes. However, as explained by D'Angelo, "Psychotherapy does not impose restrictive gender stereotypes, as is sometimes claimed, but critically examines them" (D'Angelo, 2023, p. 1). Such examination is necessary, because restrictive stereotypes could plausibly have contributed to the patient's GD.

[85] The 2020 United Nations (UN) Report on Conversion Therapy begins by explaining that "conversion therapy" refers to "interventions of a wide-ranging nature, all of which have in common the belief that a person's sexual orientation or gender identity (SOGI) can and should be changed. Such practices aim (or claim to aim) at changing people from gay, lesbian or bisexual to heterosexual and from trans or gender diverse to cisgender" (United Nations, 2020). See Lawford-Smith (2024) for discussion of recent legislation banning "conversion therapy" as the UN understands it.

[86] Once it is recognized that the operative notion of "gender identity" has not been properly explained (Chapter 2), the charge of "conversion therapy" makes little sense. If gender identity is obscure, the goal of changing the patient's gender identity is equally obscure.

[87] E.g., D'Angelo (2023); D'Angelo et al. (2021); Edwards-Leeper & Anderson (2021); Jenkins & Panozzo (2024); McDeavitt (2025); Sinai & Sim (2024). Also, as noted in the Cass Review, "The role of

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labeled a “conversion therapist”— a damaging accusation given the profession’s history with the mistreatment of gay people—has created a climate of anxiety among mental health professionals. Therapists worry that failing to affirm or recommend medical interventions for youth who meet the World Professional Association for Transgender Health’s (WPATH) eligibility criteria could jeopardize their careers and reputations.[88]

Equating “exploratory therapy” with “conversion therapy” is misguided for two additional key reasons. First, exploratory therapy was a fundamental and mandatory element of the original Dutch Protocol, which serves as the foundation for the current PMT model.[89] Second, quality psychotherapy is exploratory *by definition*: it is “a process of shared decision making in which the therapist … guides the patient in exploration of their material but does not input their own beliefs or ideas.”[90]

The conflation of psychotherapy with conversion therapy has been condemned not only by expert therapists who question the current emphasis on medical transition and surgical transition for youth, but also by practitioners and researchers in the PMT field itself.[91]

14.5.2.2 Psychotherapeutic approaches

The effectiveness of psychotherapy for a wide range of mental health problems, including those that often present with GD, suggests it may also be beneficial for GD specifically. The Cass Review’s emphasis on the de-exceptionalization of youth with GD underscored the observation that clinicians

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psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an unhelpfully polarised debate around conversion practices. Terms such as ‘affirmative’ and ‘exploratory’ approaches have been weaponised to the extent that it is difficult to find any neutral terminology” (Cass, 2024a, p. 150).

[88] Jenkins & Panozzo (2024). As summarized in McDeavitt (2025): “Some therapists who engage in exploratory talk therapy with [transgender and gender diverse] youth have faced licensure complaints related to accusations of “conversion therapy”—complaints made not by patients, but by activists and colleagues. One therapist reported having attended a workshop … in which activists described “hunting” for such therapists with the goal of bringing lawsuits and prompting licensure revocation.”

[89] Weaknesses of the original Dutch research are discussed in Chapter 4.

[90] Sinai & Sim (2024, p. 148); see also Churcher Clarke & Spiliadis (2019).

[91] For example, psychologist Laura Edwards Leeper has stated that “Conflating conversion therapy and identity exploration is perhaps the largest threat to both gender-distressed cisgender youth and transgender youth, alike. The rhetoric being used to conflate the two must stop immediately” (McDeavitt, 2025, p. 1298). See also Edwards-Leeper & Anderson (2021).

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> just need the appropriate training, support and most importantly the confidence to do what [they] have been trained to do and treat this population as [they] would any other young person in distress.[92]

Unfortunately, efforts to research the influence of cultural and social factors, trauma, or co-occurring mental health conditions on GD have been denigrated as "harmful."[93] When combined with the highly charged accusation of "conversion therapy," therapists may be under significant pressure to assume—often without critical evaluation—that mental health issues co-occurring with GD are primarily the result of minority stress.[94] This pressure may cause clinicians to overlook the significant possibility that in some patients, GD has *arisen from* trauma, "primary" mental health concerns, or neurodevelopmental conditions (see Section 14.1 above). Publications by psychotherapists working with this population have noted that patients with GD may seek hormonal or surgical interventions in response to experiences of sexual violence, negative attitudes towards homosexuality, or bullying related to self-expression, interests, or behaviors that deviate from sex stereotypes.[95]

If these possibilities are ignored, medical and surgical interventions may be recommended as the obvious treatment.[96] The mischaracterization of psychotherapy for GD as "conversion therapy" or "doing nothing" may also contribute to a nocebo effect, disincentivizing therapists from providing care and patients from engaging in it.[97] In this way, the denigration of psychotherapy has "a chilling effect on the ethical

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[92] Cass (2024a, p. 15).
[93] E.g. Coalition for the Advancement and Application of Psychological Science (2021).
[94] Application of minority stress theory to mental health disparities in sexual minority adults was originally done in Meyer (2003). As defined in Chelliah et al. (2024), the "minority stress framework…has been used to conceptualize relationships between…mental health disparities and stressors associated with a minority identity or status." This framework, which (like all other conceptual frameworks) has its limitations (Bailey, 2020; Zucker et al., 2016), has over the past 5-10 years been widely-relied upon in the pediatric gender medicine literature (see examples in Chapter 13). Although it is important for therapists to elucidate patient experiences of bullying or hostility, it is not psychotherapeutically sound practice to make reflexive assumptions, especially when these assumptions could lead to inappropriate treatment recommendations.
[95] Churcher Clarke & Spiliadis (2019); D'Angelo et al. (2021); Lemma (2018); Sinai & Sim (2024); Spiliadis (2019).
[96] E.g. Tordoff (2022).
[97] Clayton (2023).

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psychotherapists' willingness to take on complex GD patients, which will make it much harder for GD individuals to access quality mental health care."[98]

The practice of reflexive assumption contravenes fundamental principles of the psychotherapeutic approach, which emphasizes curiosity and consideration of *all* factors that may have contributed to the patient's problems.[99] It is also challenged by research on desistance and detransition.[100]

Stephen Levine, professor of psychiatry at Case Western Reserve University, has explained how the psychotherapeutic approach includes biological, psychological and social factors to formulate GD holistically:

> [If] the evaluator understands the focus of the [mental health assessment] to be on identifying the predisposing, precipitating, and maintaining forces on the patient's identity, a long list of influences will be explored. Problems such as autism, ADHD, difficulty making friends, crises of loneliness, depression, restrictive or excess eating, sexual abuse, and feedback from virtual friends will be investigated. The [therapist] will explore suicidality, self-harm, pre- and post-trans-identity psychiatric problems, and relationships with each parent. The parents will provide a developmental history beginning with pregnancy.[101]

Psychiatrist and psychoanalyst Roberto D'Angelo, a proponent of psychotherapy for GD, describes the role of psychotherapy for minors with GD as follows:

> Psychotherapy does not impose restrictive gender stereotypes, as is sometimes claimed, but critically examines them. It empowers young people to develop creative solutions to their difficulties and promotes agency and autonomy. Importantly, an exploratory psychotherapeutic process can help to clarify whether

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[98] D'Angelo et al. (2021, p. 13).
[99] As the Cass Review noted, "a single focus on gender raises the issue of 'diagnostic overshadowing' … children [may have] more than one presenting issue, but different services … dealing with each issue in isolation, without considering how they might impact on each other" (Cass, 2024a, p. 200). See also discussion of diagnostic overshadowing in Section 13.2.4.
[100] E.g. Littman (2021).
[101] Levine (2024, p. 775).

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gender dysphoria is a carrier for other psychological or social problems that may not be immediately apparent.[102]

Given that this population often presents with complex psychosocial histories and multiple mental health concerns, psychotherapy takes a holistic approach—addressing the full range of issues rather than focusing exclusively on GD. “Transdiagnostic psychotherapy”—that is, therapy that works across or with multiple diagnoses or problems—is already a convention.[103] While there is a clear need to develop and study therapeutic approaches tailored specifically for GD, effective therapy need not always center on a single issue. Psychotherapy for adolescents with GD is a well-suited intervention, as it is intended to help patients develop self-understanding, engage with emotional vulnerability, and build practical strategies for managing distress.

Human psychology is complex and the presence of one psychiatric diagnosis often increases the likelihood of others. A transdiagnostic psychotherapeutic approach—designed to address underlying patterns across multiple conditions—may be particularly effective in reducing distress among youth with GD, as it has been in other complex cases. The goals of psychotherapy remain the same regardless of a young person’s self-identification: to alleviate distress and improve interpersonal and social functioning.

Table 14.1 below presents a brief overview of psychotherapeutic modalities that are relevant for children and adolescents with GD.

[102] D’Angelo (2023, p. 1).
[103] Jeppesen et al. (2021).

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Table 14.1

Type of psychotherapeutic modality	Definition of modality	Application to GD
Manualized approaches[104]	These approaches are performed according to manualized instructions that provide structure and standardization. The most-studied approach is cognitive behavioral therapy (CBT), which helps patients identify thoughts, feelings, and behaviors and the way they impact one another. Manualized therapies focus on development of coping skills and behavioral activation. Dialectical behavioral therapy, commonly used to address self-harm and suicidality, fosters distress-management techniques and interpersonal effectiveness. Manualized approaches typically involve several months of weekly individual or group sessions, and patients complete therapy-related assignments between sessions.	Manualized approaches are an evidence-based treatment for mental health problems that co-occur with GD, such as depression, anxiety, and eating disorders. For GD, manualized approaches can help patients identify thoughts and feelings related to sex-based distress, including cognitive distortions. Therapists can help patients develop healthy coping skills for managing this specific type of distress and can encourage behavioral activation. For example, engaging in physical activity, in-person social socialization, and/or mindfulness practices, can over time, decrease ruminations, including ruminations on sex-related discomfort.

[104] In Austin et al. (2018), mental health outcomes (including depression) improved with CBT in 8 adolescents who identified as transgender (subgroup of study population; unclear if hormonal interventions were used). Hollinsaid et al. (2020) re-analyzed data from four RCTs of standard manualized psychotherapeutic approaches, focusing on the cohort of 64 patients who had expressed desire to be the other sex (it is unclear how many would have met criteria for GD, however; additionally, there was no information about hormonal interventions). These patients' internalizing and externalizing symptoms improved, albeit more slowly than other patients. In Lucassen et al. (2021) the depression outcome measure did not change after online CBT in 14 patients who identified as transgender. In Silveri et al. (2021) mental health outcomes improved in 62 adolescents who self-identified as transgender/gender-expansive after CBT, DBT, and family therapy, integrated into a two-week long residential treatment program for psychiatric problems. In a study reporting longitudinal data on 26 adolescents (Bluth et al., 2023), mental health outcomes (including depression and suicidality) improved after eight sessions of mindfulness-based group therapy in transgender-identified patients who were not taking hormonal interventions.

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Type of psychotherapeutic modality	Definition of modality	Application to GD
Psychodynamic approach[105]	This is a psychoanalytic approach that involves exploration of ego defenses and unconscious motivations. Through exploration of transference, patients come to better understand their interpersonal dynamics. Psychodynamic psychotherapy classically involves biweekly or weekly sessions and is not time-limited.	This approach is evidence-based for mental health conditions that co-occur with GD. Additionally, psychodynamic work around the theme of cross-sex identification or sex-related distress can facilitate exploration of patients' early childhood experiences, family of origin, beliefs/values system, and interpersonal patterns in familial and romantic relationships as well as in school/work environments. This approach can help patients gain deeper understanding of their personal identity, including any external factors that may contribute to their cross-sex identification and desire for medical/surgical interventions. Patients can gain clarity about their own wishes or desires for medical or surgical transition interventions.
Family therapy[106]	This approach identifies problems affecting the patient and the family unit and aims to strengthen familial bonds and improve communication skills, by supporting work around attachment ruptures, communication and understanding different family members' perspectives. It may involve parental education and development of strategies for improved interpersonal effectiveness within the family unit.	A child or adolescent exhibiting GD may occasionally lead to intense conflict and distress within the family unit. In family-based approaches a knowledgeable therapist can provide education about GD to parents and promote well-being of the family by bolstering effective communication and interpersonal skills. Family therapy is an evidence-based approach to treating adolescent eating disorders, where familial distress and embodied distress are heightened, as in GD. Family therapy is either the first-line intervention or the treatment of choice for many diagnoses in adolescence.

14.5.2.3 Evidence for benefit

As discussed earlier, the overview of systematic reviews conducted for this Review found that evidence for the effectiveness of psychotherapy for GD (or for co-occurring mental health problems in patients with GD) is of very low certainty. When direct evidence for the role of psychotherapy in children and adolescents with GD is lacking, the best available evidence can be obtained from the robust evidence supporting

[105] For case reports, vignettes, and case series describing the incorporation of dynamic aspects into exploratory work, see Churcher Clarke & Spiliadis (2019); D'Angelo (2020); Spiliadis (2019). For descriptions of dynamic approaches, see D'Angelo (2023); Sinai & Sim (2024).
[106] For a case report of family therapy for an adolescent with suicidality, see Russon et al. (2022). See also Silveri et al. (2021) and Churcher Clarke & Spiliadis (2019). For example of parent psychoeducation, see Levine (2024).

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treatment effectiveness for children and adolescents with similar types of psychological distress. Psychotherapy is a noninvasive intervention that can be used transdiagnostically. It generally promotes improved mental health and psychosocial functioning and carries little risk.[107] As the Cass Review noted,

> the focus on the use of puberty blockers for managing gender-related distress has overshadowed the possibility that other evidence-based treatments may be more effective.[108]

[107] See also Baron & Dierckxsens (2022); Clayton (2023); Levine et al. (2022b).
[108] Cass, 2024a (p. 31).

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Limitations, Strengths, and Conclusion

Limitations

The present Review has some limitations.[1]

1. This document is not intended to serve as a clinical practice guideline and does not aim to issue treatment recommendations.[2] The Review was shaped by a distinct set of goals: namely, to clarify the evidentiary landscape; identify areas of uncertainty; and support the development of accountable care models. As such, it does not follow formal guideline development procedures, such as the use of GRADE to inform clinical recommendations. The purview of this Review is limited to evidence and best practices for the care of minors.
2. This Review does not make any specific policy recommendations regarding the regulation of medicine. For instance, it does not make policy recommendations about the treatment of children and adolescents who have already begun puberty blockers or cross-sex hormones.

Strengths

This Review also has some strengths.

1. Although not a CPG, this document provides clinicians and other decision makers with essential pieces of knowledge regarding PGM.
    a. *Quality of evidence*: This Review describes the very low-quality evidence underpinning treatment approaches in pediatric gender medicine (Chapter 5).
    b. *Risk profile of hormones and surgeries*: This Review contains an extensive description of potential or plausible harms associated with certain treatment options (namely, hormonal interventions and surgeries), some of which are significant (Chapter 7).

[1] For strengths and limitations specific to the overview of systematic reviews (SRs), see Chapter 5.
[2] This is not technically a limitation (as this Review does not purport to be a CPG), but a clarification.

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c. *Ethics review*: This Review contains an ethical assessment of the use of hormonal interventions and surgeries for treatment of GD in children and adolescents. It concludes that these interventions are inconsistent with widely endorsed principles of medical ethics (Chapter 13).

d. *Consideration of alternative treatments*: The role of psychotherapy, which has been sidelined in discussions of PGM, is one focus of this Review. This Review examines psychotherapy for GD in detail and concludes that its risk/benefit profile is favorable (Chapter 14).

2. The review of guidelines (Chapter 9) demonstrates that CPGs recommending psychotherapy for pediatric GD are higher-quality and are commensurate with evidence from PGM SRs. In contrast, CPGs recommending an approach involving standard-of-care use of PBs, CSH, or surgery are lower-quality, with recommendations that are not commensurate with evidence from SRs. CPGs followed in the U.S., in particular that of WPATH, are of the latter type and are inadequate to inform clinical practice for a vulnerable and distressed population of children and adolescents. High quality CPGs are urgently needed in this field.
3. This Review describes the enforced professional insularity of the field of pediatric gender medicine and the intense and hostile nature of the debates around PGM. Stakeholders should keep these in mind when presented with claims of medical consensus among U.S. medical organizations (Chapter 12).

Conclusion

> The delegation of authority to the medical profession rests on an implicit social contract: Doctors as a profession receive the 'privilege of self-regulation' and financial awards on the expectation that they will serve the health needs of individual patients and society.[3]

A central theme of this Review is that many U.S. medical professionals and associations have fallen short of their duty to prioritize the health interests of young patients. First,

[3] Patashnik et al. (2017, p. 10).

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there was a rapid expansion and implementation of a clinical protocol that lacked sufficient scientific and ethical justification. Second, when confronted with compelling evidence that this protocol did not deliver the health benefits it promised, and that other countries were changing their policies appropriately, U.S. medical professionals and associations failed to reconsider the “gender-affirming” approach. Third, conflicting evidence—evidence that challenged the foundational assumptions of the protocol and the professional standing of its advocates—was mischaracterized or insufficiently acknowledged. Finally, dissenting perspectives were marginalized, and those who voiced them were disparaged.

While no clinician or medical association intends to fail their patients—particularly those who are most vulnerable—the preceding chapters demonstrate that this is precisely what has occurred.

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APPENDICES

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Appendix 1. Abbreviations

AACAP	American Academy of Child and Adolescent Psychiatry
AAP	American Academy of Pediatrics
AGREE	Appraisal of Guidelines for Research and Evaluation
AHRQ	Agency for Healthcare Research and Quality
AMA	American Medical Association
AMSTAR	A MeaSurement Tool to Assess systematic Reviews
APA	American Psychological Association/American Psychiatric Association
ASD	Autism Spectrum Disorder; also ASC (Autism Spectrum Condition)
BDD	Body Dysmorphic Disorder
BMI	Body Mass Index
CBT	Cognitive Behavioral Therapy
CDC	Centers for Disease Control and prevention
CMS	Centers for Medicare and Medicaid
COHERE	Council for Choices in Health Care (Finland)
COI	Conflict of Interest
CPG	Clinical Practice Guideline
CPP	Central Precocious Puberty
CSH	Cross-Sex Hormones
DBT	Dialectical Behavioral Therapy
DSD	Disorder (Difference) of Sex Development
DSM	*Diagnostic and Statistical Manual of Mental Disorders*
DSM-5-TR	DSM, 5th edition, Text Revision (latest version, 2024)
DSM-5	DSM, 5th edition (2013)
DSM-IV	DSM, 4th edition (1994)
DSM-III	DSM, 3rd edition (1980)
EBM	Evidence-Based Medicine
EPC	Evidence-based Practice Center (at Johns Hopkins)
ES	Endocrine Society
FAERS	FDA's Event Reporting System

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FBT	Family-Based Treatment
FDA	Food and Drug Administration
FM	Female-to-Male
FP	Fertility Preservation
FSH	Follicle-Stimulating Hormone
FT-ED	Family Therapy for Eating Disorders
GD	Gender Dysphoria (DSM-5; formerly Gender Identity Disorder (GID) in the DSM-IV)
GDG	Guideline Development Group
GeMS	Gender Multispeciality Service (at Boston Children's; formerly Gender Management Service)
GICE	Gender Identity Conversion Efforts
GIDS	Gender Identity Development Service (U.K.)
GnRHa	Gonadotropin Releasing Hormone Agonist
GRADE	Grading of Recommendations Assessment, Development and Evaluation
HBIGDA	Harry Benjamin International Gender Dysphoria Association
HH	Hypogonadotropic Hypogonadism
HPG	Hypothalamic-Pituitary Gonadal axis
HRC	Human Rights Campaign
ICD-11	WHO's International Classification of Diseases, 11th edition (latest version, 2022)
IQ	Intelligence Quotient
ITJH	*International Journal of Transgender Health*
JAMA	*Journal of the American Medical Association*
JHU	Johns Hopkins University
LH	Luteinizing Hormone
MDC	Medical Decision-making Competence
MDT	MultiDisciplinary Teams
MF	Male-to-Female
MHP	Mental Health Professional
MMHA	Major Medical and mental Health Association

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NAM	National Academy of Medicine
NEJM	*New England Journal of Medicine*
NGCF	Netherlands Gender Care Foundation
NHS	National Health Service (U.K.)
NICE	National Institute for Health and Care Excellence (U.K.)
NIH	National Institutes of Health
NLM	National Library of Medicine
NOS	Newcastle-Ottawa Scale
OCD	Obsessive Compulsive Disorder
PBs	Puberty Blockers
PCOS	Polycystic Ovary Syndrome
PDT	PsychoDynamic Therapy
PGM	Pediatric Gender Medicine
PICO	Population, Intervention, Comparator, Outcome
PMT	Pediatric Medical Transition
PRISMA	Preferred Reporting Items for Systematic reviews and Meta-Analyses
RCT	Randomized Controlled Trial
RoB 2	Cochrane Risk-of-Bias tool
ROBINS-I	Risk Of Bias In Non-randomized Studies - of Interventions
ROBIS	Risk of Bias In Systematic reviews
ROGD	Rapid-Onset Gender Dysphoria
RSG	Review of Data, Statistics and Research on Sex and Gender (U.K., 2025)
SAMHSA	Substance Abuse and Mental Health Services Administration
SOC-8	*Standards of Care for the Health of Transgender and Gender Diverse People*, Version 8 (latest version, 2022)
SOC-7	*Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People*, Version 7 (2012)
SOC-6	*Standards of Care for Gender Identity Disorders*, Version 6 (2001)
SR	Systematic Review
SRS	Sex Reassignment Surgery
SSRI	Selective Serotonin Reuptake Inhibitor

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TGD	Transgender and Gender Diverse
UCSF	University of California, San Francisco
USPATH	United States Professional Association for Transgender Health
USTS	US Transgender Survey
WHO	World Health Organization
WPATH	World Professional Association for Transgender Health

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Appendix 2. Diagnostic Criteria

DSM-III (1980)[1]

Diagnostic criteria for Transsexualism

A. Sense of discomfort and inappropriateness about one's anatomic sex.

B. Wish to be rid of one's own genitals and to live as a member of the other sex.

C. The disturbance has been continuous (not limited to periods of stress) for at least two years.

D. Absence of physical intersex or genetic abnormality.

E. Not due to another mental disorder, such as Schizophrenia.

Diagnostic criteria for Gender Identity Disorder of Childhood

For females:

A. Strongly and persistently stated desire to be a boy, or insistence that she is a boy (not merely a desire for any perceived cultural advantages from being a boy).

B. Persistent repudiation of female anatomic structures, as manifested by at least one of the following repeated assertions:

(1) that she will grow up to become a man (not merely in role)

(2) that she is biologically unable to become pregnant

(3) that she will not develop breasts

(4) that she has no vagina

(5) that she has, or will grow, a penis

C. Onset of the disturbance before puberty.

For males:

[1] American Psychiatric Association (1980, pp. 261-266).

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A. Strongly and persistently stated desire to be a girl, or insistence that he is a girl.

B. Either (1) or (2):

(1) persistent repudiation of male anatomic structures, as manifested by at least one of the following repeated assertions:

(a) that he will grow up to become a woman, (not merely in role)

(b) that his penis or testes are disgusting or will disappear

(c) that it would be better not to have a penis or testes

(2) preoccupation with female stereotypical activities as manifested by a preference for either cross-dressing or simulating female attire, or by a compelling desire to participate in the games and pastimes of girls

C. Onset of the disturbance before puberty.

DSM-IV (1994)[2]

Diagnostic criteria for Gender Identity Disorder

A. A strong and persistent cross-gender identification (not merely a desire for any perceived cultural advantages of being the other sex). In children, the disturbance is manifested by four (or more) of the following:

(1) repeatedly stated desire to be, or insistence that he or she is, the other sex

(2) in boys, preference for cross-dressing or simulating female attire; in girls, insistence on wearing only stereotypical masculine clothing

(3) strong and persistent preferences for cross-sex roles in make-believe play or persistent fantasies of being the other sex

[2] American Psychiatric Association (1994, pp. 537-538).

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(4) intense desire to participate in the stereotypical games and pastimes of the other sex

(5) strong preference for playmates of the other sex

In adolescents and adults, the disturbance is manifested by symptoms such as a stated desire to be the other sex, frequent passing as the other sex, desire to live or be treated as the other sex, or the conviction that he or she has the typical feelings and reactions of the other sex.

B. Persistent discomfort with his or her sex or sense of inappropriateness in the gender role of that sex.

In children, the disturbance is manifested by any of the following: in boys, assertion that his penis or testes are disgusting or will disappear or assertion that it would be better not to have a penis, or aversion toward rough-and-tumble play and rejection of male stereotypical toys, games, and activities; in girls, rejection of urinating in a sitting position, assertion that she has or will grow a penis, or assertion that she does not want to grow breasts or menstruate, or marked aversion toward normative feminine clothing.

In adolescents and adults, the disturbance is manifested by symptoms such as preoccupation with getting rid of primary and secondary sex characteristics (e.g., request for hormones, surgery, or other procedures to physically alter sexual characteristics to simulate the other sex) or belief that he or she was born the wrong sex.

C. The disturbance is not concurrent with a physical intersex condition.

D. The disturbance causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.

DSM-5 (2013)[3]

Gender Dysphoria

[3] American Psychiatric Association (2013, pp. 452-453).

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Diagnostic Criteria

Gender Dysphoria in Children

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least six of the following (one of which must be Criterion A1):

1. A strong desire to be of the other gender or an insistence that one is the other gender (or some alternative gender different from one's assigned gender).

2. In boys (assigned gender), a strong preference for cross-dressing or simulating female attire: or in girls (assigned gender), a strong preference for wearing only typical masculine clothing and a strong resistance to the wearing of typical feminine clothing.

3. A strong preference for cross-gender roles in make-believe play or fantasy play.

4. A strong preference for the toys, games, or activities stereotypically used or engaged in by the other gender.

5. A strong preference for playmates of the other gender.

6. In boys (assigned gender), a strong rejection of typically masculine toys, games, and activities and a strong avoidance of rough-and-tumble play; or in girls (assigned gender), a strong rejection of typically feminine toys, games, and activities.

7. A strong dislike of one's sexual anatomy.

8. A strong desire for the primary and/or secondary sex characteristics that match one's experienced gender.

B. The condition is associated with clinically significant distress or impairment in social, school, or other important areas of functioning.

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Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration, as manifested by at least two of the following:

1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics).

2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics).

3. A strong desire for the primary and/or secondary sex characteristics of the other gender.

4. A strong desire to be of the other gender (or some alternative gender different from one's assigned gender).

5. A strong desire to be treated as the other gender (or some alternative gender different from one's assigned gender).

6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender).

B. The condition is associated with clinically significant distress or impairment in social, occupational or other important areas of functioning.

ICD-11 (2022)[4]

Gender incongruence of adolescence or adulthood

[4] World Health Organization (2022b).

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Gender Incongruence of Adolescence and Adulthood is characterized by a marked and persistent incongruence between an individual's experienced gender and the assigned sex, which often leads to a desire to 'transition', in order to live and be accepted as a person of the experienced gender, through hormonal treatment, surgery or other health care services to make the individual's body align, as much as desired and to the extent possible, with the experienced gender. The diagnosis cannot be assigned prior to the onset of puberty. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.

Gender incongruence of childhood

Gender incongruence of childhood is characterized by a marked incongruence between an individual's experienced/expressed gender and the assigned sex in pre-pubertal children. It includes a strong desire to be a different gender than the assigned sex; a strong dislike on the child's part of his or her sexual anatomy or anticipated secondary sex characteristics and/or a strong desire for the primary and/or anticipated secondary sex characteristics that match the experienced gender; and make-believe or fantasy play, toys, games, or activities and playmates that are typical of the experienced gender rather than the assigned sex. The incongruence must have persisted for about 2 years. Gender variant behavior and preferences alone are not a basis for assigning the diagnosis.

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Appendix 3. Systematic Reviews and Evidence-Based Medicine

Imagine a courtroom where guilt or innocence is decided solely by the police, drawing on their extensive experience of investigating crime. Someone can be convicted of murder, say, on the verdict of these criminal experts, who have seen many murders before, and who have firm opinions about the sort of people most likely to commit them.

Such a courtroom would be better than nothing. The police have relevant knowledge and experience and are not simply guessing. But it would be far inferior to a real courtroom, where police testimony is just part of the evidence brought before judge and jury: the blood-stained knife, fingerprints, cellphone records, eyewitness testimony, and so on, are all included. Moreover, every piece of evidence is critically examined, weighed, and compared. The attitude is more scientific. Not all evidence is equal: eyewitness testimony can be unreliable, whereas properly collected DNA evidence is of high quality. Independent pieces of evidence (DNA, cellphone records) can point to the same conclusion, making the verdict more secure. Of course, the process is imperfect, but it's a vast improvement over simply relying on the opinions of police officers.

Medicine used to be more like the first (hypothetical) courtroom than the second:

> Clinical practice was historically viewed as the "art of medicine." Expert opinion, experience, and authoritarian judgment were the foundation for decision making. The use of scientific methodology, as in biomedical research, and statistical analysis, as in epidemiology, were rare in the world of medicine.[1]

Starting in the 1970s, evidence-based medicine (EBM) has attempted to move medicine from the first courtroom to the second, towards more empirical rigor.

EBM "is the conscientious, explicit, and judicious use of current best evidence in making decisions about the care of individual patients."[2] The fundamental EBM principle is that clinical practice and practice guidelines should be based on the totality of evidence,

[1] Sur & Dahm (2011, p. 487).
[2] Sackett et al. (1996, p. 71).

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assessed and synthesized in clear and reproducible ways from the medical literature. EBM contrasts with "eminence-based medicine," in which physicians make clinical decisions based on personal experience and expertise, and treatment guidelines themselves are created using a process humorously described as "GOBSAT" ("good old boys sitting around a table").[3]

It is important to emphasize that EBM does not say that evidence about treatments should be the *only* factor in medical decisions. Quite the opposite. According to the American Medical Association's (AMA) *User's Guides to Medical Literature: Essentials of Evidence-Based Clinical Practice*:

> [E]vidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits and risks, burden, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and values and preferences.[4]

Evidence is never sufficient to make health policy either, although policy makers have different priorities than clinicians. A clinician's primary concern is for the individual patient and their "unique predicament"; policy makers need to set general rules and standards with public health in mind. They may consider the cost-effectiveness of treatment, public values and preferences, the feasibility of widely offering the treatment, how its benefits can be distributed fairly, and so forth.

EBM uses a "hierarchy of evidence," often depicted as pyramid with colored layers, as in Figure A.1. Since the layers represent different types of study, the hierarchy is more strictly a hierarchy of *research methods* than a hierarchy of evidence. The pyramid in Figure A.1 should not be taken too seriously: many pyramids have been proposed, with varying numbers of layers and kinds of labels, not to mention colors.[5] In fact, the AMA's

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[3] Lima, Tangamornsuksan et al. (2023, p. 1).
[4] Guyatt et al. (2015, p. 10, emphasis omitted). "Burden [of treatment]" means "the inconvenience of attending to the treatment's optimal use, of its monitoring, the limitations in lifestyle that it entails, and the possibility of interactions with other treatments" (p. 426). "Values and preferences" refer to "the collection of goals, expectations, predispositions, and beliefs that individuals have for certain decisions and their potential outcomes. The incorporation of patient values and preferences in decision making is central to evidence-based medicine" (p. 490).
[5] Blunt (2022). For another pyramid, see Cass (2024a, p. 55).

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User's Guides to Medical Literature contains no such illustration.[6] But the basic point these pyramids make is sound: some ways of gathering evidence about the effects of a treatment are better than others. Systematic reviews (SRs, to be explained below) and meta-analyses are better than randomized controlled trials (RCTs), which are better than cohort studies and case reports,[7] with expert opinion coming in last. The medical consensus based on expert opinion or experience has been shown to be wrong many times before, after rigorous experimental studies were conducted. (See Section 1.2.2.)

EBM prioritizes findings from population-level research, such as RCTs and observational epidemiological studies. This can have drawbacks, sometimes resulting in insufficient consideration of biochemical or physiological evidence from laboratory, animal, or in vitro studies.[8]

In the last few decades EBM has been refined and improved. This appendix includes a brief introduction to SRs, the methodology to systematically identify, synthesize, and assess the best available evidence, and to Grading of Recommendations Assessment, Development, and Evaluations (GRADE), the methodology to assess the quality of evidence and determine the strength of recommendations.

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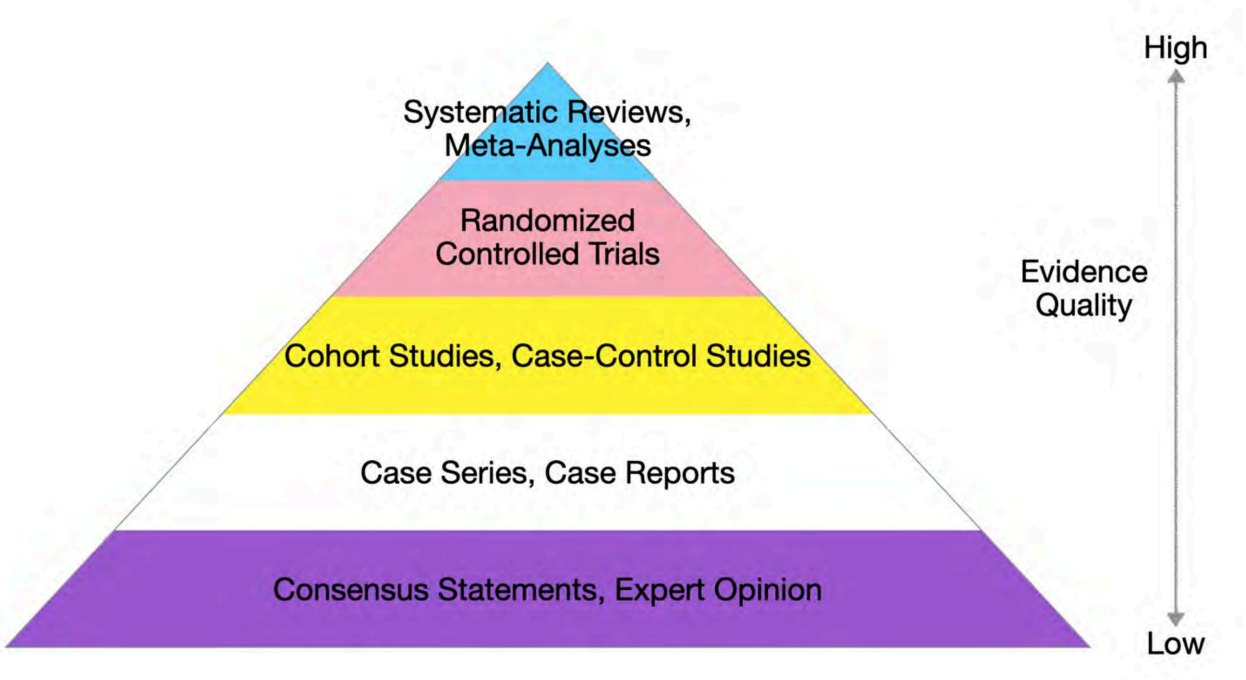
[6] See Guyatt et al. (2015, p. 48, Figure 4-1), which displays a simple three-level hierarchy of evidence in a blue box.

[7] A *meta-analysis* combines data from separate similar studies and statistically analyses the result. Two studies may investigate the same treatment in sufficiently different ways so that a meta-analysis of both is not possible. SRs may involve meta-analyses but need not. A *randomized controlled trial* (RCT) allocates treatment/non-treatment randomly to a group (*cohort*) of patients and follows them over time; the no-treatment group is the *control* group. Control groups may receive another kind of treatment, a *placebo* (an inert pill or procedure that superficially mimics the treatment), or no treatment at all. In a *double-blind* RCT neither the patients nor the attending medical staff know who is in the treatment group and who is in the control group. *Cohort studies* (or *longitudinal* studies) examine groups of patients over time, either *prospectively* (data collected as the study proceeds) or *retrospectively* (the data has already been collected, say in past medical records); there is no randomization to treatment/non-treatment as in an RCT. A *case-control* study starts with two groups, those who have the disease or condition of interest (the *cases*), and those who don't (the *controls*), and examines them retrospectively. The latter two kinds of study are called *observational*, to contrast them with RCTs. A *case report* describes a single patient's treatment and outcome; a *case series* is a collection of similar case reports.

[8] Clarke et al. (2014).

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Figure A1.1 Example EBM Pyramid



1. Systematic reviews

Systematic reviews (SRs) synthesize evidence from multiple studies in the medical literature and assess its quality, using a standard and reproducible methodology. The general steps are outlined below:[9]

Research questions and study eligibility criteria

SRs begin by asking four questions. What is the population being studied? What is the intervention or treatment? What groups are being compared to the group that received the treatment? What results or outcomes are of interest? This is the "PICO" framework: Population, Intervention, Comparator, Outcome. Study eligibility criteria are defined accordingly and documented.

Comprehensive search

Having defined the eligibility criteria for studies, the next step is to locate them. A properly conducted search requires expertise, and includes searching a variety of

[9] What follows is simplified; for more detail see Higgins et al. (2019).

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medical databases, for instance Embase (produced by the publisher Elsevier) and Medline (produced by the U.S. National Library of Medicine (NLM)). The search could also cover registries of clinical trials and so-called grey literature (material outside academic publishing, such as reports and government documents).

Study selection

Reviewers then screen the search results, looking at a study's title and abstract, and then its full text to determine if the study is eligible to be included in the SR. This study selection process follows the pre-defined eligibility criteria. To minimize the risk of bias in the review process, independent duplicate screening may be applied in both the stage of title and abstract screening, and the stage of full text screening.

Data extraction and effect estimate computation

The reviewers extract all relevant data from the studies. The procedure is standardized, and the same kind of data is extracted from all studies. Most of this is in the methods and results sections of the study (and the supplementary material). Depending on the data, there are various ways of measuring the effect of an intervention; the extracted data may need to be converted to a consistent format so the treatment effect estimates reported across eligible studies can be combined as a pooled effect estimate.

Risk of bias assessment

Bias is "systematic error, or deviation from the truth, in results. Biases can lead to under-estimation or over-estimation of the true intervention effect and can vary in magnitude: some are small (and trivial compared with the observed effect) and some are substantial (so that an apparent finding may be due entirely to bias)."[10] Two or more independent reviewers assess the risk of bias of each study, using appropriate tools. One major consideration for choosing a risk of bias tool is the type of study design. For example, Version 2 of the Cochrane Risk-of-Bias tool for randomized trials (RoB 2) is the recommended tool to assess the risk of bias in randomized trials included in

[10] Higgins et al. (2019, pp. 177-178). Note that "biased" here does not mean *prejudiced*. Fair and impartial researchers may produce a "biased" study in the sense relevant to this Appendix.

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Cochrane Reviews, while Risk Of Bias In Non-randomized Studies - of Interventions (ROBINS-I) is the recommended tool to assess the risk of bias in non-randomized studies.

Data synthesis and analysis

One key step for SRs is evidence synthesis, which means the results from the different studies are synthesized or combined. Meta-analyses of effect estimates, the quantitative synthesis strategy, may be performed, as well as sensitivity analyses (which examine whether the results would change if different statistical assumptions were made, if outcomes were defined slightly differently, and so on). If a meta-analysis is not feasible, other ways of synthesizing the results are available. A narrative that describes results study by study is not acceptable.[11]

Quality of evidence assessment

The quality of the evidence is now evaluated using, e.g., the methodological framework Grading of Recommendations Assessment, Development, and Evaluations (GRADE) (explained in the following section).

Discussion and conclusion

The discussion section of the SR includes: "Summary of main results (benefits and harms); potential biases in the review process; overall completeness and applicability of evidence; certainty of the evidence; agreements and disagreements with other studies or reviews."[12] The conclusions section considers the implications for clinical practice and for research.

High-quality SRs organize their PICO information, search strategy, methodologies, and findings according to the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement, which facilitates completeness, accuracy, transparency,

[11] McKenzie & Brennan (2024).
[12] Higgins et al. (2019, p. 404, quotation marks and capitalization omitted).

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and replicability.[13] Registering the protocol for a SR in a system such as PROSPERO increases transparency and trustworthiness of an SR.

2. GRADE

Grading of Recommendations Assessment, Development, and Evaluations (GRADE) is a widely adopted framework for assessing the quality (or "certainty") of the evidence and strength of recommendations.[14] GRADE uses four tiers to classify quality:

> *High*: We are very confident that the true effect lies close to that of the estimate of the effect.
>
> *Moderate*: We are moderately confident in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different
>
> *Low*: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
>
> *Very low*: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect.[15]

There is frequent confusion about the relationship between GRADE and tools that assess individual studies for risk of bias such as RoB 2 and ROBINS-I. When assessing risk of bias, the reviewers are assessing individual studies. When SR authors assess the quality or certainty of evidence with GRADE, they are assessing the total body of evidence. They ask: How confident should we be in the effect estimate (e.g., the estimate of average mortality, level of depression, degree of disease progression), given the evidence derived from all the included studies? GRADE does consider risk of bias in the individual studies that yielded the estimate, but that is just one of five factors that can downgrade the quality of the evidence. The other four are *inconsistency* (how consistent the results are across all the studies reporting on the same outcome);

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[13] Page et al. (2021). See also Santesso et al. (2020).
[14] However, because GRADE "has become increasingly complex, such that new as well as existing users may find it unwieldy," a simplified and slightly revised version has recently been proposed, "Core GRADE" (Guyatt et al., 2025).
[15] Balshem et al. (2011, Table 2). See also M. Prasad (2024, p. 2).

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indirectness (how applicable the evidence is to the PICO in question); *imprecision* (whether the sample is too small or confidence intervals[16] surrounding the estimates too wide), and *publication bias* (e.g. whether studies with negative results have not been published).[17] Evidence quality can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors would likely reduce the observed effect but did not.

GRADE not only provides guidance on assessing the quality of evidence, but guidance on recommending treatments. Key determinants for the strength of recommendations include the balance between benefits and harms of the alternative treatments, the certainty of evidence, values and preferences, and cost and resource allocation. Values and preferences of patients are a major consideration, especially when the certainty of evidence is low or very low.

In GRADE, there is an "explicit separation of the process for assessing the quality of a body of evidence from the process for making recommendations based in part on those assessments. Although higher quality evidence is more likely to be associated with strong recommendations than lower quality evidence, a particular level of quality does not imply a particular strength of recommendation. Sometimes, low or very low-quality evidence can lead to a strong recommendation."[18] For example, a low-cost safe treatment supported by low-quality evidence could lead to a strong recommendation if the potential benefits are large and there is no alternative. Conversely, a treatment might be supported by high quality evidence and yet not be strongly recommended, because it has side effects that some patients would not be willing to accept.

A treatment might be potentially promising but have harmful side effects with only weak evidence of benefit. In such cases a recommendation for "treatment-only-in-research" may be given under the following conditions:

[16] A confidence interval is a range of effect values and is used to quantify uncertainty about effect estimates.
[17] Higgins et al. (2019, Table 2-1).
[18] Balshem et al. (2011, p. 402).

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> [T]here is insufficient evidence supporting an intervention for a panel to recommend its use; further research has a large potential for reducing uncertainty about the effects of the intervention; and further research is deemed good value for the anticipated costs.[19]

3. Overviews of reviews

Overviews of reviews, or "umbrella reviews," such as the one performed to systematically assess the clinical evidence for this Review, use a similar methodology to SRs to evaluate SRs themselves. Overviews employ explicit and systematic methods to identify and analyze multiple systematic reviews that address related research questions within a common topic area, with the goal of synthesizing results across key outcomes.[20] This approach is particularly useful when multiple systematic reviews exist on overlapping or related research questions within the same topic area, or when stakeholders need a high-level synthesis to inform clinical, policy, or public health decision-making. Like SRs, overviews use GRADE or related tools and standardized reporting practices.

The process of an overview follows these steps:

1. Systematically search for all SRs addressing the relevant PICOs.

2. Identify and include the eligible SRs

3. Extract information about the estimated treatment effects, and assess each SR for risk of bias using the tool such as "Risk of Bias In Systematic reviews" (ROBIS)

4. Collect, analyze, and present the data from included systematic reviews, including characteristics of the SRs and their included primary studies; risk of bias of included primary studies; outcome data; and certainty of evidence for pre-defined, clinically important outcomes. Specifically, for each outcome of interest, reviewers summarize the information about treatment estimates from the SRs.

[19] J. Andrews et al. (2013, p. 724).
[20] Pollock et al. (2024).

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To assess the certainty of evidence, reviewers may opt to summarize and report the original GRADE ratings reported by the SRs in the included systematic reviews. However, reviewers may need to re-analyze outcome data from systematic reviews or conduct GRADE assessments themselves using the information reported in the SRs, for example, when the SRs do not include GRADE assessment, or when there is disagreement across included SRs.

Performing a new SR is preferred when there is a lack of recent SRs or when existing SRs are limited in quality; but if the literature contains several recent high-quality SRs the overview is an approved option.[21]

4. Other types of reviews

Not every medical publication with "review" in its title is an SR or an overview of SRs. Such publications can be useful but are not systematic and reproducible syntheses of evidence. Other types of reviews include:

Narrative reviews

Also called *literature reviews*, a narrative review is "a review article (such as a typical book chapter) that is not conducted using methods to minimize bias (in contrast to a systematic review)."[22] For this reason, narrative reviews must be treated with caution, although they can be helpful as an introduction to a research topic.

Scoping reviews

The purpose of a scoping review is to survey the available research on a specific topic. Scoping reviews are systematic and reproducible like SRs but are usually not as rigorous. The aim of a scoping review is to survey existing research and suggest areas for future study, not to assess the evidence for a particular intervention.[23]

[21] Pollock et al. (2024).
[22] Guyatt et al. (2015, p. 461).
[23] Tricco et al. (2016).

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Appendix 4. Overview of Systematic Reviews: Methodology, Evidence Synthesis, Tables

This Appendix is published separately.

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Overview of Systematic Reviews

Methodology, Evidence Synthesis, Tables

Appendix 4:

Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices

Department of Health and Human Services

May 1, 2025



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Minor corrections made May 15, 2025: see Errata

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1 Methodology

The methodology of this overview followed the recommendations for an overview of systematic reviews (SRs) in the *Cochrane Handbook for Systematic Reviews of Interventions*.[1]

Literature search: Medline, Embase, and the psychological database PsycINFO were searched for potentially eligible records. The search strategy included terms related to SRs ("systematic review," "meta-analysis," etc.) and others related to gender dysphoria ("gender incongruence," "gender-affirming hormones," "puberty blockers," etc.), using Boolean operators AND and OR as appropriate. The search was limited to items from 2015 to Feb 20, 2025. A complementary literature search was conducted in other databases including ACCESSSS (a service providing current evidence for clinical decisions) and Epistemonikos (a database of SRs), and grey literature search was conducted through the systematic review registry PROSPERO and Google Scholar, as well as a manual search of reference lists of eligible SRs. Box 1.1. provides an example of search strategies used in Medline.

Literature screening: After the removal of duplicate records, two reviewers reviewed titles and abstracts and independently determined study eligibility. Once potentially eligible records were identified, a thorough review of full-text articles with a standardized and piloted screening form was performed. Reviewers resolved disagreement by discussion.

A record was included if it met the following criteria:

1. It is an SR.
2. The study population is youth with GD whose age is below 26 years old.[2]

[1] Higgins et al. (2019).
[2] Empirically, SRs in this area are usually provided for patients under 18 or those under 26. This decision of age below 26 years balances the comprehensiveness and the directness (applicability) of the evidence review. Though there is a concern regarding the directness of evidence, the evidence for <18 and for <26 years did not identify any significant differences in outcomes.

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3. The study assesses at least one of the following: social transition, psychotherapy, puberty blockers (PBs), cross-sex hormones (CSH), or surgery.

The exclusion criteria were the following:

1. Comingling of mature adult (≥ 26 years old) and youth, which means systematic reviews with more than 25% of included studies on mature adults were excluded because these reviews were not applicable (too indirect) to inform the outcomes on youths.[3]

2. Overlapping efforts.

Data extraction and appraisal of included reviews: Data extracted included review authors, research team, and research question answered; number and characteristics of included studies; study population; treatment; outcomes of interest; analysis and synthesis strategy; risk of bias assessment used for included studies.

The Risk of Bias Assessment Tool for Systematic Reviews (ROBIS) tool[4] was used to assess the risk of bias for included SRs. The data extraction and risk of bias assessment was completed by one reviewer and checked by a second reviewer. ROBIS assesses the quality of the systematic review according to four domains: 1) study eligibility criteria; 2) identification and selection of studies; 3) data collection and study appraisal; and 4) synthesis of findings. Additionally, ROBIS assesses the overall risk of bias in a systematic review process and SRs with concerns identified in the four domains can still be assessed at low risk of bias if the SRs have properly addressed these concerns in the evidence interpretation.

Evidence synthesis and certainty of evidence: The evidence synthesis summarizes the outcome data across SRs that were published in English and classified at low risk of bias.[5] The evidence synthesis was organized by types of treatment, and the outcomes

[3] The SRs including both >26 years old and <26 years old skew toward the >26 population, and so are less directly applicable to this overview than SRs on youth with GD.
[4] Whiting et al. (2016).
[5] One non-English systematic review was considered eligible and included and classified at low risk of bias. This overview did not summarize the results by outcomes from this review. Nevertheless, its conclusions were similar.

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of interest included GD, mental health and well-being, treatment goal (for example, puberty suppression for puberty blockers), need for or progression to further treatment, safety outcomes including side effects and adverse outcomes, and regret. For each outcome, this overview summarized the effect estimates and the certainty of evidence (confidence in the effect estimates, the quality of evidence).

The certainty of evidence was summarized following the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) methodology.[6] In GRADE, certainty of evidence can be downgraded for: risk of bias (study limitations), inconsistency (unexplained variation in results), indirectness (evidence not directly applicable), imprecision (wide confidence intervals or small samples), and publication bias (selective reporting).[7] Evidence can be upgraded if there is a large effect size, a clear dose-response relationship, or if confounding factors expected to reduce the observed effect did not do so.[8] Evidence could be classified into four levels of certainty: high, moderate, low, or very low.[9] This overview summarized the GRADE rating from the original review for the respective outcome wherever it is available. Nevertheless, there were two modifications made:

1. Where a formal GRADE appraisal had not been performed by the systematic review, but expressions such as “we are very uncertain” and “no conclusions could be drawn” were used in SRs’ conclusions, these statements were considered equivalent to a “very low quality” GRADE assessment.[10]

[6] In GRADE, quality of evidence is equivalent to certainty of evidence. “The quality of evidence is very low” is equivalent to “the certainty of evidence is very low.” See Guyatt et al. (2008), Balshem et al. (2011).
[7] Balshem et al. (2011); Guyatt et al. (2008); Guyatt, Oxman, Kunz, Brozek, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Falck-Ytter, et al. (2011); Guyatt, Oxman, Kunz, Woodcock, Brozek, Helfand, Alonso-Coello, Glasziou, et al. (2011); Guyatt, Oxman, Montori, et al. (2011); Guyatt, Oxman, Vist, et al. (2011).
[8] Guyatt, Oxman, Sultan, et al. (2011).
[9] According to GRADE, high certainty evidence means that “we are very confident that the true effect lies close to that of the estimate of the effect” and very low certainty evidence indicates that “we have very little confidence in the effect estimate: the true effect is likely to be substantially different from the estimate of effect” (Balshem et al., 2011).
[10] Balshem et al. (2011); Santesso et al. (2020).

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2. If SRs disagreed on GRADE assessment for the same outcome, this overview resolved the disagreement with *de novo* assessment following the GRADE methodology and reported the rationale for the assessment.

Box 1.1 Search strategy in Ovid MEDLINE(R) and Epub Ahead of Print, In-Process, In-Data-Review & Other Non-Indexed Citations 1996 to Feb 20, 2025

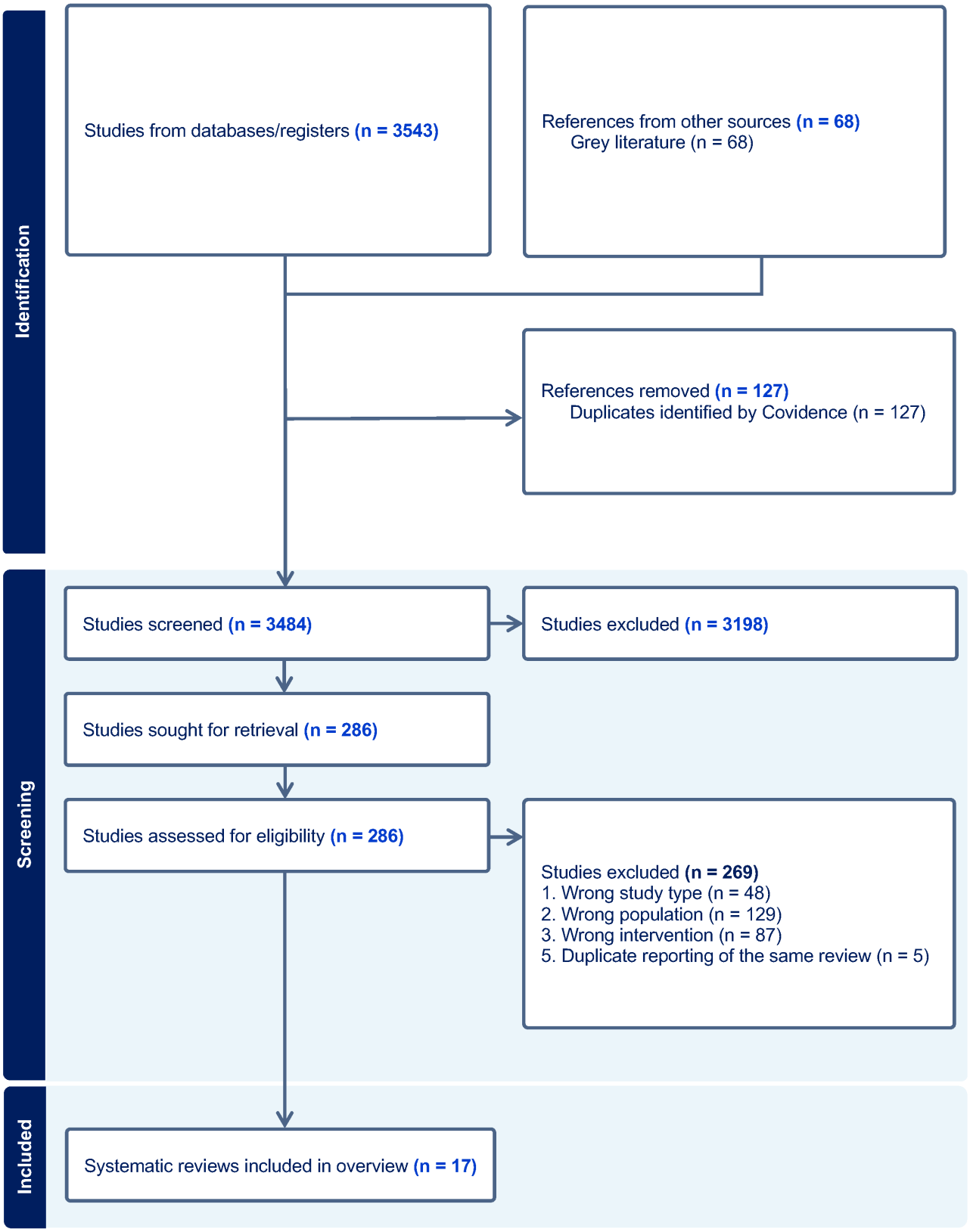
1	exp "Sexual and Gender Minorities"/
2	Gender Dysphoria/
3	Gender Identity/
4	Gender Role/
5	"Sexual and Gender Disorders"/
6	Transsexualism/
7	Transgender Persons/
8	Health Services for Transgender Persons/
9	exp Sex Reassignment Procedures/
10	gender identity disorder.mp.
11	non-binary.mp.
12	transgender.mp.
13	(gender* adj3 (dysphori* or disorder* or distress or nonconform* or non-conform* or atypical or incongru* or identi* or disorder* or confus* or minorit* or queer* or variant or diverse or creative or explor* or question* or expan* or fluid)).tw.
14	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
15	(transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw.
16	(genderfluid or genderqueer or agender).mp.
17	((correct or chosen) adj3 name).mp.
18	(trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw.
19	((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)).tw.
20	(male-to-female or m2f or female-to-male or f2m).tw.
21	or/1-20
22	exp Child/ or Child Behavior/ or Child Health/ or Child Welfare/ or Psychology, Child/ or Child Psychiatry/ or Child Health Services/ or Child Development/
23	Minors/
24	(child$ or minor or minors or boy or boys or boyhood$ or girl or girls or girlhood$ or kid or kids or youngster$ or emerging adult$).ti,ab,kf,jn.
25	(young$ adj (people$ or person$1 or adult$ or man$1 or men$1 or woman$ or women$ or male$1 or female$1)).ti,ab,kf,jn.
26	pediatrics/
27	(pediatric$ or paediatric$ or peadiatric$).ti,ab,kf,jn.
28	Adolescent/ or Adolescent Behavior/ or Adolescent Health/ or Psychology, Adolescent/ or Adolescent Psychiatry/ or Adolescent Health Services/ or Adolescent Medicine/ or Adolescent Development/
29	Puberty/
30	(adolescen$ or pubescen$ or prepubescen$ or postpubescen$ or pubert$ or prepubert$ or postpubert$ or teen or teens or teenag$ or tween$ or preteen$ or preadolescen$ or juvenil$ or youth$ or underage$ or under-age$).ti,ab,kf,jn.
31	Schools/ or Schools, Nursery/
32	exp Child Day Care Centers/ or Child Care/

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33	(school$ or highschool$ or preschool$ or kindergar$ or nursery or nurseries or pupil$1).ti,ab,kf,jn.
34	22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33
35	systematic review/
36	meta-analysis/
37	(meta anal* or meta-anal* or metaanal*).ti,ab.
38	((systematic or evidence) adj2 (review* or overview*)).ti,ab.
39	((pool* or combined) adj2 (data or trials or studies or results)).ab.
40	(search strategy or search criteria or systematic search or study selection or data extraction).ab.
41	(search* adj4 literature).ab.
42	or/35-41
43	21 and 34 and 42

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Figure 1.1 Searching, screening, and inclusion process



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2 Literature screening results

Following the removal of duplicates, 3,484 records were screened by title and abstract. Of these, 286 full-text articles were assessed for eligibility. A total of 269 full-text articles were excluded for the following reasons: 48 were not SRs (incorrect study type), 129 did not focus on children or adolescents with GD, 87 did not address the treatment of interest, and 5 were excluded due to duplicate reporting (See Figure 1.1). After screening, 17 SRs met the inclusion criteria, examining the effects of psychotherapy (n = 5),[11] social transition (n = 2),[12] PBs (n = 9),[13] CSH (n = 8),[14] and surgeries (n = 3)[15] among children or adolescents with GD.

2.1 Risk of bias assessment in included SRs

Of the 17 included SRs, ten were rated as having a low risk of bias (see Table 2.1).[16]

The low risk of bias SRs could be organized into five groups:

1. The SRs by scholars from McMaster University in Canada on PBs (Miroshnychenko 2025a[17]), CSH (Miroshnychenko 2025b[18]), and mastectomy (Miroshnychenko 2024[19]).

[11] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[12] Dopp et al. (2024); Hall et al. (2024).
[13] Chew et al. (2018); Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Ramos et al. (2021); Rew et al. (2021); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[14] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[15] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[16] Dopp et al. (2024); Hall et al. (2024); Heathcote et al. (2024); Ludvigsson et al. (2023); Miroshnychenko et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024); Zepf et al. (2024).
[17] Miroshnychenko, Roldan, et al. (2025).
[18] Miroshnychenko, Ibrahim, et al. (2025).
[19] Miroshnychenko et al. (2024).

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2. The SRs conducted by scholars from University of York to inform the Cass Review, comprising the reviews of PBs (Taylor 2024a[20]), CSH (Taylor 2024b[21]), psychotherapy (Heathcote 2024[22]), and social transition (Hall 2024[23]).
3. The systematic review by researchers from Rand Corporation on all treatment strategies (Dopp 2024[24]).
4. The systematic review by Swedish Agency for Health Technology Assessment and Assessment of Social Services on hormone therapies (Ludvigsson 2023[25]).
5. The systematic review by Zepf et al., which was an update and followed the same methodology of the two SRs published in German.

SRs within each group generally followed the same methodological approach. The three SRs by McMaster University scored as having a low risk of bias across all four domains, as well as low risk of bias overall.[26] Other SRs rated at low risk of bias had limitations in one or more domains. For instance, though published in 2024, the literature search for the University of York SRs was conducted in April 2022. Additionally, there were concerns regarding the risk of bias assessment. Though the Newcastle-Ottawa Scale is an appropriate tool for the study types included in the systematic reviews, the high quality studies (for example, high quality cross-sectional or retrospective studies) are not adequate to provide high certainty evidence on the treatment effect.[27] While narrative descriptors such as “very uncertain” and “no conclusions can be drawn” correspond to the rating of “low/very low certainty” using GRADE, no formal GRADE assessment was performed. The Dopp et al. (2024)[28] review had limitations in the domain of study eligibility criteria as it included case reports and qualitative studies for

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[20] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[21] Taylor, Mitchell, Hall, Langton, et al. (2024).
[22] Heathcote et al. (2024).
[23] Hall et al. (2024).
[24] Dopp et al. (2024).
[25] Ludvigsson et al. (2023).
[26] Hall et al. (2024); Heathcote et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).
[27] van der Miesen 2020 was the only high-quality study in the systematic review on PBs, though it is a cross-sectional study and not adequate to assess treatment effect. Jensen 2019 was assessed as the only high-quality study in the systematic review on CSH, and it was a retrospective chart review and only reported side-effects, not treatment effects.
[28] Dopp et al. (2024).

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estimating treatment effects, and in the domain of identification and selection of studies was limited by searching in only one database.

A total of seven SRs[29] were rated at high risk of bias overall, often due to limited or poorly defined research questions and eligibility criteria, lack of risk of bias assessments, and inadequate synthesis of findings. This appendix includes a detailed summary of study characteristics and risk of bias considerations for all included SRs. The variation in methodological rigor highlights the need for cautious interpretation of findings, especially from reviews rated at high risk of bias.

[29] Chew et al. (2018); Expósito-Campos et al. (2023); Karalexi et al. (2020); Malpas et al. (2022); Ramos et al. (2021); Rew et al. (2021); Thompson et al. (2023).

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Table 2.1. Scope of included SRs

Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Chew 2018[30]	Y	Y				High risk of bias	Low risk of bias	High risk of bias	High risk of bias	High risk of bias
Dopp 2024[31]	Y	Y	Y	Y	Y	High risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Expósito-Campos 2023[32]				Y		High risk of bias	High risk of bias	Low risk of bias	High risk of bias	High risk of bias
Hall 2024[33]					Y	Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Heathcote 2024[34]				Y		Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Karalexi 2020[35]		Y				High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Ludvigsson 2023[36]	Y	Y				Low risk of bias	High risk of bias	Low risk of bias	High risk of bias	**Low risk of bias**

[30] Chew et al. (2018).
[31] Dopp et al. (2024).
[32] Expósito-Campos et al. (2023).
[33] Hall et al. (2024).
[34] Heathcote et al. (2024).
[35] Karalexi et al. (2020).
[36] Ludvigsson et al. (2023).

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Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Malpas 2022[37]				Y		High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Miroshnychenko 2025a[38]	Y					Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2025b[39]		Y				Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Miroshnychenko 2024[40]			Y			Low risk of bias	Low risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Ramos 2021[41]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Rew 2021[42]	Y					High risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Taylor 2024a[43]	Y					Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**

[37] Malpas et al. (2022).
[38] Miroshnychenko, Roldan, et al. (2025).
[39] Miroshnychenko, Ibrahim, et al. (2025).
[40] Miroshnychenko et al. (2024).
[41] Ramos et al. (2021).
[42] Rew et al. (2021).
[43] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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Review ID	PBs	CSH	Surgeries	Psychotherapy	Social Transition	Study Eligibility Criteria	Identification and Selection of Studies	Data Collection and Appraisal	Synthesis and Findings	Risk of bias in the review
Taylor 2024b[44]		Y				Low risk of bias	High risk of bias	Low risk of bias	Low risk of bias	**Low risk of bias**
Thompson 2023[45]	Y	Y	Y	Y		Low risk of bias	High risk of bias	High risk of bias	High risk of bias	High risk of bias
Zepf 2024[46]	Y	Y				Low risk of bias	Low risk of bias	High risk of bias	Low risk of bias	**Low risk of bias**

[44] Taylor, Mitchell, Hall, Langton, et al. (2024).
[45] Thompson et al. (2023).
[46] Zepf et al. (2024).

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2.2 Excluded SRs

Box 2.1 provides examples of excluded SRs due to focusing on a mixed population, or interventions not relevant to this overview.

Box 2.1 Examples of excluded SRs

SRs that were a mixed population (with more than 25% included studies on mature adults):

Baker 2021

Baker, K. E., Wilson, L. M., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2021). Hormone therapy, mental health, and quality of life among transgender people: A systematic review. Journal of the Endocrine Society, 5(4), 1-16.

Doyle 2023

Doyle, D. M., Lewis, T. O. G., & Barreto, M. (2023). A systematic review of psychosocial functioning changes after gender-affirming hormone therapy among transgender people. Nature Human Behaviour.

Dunford 2021

Dunford, C., Bell, K., & Rashid, T. (2021). Genital reconstructive surgery in male to female transgender patients: A systematic review of primary surgical techniques, complication profiles, and functional outcomes from 1950 to present day. European Urology Focus, 7(2), 464-471.

Haupt 2020

Haupt, C., Henke, M., Kutschmar, A., Hauser, B., Baldinger, S., Saenz, S. R., . . . Schreiber, G. (2020). Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women. Cochrane Database of Systematic Reviews(11).

Javier 2022

Javier, C., Crimston, C. R., & Barlow, F. K. (2022). Surgical satisfaction and quality of life outcomes reported by transgender men and women at least one year post

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KS-AG-26-1037-A-001623

gender-affirming surgery: A systematic literature review. International Journal of Transgender Health, 23(3), 255-273.

Kloer 2021

Kloer, C., Parker, A., Blasdel, G., Kaplan, S., Zhao, L., & Bluebond-Langner, R. (2021). Sexual health after vaginoplasty: A systematic review. Andrology, andr.13022.

Kotamari 2021

Kotamarti, V. S., Greige, N., Heiman, A. J., Patel, A., & Ricci, J. A. (2021). Risk for venous thromboembolism in transgender patients undergoing cross-sex hormone treatment: A systematic review. The Journal of Sexual Medicine, 18(7), 1280-1291.

Thornton 2024

Thornton, S. M., Edalatpour, A., & Gast, K. M. (2024). A systematic review of patient regret after surgery- a common phenomenon in many specialties but rare within gender-affirmation surgery. The American Journal of Surgery.

van Leerdam 2021

van Leerdam, T. R., Zajac, J. D., & Cheung, A. S. (2021). The effect of gender-affirming hormones on gender dysphoria, quality of life, and psychological functioning in transgender individuals: A systematic review. Transgender Health, trgh.2020.0094.

Wilson 2020

Wilson, L. M., Baker, K. E., Sharma, R., Dukhanin, V., McArthur, K., & Robinson, K. A. (2020). Effects of antiandrogens on prolactin levels among transgender women on estrogen therapy: A systematic review. *International journal of transgender health*, *21*(4), 391–402.

SRs that were not on the interventions of interest:

Diana 2024

Diana, P., Belluzzi, B., Corona, F., Barbi, E., & Tornese, G. (2024). Nonmedical gender-affirming practices in transgender and gender diverse adolescents: A narrative review. Transgender Health.

di Giacomo 2018

di Giacomo, E., Krausz, M., Colmegna, F., Aspesi, F., & Clerici, M. (2018). Estimating the Risk of Attempted Suicide Among Sexual Minority Youths: A Systematic Review and Meta-analysis. *JAMA pediatrics*, *172*(12), 1145–1152.

Notably, this overview excluded two SRs by National Institute for Health and Care Excellence (NICE) in October 2020.[47] This was because these two SRs were commissioned by NHS England to inform Dr Hilary Cass' independent review. In 2024, several SRs funded and commissioned by NHS England to inform the Cass review were published and were more comprehensive and updated than the two NICE SRs.

2.3 Baker et al. 2021

This overview also excluded the SR by Baker and colleagues,[48] which was funded by the World Professional Association for Transgender Health (WPATH), because it predominantly included studies on mature adults and was therefore too indirect to inform the healthcare of children or adolescents with GD. However, since the Baker et al. review supported the recommendations in the Adolescent chapter of WPATH SOC-8 it was subjected to a separate ROBIS analysis and was found to be at "high risk of bias" due to limitations in data collection and risk of bias assessment, and synthesis of results.

Study eligibility criteria: Low risk of bias.

The systematic review authors registered a protocol and had explicit and appropriate eligibility criteria. The systematic review excluded studies with follow up less than 3 months and studies that did not provide sufficient information about regimen of intervention.

Identification and selection of studies: Low risk of bias.

The authors searched in several databases and other resources. The authors also reported duplicate screening process.

[47] National Institute for Health and Care Excellence (2020b, 2020a).
[48] Baker et al. (2021).

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Data collection and study appraisal: High risk of bias.

The authors reported using a standardized form and they performed screening and risk of bias assessment in duplicate, suggesting that data collection was also done in duplicate. The authors described the most important characteristics of the included studies. The results collected, however, are not standardized across studies. For some studies, authors reported magnitudes of effect and confidence intervals, whereas for others they reported only that "no changes were observed."[49] Although the authors aimed to use the correct tools, when assessing risk of bias they did not consider that the design of the studies was not the same for the researchers of the primary studies versus the systematic review's question, leading the authors to assess studies using an inappropriate tool: for example, the systematic review authors assessed a primary study as a trial while it should have been assessed as a case series for the review purposes.

Synthesis and findings: High risk of bias.

Although reported per outcome, Baker et al. describe the results at the study level instead of across studies without justifying why they did not conduct a meta-analysis or reporting whether they planned to do so. Therefore, it is challenging for readers to draw any conclusions at the outcome level. While the review used the AHRQ guidelines for assessing strength of evidence, the authors did not comment on a formal assessment of heterogeneity, regardless of apparent between-study variation. The AHRQ guidelines do not consider publication bias. The authors did comment on risk of bias at the outcome level.

Risk of bias in the review: High risk of bias.

While the authors mention some limitations of the evidence, they did not comment on applicability or address all concerns identified with the evidence.

3 Synopses of SRs assessed at low risk of bias

Dopp et al. 2024:[50] This RAND SR examined evidence on interventions for GD and related health problems in youth with GD. The SR applied a strategy of combining

[49] Baker et al. (2021).
[50] Dopp et al. (2024).

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targeted search from existing clinical guidelines, reviews, and legal proceedings, and a broad search from PubMed. It included 105 studies and organized them into seven categories of interventions: psychosocial interventions, PBs, CSH, surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, and other treatments described as "gender identity and expression change efforts." Although this systematic review is comprehensive (49 studies for PBs, 56 studies for CSH, and 18 studies for surgery), a notable limitation is the inclusion of case reports. Case reports are inherently limited in their ability to establish treatment effects due to the lack of control groups and high risk of bias. The inclusion of case reports inflated the number of included studies but provided no additional benefits in informing about treatment effectiveness, which was reflected by the very low certainty of evidence despite a large number of eligible studies. This SR is limited by having systematically searched PubMed but no other databases. Compared with other low risk of bias SRs on hormonal and surgical treatment (Miroshnychenko 2024, Miroshnychenko 2025a,[51] Miroshnychenko 2025b,[52] Taylor 2024a,[53] Taylor 2024b[54]), the Dopp et al. 2024 review missed more case series and before-after studies while including more case reports. It summarized effect estimates by reviewing all reports of outcomes across studies and applied the GRADE methodology to assess the certainty of evidence. This SR reported that the evidence was limited by lack of long-term outcomes, lack of randomized controlled trials, and inconsistent measurement of outcomes, concluding that the certainty of evidence was frequently low or very low. For interventions including PBs, CSH, and surgeries, the certainty of evidence was very low for GD and mental health outcomes.

Hall et al. 2024:[55] This SR is part of the systematic review effort commissioned by the Cass Review. It assessed the effects of social transition (e.g., name/pronoun use, clothing changes) in patients under 18 with GD/incongruence. The authors included 11

[51] Miroshnychenko, Roldan, et al. (2025).
[52] Miroshnychenko, Ibrahim, et al. (2025).
[53] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[54] Taylor, Mitchell, Hall, Langton, et al. (2024).
[55] Hall et al. (2024).

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studies, most from the US and of low quality, using cross-sectional and cohort designs. The literature search was conducted in April 2022. The authors used an adapted version of the Newcastle-Ottawa Scale for cohort studies. Notably, the Newcastle-Ottawa Scale is suitable for the study type, but a high-quality study as assessed by this tool may be assessed as having high risk of bias according to other tools such as ROBINS-I, which has been developed to consider both the study design and the appropriateness of a study for answering questions about treatment effects. This SR did not conduct meta-analysis to synthesize evidence quantitatively; instead, it narratively summarized the effect estimates by outcomes. The review authors interpreted the evidence with caution, considering the limitations of the evidence (small sample sizes, lack of longitudinal or controlled designs, and heterogeneous outcomes across included studies), but did not use GRADE methodology to explicitly assess the certainty of evidence. The authors concluded that there is insufficient evidence to determine benefits or harms of social transition.

Heathcote et al. 2024:[56] This SR is part of the systematic review effort commissioned by the Cass Review. It evaluated psychosocial support interventions for children and adolescents experiencing GD. Ten studies with diverse designs (cohort, pre–post, mixed methods) were included. The literature search was conducted in April 2022. This SR used the Mixed Methods Appraisal Tool for quality assessment. Although the review followed systematic methods and focused on interventions beyond medical or surgical treatments, the evidence base was limited by the small number of studies, low quality, lack of comparators, and heterogeneity in interventions and outcomes. According to the authors, conclusions were limited due to poor reporting and inconsistent measurement. The authors called for clarity in intervention description and core outcome sets to enhance future research synthesis.

[56] Heathcote et al. (2024).

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Ludvigsson et al. 2023:[57] This systematic review by the Swedish National Board of Health and Welfare synthesized evidence on hormonal and surgical interventions in adolescents with GD. The review conducted a literature search in 2022 and included 24 studies (eight studies on GnRH alone, 13 studies on GnRH and CSH, and three studies on CSH alone). The review applied the GRADE methodology and downgraded the evidence due to concerns related to risk of bias and imprecise outcome measurement. However, the review authors mistakenly concluded that the certainty of evidence "cannot be assessed." Based on the authors' assessment to downgrade the evidence, the certainty of evidence should be "very low" for all outcomes assessed, including global function, suicidal ideation, GD, depression, anxiety, and quality of life. The SR concluded that evidence for benefits and harms of hormonal and surgical interventions remains insufficient for routine clinical use in adolescents.

Miroshnychenko et al. 2024:[58] This systematic review and meta-analysis examined the psychological and physical effects of mastectomy in birth-registered females under 26 years with GD. The search included databases through June 2023, yielding 39 studies (3 comparative observational, 2 before–after, and 34 case series). Outcomes included mental health measures, GD, body satisfaction, and surgical complications. The review used ROBINS-I for risk of bias assessment, conducted meta-analyses for evidence synthesis, and applied the GRADE methodology for certainty of evidence assessments. Comprehensive and methodologically sound, the SR found the certainty of evidence was limited by a predominance of case series, lack of prospective comparative studies, and other risk of bias concerns in the included studies, as well as small sample sizes. Indirectness was also a concern when participants' age at surgery was above the eligibility threshold. The authors found very low to low certainty evidence regarding mental health outcomes including global functioning, suicide attempt, and non-suicidal self-injuries.

[57] Ludvigsson et al. (2023).
[58] Miroshnychenko et al. (2024).

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Miroshnychenko et al. 2025a:[59] This SR evaluated the effects of PBs in individuals under 26 years with GD. The authors searched ten databases up to September 2023 and included studies employing observational and interventional designs. Outcomes assessed included psychological functioning, bone health, growth, and progression to CSH. The methodology of this systematic review was the same as that of another systematic review on mastectomy by the same group of researchers (Miroshnychenko 2024). The SR included 10 studies, including 3 comparative observational studies and 7 before-after studies. The review authors concluded that the certainty of evidence for psychological and physical health is very low. This SR found that 92% of individuals who received PBs progressed to receiving CSH, though the evidence on the impact of PBs on this outcome is very uncertain (very low certainty of evidence).

Miroshnychenko et al. 2025b:[60] This SR and meta-analysis assessed the effects of cross-sex hormone therapy in individuals with GD aged under 26 years. The authors searched ten databases through September 2023 and included 24 studies (9 comparative observational, 13 before–after, and 2 case series). Outcomes assessed included psychological (e.g., depression, global function) and physical effects (e.g., bone mineral density, cardiovascular events). The review followed the same methodology as two other SRs (on PBs and surgery) by the same group of researchers (Miroshnychenko 2024, Miroshnychenko 2025a[61]). The review found very low to low certainty evidence for psychological outcomes, and very low certainty evidence on bone mineral density. This SR found high certainty evidence on the proportion of natal females experiencing cardiovascular events during a 7 to 109 months of follow-up, which was 40 per 1000 following CSH use.

[59] Miroshnychenko, Roldan, et al. (2025).
[60] Miroshnychenko, Ibrahim, et al. (2025).
[61] Miroshnychenko, Roldan, et al. (2025).

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Taylor et al. 2024a:[62] This SR is part of the systematic review effort commissioned by the Cass Review. It focused on the outcomes of puberty blocker treatment in adolescents with GD or gender incongruence. The authors searched the literature through April 2022 and narratively synthesized studies on psychological, physical, and developmental effects. The SR followed the same methodology as the other reviews by the same research group (Hall 2024), including using the Newcastle-Ottawa scale to assess the risk of bias for included studies. This SR included 50 studies, including one high quality cross-sectional study and 25 moderate-quality observational studies. Notably, "moderate-quality observational studies" is not equivalent to "moderate-quality evidence." Moderate-quality observational studies or high-quality cross-sectional studies are inherently limited in evaluating treatment effects. Moreover, most included studies were observational with small sample sizes and varying outcome definitions. The review employed a narrative synthesis, including only moderate- and high-quality studies but did not explicitly assess the certainty of evidence using the GRADE methodology. The review findings were inconclusive, with inconsistent evidence on psychological benefits and concerns about effects on bone health and growth.

Taylor et al. 2024b:[63] This SR is part of the systematic review effort commissioned by the Cass Review. It synthesized studies on the outcomes of masculinising and feminising hormone therapy in adolescents with GD. It included 53 studies (12 cohort, 9 cross-sectional, 32 pre–post) identified through a search conducted in April 2022. Of all included studies, there was only one high-quality cohort study, which measured adverse outcomes only. The other included studies were moderate-quality studies. The review employed a narrative synthesis, which was limited by heterogeneity in study designs and outcome measures. Compared with other low risk of bias reviews, not using GRADE methodology to explicitly assess the certainty of evidence is a limitation and creates confusion among users: the review authors discuss "moderate quality" studies, rather than moderate certainty of evidence. The authors found inconsistent or insufficient evidence for the effect of CSH on GD, body satisfaction, psychosocial,

[62] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[63] Taylor, Mitchell, Hall, Langton, et al. (2024).

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cognitive, and physical health outcomes and concluded that robust evidence is lacking. This conclusion is consistent with other SRs of similar scope (Dopp 2024,[64] Miroshnychenko 2025b[65]), which suggested very low certainty of benefits.

[64] Dopp et al. (2024).
[65] Miroshnychenko, Ibrahim, et al. (2025).

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4 Summary of all included SRs

Chew et al. 2018[66]	
Study population description	Young people with gender dysphoria
Intervention	Hormonal treatment including PBs and CSH
Outcomes	Physical effects (including physical sex characteristics, side effects, bone mineral density, etc.), psychological effects, cognitive effects
Included studies	13 studies including 9 on GnRHas, 3 on estrogen, 5 on testosterone, 1 on antiandrogen (cyproterone acetate), and 1 on progestin (lynestrenol). There were no randomized trials included, and only 2 studies included control groups.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol available, though the authors describe the eligibility criteria with details for the population (age and diagnosis) and intervention, which seem appropriate for the question and are clear and unambiguous. Identification and selection of studies: The authors searched in the largest electronic databases, and although they did not use a formal search strategy, their search terms were broad enough to have likely captured all relevant studies. They also searched the reference list of relevant studies. Data collection and study appraisal: Data extraction captured relevant outcomes including mental health and physical parameters. The authors describe the most important characteristics of the included studies. The results collected, however, are not standardized across studies. Although the authors reported that two reviewers performed risk of bias assessments, they used a tool not designed for these types of study. Synthesis and findings: Only narrative synthesis was used. Although reported per outcome, the authors describe the results at the study level. For some outcomes, they provide a summary that focuses on counting the number of studies with statistically significant results. Risk of bias in the review: The authors mentioned some of the limitations of the evidence; however, they ignored these when interpreting the results and made claims about the presence of associations.
Results	Most of the included studies were assessed as studies with high risk of bias. This systematic review did not conduct evidence synthesis and instead relied on narrative description of individual studies. There was no formal assessment of the certainty of evidence. Nevertheless, the review authors concluded that hormonal treatments effectively achieved their intended physical effects, with GnRHas and cyproterone acetate suppressing sex hormones, and estrogen or testosterone promoting the development of feminized or masculinized secondary sex characteristics. GnRHa treatment was associated with improvements in several domains of psychological functioning, though not in gender dysphoria itself.

[66] Chew et al. (2018).

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Dopp et al. 2024[67]	
Study population description	Transgender and gender-expansive youth
Intervention	A health intervention related to recipients' transgender and gender-expansive identity (i.e., targeting gender dysphoria, related health problems, or both): psychosocial interventions, puberty-suppressing hormones, CSH, and surgeries, reproductive health interventions, treatment of co-occurring mental health or developmental disorders, other treatments described as "gender identity and expression change efforts."
Outcomes	Psychosocial interventions: suicidality, mental health outcomes (including both depression or mood symptoms, and functioning), regret or dissatisfaction, family support. Puberty-suppressing hormones: decrease in pubertal changes targeted for suppression, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. CSH: increase in pubertal changes targeted for initiation, gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Surgeries: gender dysphoria, mental health functioning, regret or dissatisfaction, side effects and complications, bone health metrics, fertility. Reproductive health interventions: successful cryopreservation of oocytes and embryos, successful cryopreservation of semen. Treatment of co-occurring mental health or developmental disorders: eating disorder symptoms co-occurring with gender dysphoria, depression and/or anxiety symptom co-occurring with gender dysphoria, gender dysphoria co-occurring with autism spectrum disorder. "Gender identity and expression change efforts": suicidality, mental health symptoms.
Included studies	Psychosocial interventions: 22 studies, including 1 randomized controlled trial (intervention as video narratives of lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities of overcoming coming-out-related difficulties),[68] 2 cohort studies, 6 quasi-experimental studies, 9 cross-sectional studies, 3 case reports, and 1 qualitative study. Puberty-suppressing hormones: 49 studies, including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study. CSH: 56 studies, including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study. Surgeries: 18 studies, including 6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study. Reproductive health interventions: 9 studies, using cross-sectional or case report designs with small samples (one to 20 transgender youth per sample). Treatment of co-occurring mental health or developmental disorders: 7 studies, all studies using case report design. "Gender identity and expression change efforts": 4 studies, including 3 using retrospective survey designs with community samples, and 1 case report.

[67] Dopp et al. (2024).
[68] This randomized controlled trial compared "coping-oriented brief videos" as an intervention for suicidality among sexual or gender minority. It was not a trial comparing psychotherapy with no psychotherapy for youth with gender dysphoria.

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Dopp et al. 2024[67]	
Risk of bias assessment consideration	Study eligibility criteria: The review did not include a preregistered protocol. The eligibility criteria focused on youth with gender dysphoria under 26 years old and required post-intervention outcomes. However, case reports and qualitative studies were included, which may be limited in estimating the treatment effects. Identification and selection of studies: There were two phases of literature search, and a comprehensive search was conducted in PubMed. However, other databases were not searched. Data collection and study appraisal: Data collection followed a structured form with critical appraisal procedures. Reviewers conducted risk of bias assessments using the JBI critical appraisal checklist. The tool was appropriate for the study research design. The reviewers discussed disagreements for consensus. Synthesis and findings: The review synthesized all identified studies for each intervention into a summary of effect estimates for each outcome that had been studied. Results for all prespecified outcomes reported and summarized. However, this review only narratively described the results for each outcome, without details on the evidence synthesis strategy or rationale. The interpretation of review findings were based on study quality and the limitations of included studies. Applicability of evidence was discussed, including study demographics, and statistical results were not overemphasized.
Results	Psychosocial interventions: very low certainty evidence for all outcomes. Puberty-suppressing hormones: low certainty evidence for decrease in pubertal changes targeted for suppression, very low certainty evidence for all the other outcomes. CSH: low certainty evidence for increase in pubertal changes targeted for initiation, very low certainty evidence for all the other outcomes. Surgeries: low certainty evidence for decrease in gender dysphoria after mastectomy, very low certainty evidence for decrease in gender dysphoria after other surgeries and other outcomes. Reproductive health interventions: very low certainty evidence for two outcomes. Treatment of co-occurring mental health or developmental disorders: very low certainty for all outcomes. “Gender identity and expression change efforts”: low certainty evidence in increases in suicidality, very low certainty for mental health symptoms.

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Expósito-Campos et al. 2023[69]	
Study population description	Transgender and non-binary youth and adults
Intervention	Empirically supported affirmative psychological intervention.
Outcomes	Mental health outcomes including anxiety, depression, trauma, suicidality, substance abuse, etc.
Included studies	22 studies, with 10 studies reporting outcome information for transgender and non-binary people (3 randomized controlled trials and 7 uncontrolled before-after studies), while 12 studies reporting mixed outcome information for transgender and non-binary and non-transgender populations.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were vague, for example, "well-described psychological interventions" introduces subjectivity. It is unclear whether studies following up parallel groups of study participants were considered as "quasi-experimental designs" and included or not. Identification and selection of studies: The search strategy combined five blocks with Boolean logic "AND", including "transgender" "distress" "affirming" "psychotherapy" and "intervention". This strategy was narrow. Data collection and study appraisal: Duplicate efforts and consensus process were reported. Synthesis and findings: The planned meta-analysis was not feasible. However, the narrative synthesis was reported inappropriately. The synthesis was by studies, according to the study population, types of study design, and interventions, while preferably it should be by outcomes and types of interventions. Risk of bias in the review: The interpretation of evidence did not address the concerns in the systematic review process.
Results	This systematic review did not conduct evidence synthesis by outcome, and there was no formal certainty of evidence assessment. The review authors concluded found “improvements in psychological distress, depression, anxiety, suicidality, substance-related risk behaviors, coping skills/emotion regulation, stress appraisal, self-esteem, self-acceptance, social support, minority stress, resilience, hope, positive identity, and identity acceptance” but also noted that conclusions are limited by moderate-to-high risk of bias.

[69] Expósito-Campos et al. (2023).

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Hall et al. 2024[70]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Social transition
Outcomes	Mental health outcomes including depression, anxiety, substance use, and suicidality, gender identity outcomes (e.g., persistence of gender dysphoria/incongruence)
Included studies	11 studies including 8 cross-sectional studies, 1 reanalysis of previously published cross-sectional data, 1 prospective longitudinal study, and 1 retrospective cohort study
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in July 2023, and published in April 2024. Databases were searched comprehensively and search dates accurately reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	No prospective longitudinal studies with suitable comparator groups have evaluated the effects of social transition on mental health or gender-related outcomes in children and adolescents. Existing studies consistently found no significant differences in mental health outcomes among children who had socially transitioned. For adolescents, the findings were mixed.

[70] Hall et al. (2024).

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Heathcote et al. 2024[71]	
Study population description	Children and adolescents experiencing gender dysphoria or incongruence
Intervention	Psychosocial support
Outcomes	Mental health outcomes (including depression, anxiety, combined outcome measurement, emotional dysregulation, suicidality), psychological change (including relationship, resilience, self-compassion, self-care, coping, and problem solving, anger, life satisfaction), psychosocial change (including quality of life, well-being).
Included studies	10 studies including 4 cohort studies, 2 pre–post studies, 3 mixed methods, and 1 was a secondary analysis of intervention group data from four randomised controlled trials (these trials were not eligible).
Risk of bias assessment consideration	Study eligibility criteria: There is a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that the literature search was updated until April 2022, while the review was submitted for publication in September 2023, and published in April 2024. Databases searched comprehensively and search dates were reported. Though one overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool was Mixed Methods Appraisal Tool. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	Research on the outcomes of psychosocial interventions for children and adolescents with gender dysphoria or incongruence is limited. The risk of bias and poor reporting of the 10 included studies limited the conclusions about the effectiveness of psychosocial support.

[71] Heathcote et al. (2024).

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Karalexi et al. 2020[72]	
Study population description	Transgender young adults
Intervention	Hormone therapy
Outcomes	Cognitive outcomes including visuospatial ability, verbal memory, verbal reasoning, verbal working memory, computation, motor coordination.
Included studies	10 studies, including 6 cohort studies, 3 cross-sectional studies, and 1 with both longitudinal and cross-sectional analysis.
Risk of bias assessment consideration	Study eligibility criteria: The review included cohorts and cross-sectional studies. It is unclear whether a single group of participants with before-after study design but not labeled as "cohort" would be included or not. Identification and selection of studies: Literature search was conducted only in one database, MEDLINE. The search strategy included terms for "outcome", which may exclude records that are eligible but not indexed by reported outcomes. The number of records was low compared with other reviews. Data collection and study appraisal: Data collection seemed to be appropriate. Risk of bias was assessed using Newcastle-Ottawa Scale; However, the description of how the assessment was done suggested that the assessment may not be properly done. For example, all cohort studies were awarded with two stars in the ''Comparability'' section. Synthesis and findings: Meta-analysis was conducted where appropriate; but the review also conducted narrative synthesis elsewhere. Sources of heterogeneity was assessed using I^2 and this review briefly described the heterogeneity was not evident. No certainty of evidence assessed. Risk of bias in the review: No discussion or interpretation was included considering the risk of bias of included studies, and the limitation of the evidence.
Results	The review included meta-analyses on the cognitive functions, but did not formally assess the certainty of evidence. The systematic review did not identify evidence on adverse impact of hormone therapy on cognitive function.

[72] Karalexi et al. (2020).

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Ludvigsson et al. 2023[73]	
Study population description	Children with gender dysphoria
Intervention	Hormone therapy
Outcomes	Psychosocial and mental health outcomes (including gender dysphoria, depression, anxiety), cognitive outcomes, bone health outcomes, body composition and metabolic markers.
Included studies	24 studies, all observational studies, including 8 studies on GnRH alone, 13 studies on GnRH and CSH, and 3 studies on cross-sex hormone alone.
Risk of bias assessment consideration	Study eligibility criteria: This review followed PRISMA and internally register the protocol in the Swedish health technology assessment agency- However, the original protocol was not accessible. Identification and selection of studies: The literature search was comprehensive and reported in detail. However, the search may be outdated when the report was submitted for publication. Data collection and study appraisal: Two independent reviewers extracted data and conducted risk of bias assessment. Synthesis and findings: Narrative synthesis by outcome groups was justified given heterogeneity in studies. Robustness of results was considered through methodological description and bias discussion. Risk of bias in the review: The interpretation of review findings considered study quality and limitations of included studies. Conclusions aligned with evidence and noted significant research gaps. Though the GRADE assessment was labelled as "cannot be assessed", when four or more levels of downgrading happened. It should be very low.
Results	This systematic review did not identify any randomized control trails. The limited number of longitudinal observational studies were constrained by small sample sizes and high dropout rates. The evidence of long-term psychosocial effects of hormone therapy was limited. Treatment with GnRHas was found to delay bone maturation and the accrual of bone mineral density; however, partial recovery was observed during cross-sex hormone therapy when assessed at age 22.

[73] Ludvigsson et al. (2023).

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Malpas et al. 2022[74]	
Study population description	Transgender and gender expansive youth
Intervention	Family-based interventions: (1) providing psychoeducation, (2) allowing space for families to express reactions to their child's gender, (3) emphasizing the protective power of family acceptance, (4) utilizing multiple modalities of support, (5) giving families opportunities for allyship and advocacy, (6)connecting families to transgender and gender expansive youth community resources, and (7) centering intersectional approaches and concerns.
Risk of bias assessment consideration	Study eligibility criteria: There was no registration or protocol. This review included three review processes, and the inclusion criteria were vague. For example, for Review 1, the inclusion criteria were: "(1) the article was published in English, and (2) the article provided treatment strategies, best practices, clinical recommendations, or outcome data related to family therapy or interventions to increase family engagement with transgender and gender expansive (TGE) youth." Identification and selection of studies: This review included three stages of search. Review 1 was the part that best met the scope of this overview. However, the number of results was low compared with other reviews. Separating Review 1 and Review 2 may have introduced bias in the review process. Though the search was updated until 2018, while the review was published in 2022. Data collection and study appraisal: No details were reported other than only "Relevant information was then coded ...". There was very brief information for included studies. No formal risk of bias assessment was applied. Synthesis and findings: The review did not identify quantitative outcome information; thus, this review narratively describe the qualitative results. The themes identified through this review included "(1) the change of clinical stance on families of youth with gender dysphoria over time, (2) the theoretical models often cited and used, (3) the most frequently recommended best clinical practices when working with youth with gender dysphoria and their families, and (4) the commonalities of these best practices with outcome data on family therapy with lesbian, gay, and bisexual youth." The review results and analyses deviated from the purpose of summarizing the evidence on family-based intervention. Risk of bias in the review: The concerns identified were not addressed in the interpretation of evidence.
Outcomes	No quantitative outcome for effectiveness. This systematic review identified four themes related to family-based intervention.
Included studies	32 studies on clinical practice recommendations for family-based interventions for transgender and gender expansive youth.
Results	This systematic review found that clinical strategies have moved from pathologizing to affirming of transgender and gender expansive youths' gender journey.

[74] Malpas et al. (2022).

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Miroshnychenko et al. 2024[75]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	Mastectomy
Outcomes	Mental health measures (including distress, suicide), gender dysphoria, body satisfaction, and surgical complications (including death, necrosis, and scarring).
Included studies	39 studies, including 3 comparative observational studies, 2 before–after, and 34 case series.
Risk of bias assessment consideration	Study eligibility criteria: The protocol was registered, and the eligibility criteria were clear. Identification and selection of studies: The literature search covered multiple databases with support from an information specialist. The authors described their duplicate screening and consensus processes. Data collection and study appraisal: Standardized data extraction form and duplicate extraction efforts were used; and a third reviewer was available for consensus. The risk of bias tool was appropriate for the review purpose. Synthesis and findings: Meta-analyses were conducted. When meta-analyses were not feasible, narrative syntheses were conducted. Certainty of evidence was rated using GRADE and considered the heterogeneity and risk of bias in included studies. Risk of bias in the review: The interpretation of evidence was appropriately cautious given very low to low certainty of much of the evidence.
Results	The authors found low certainty evidence on non-suicidal self-injuries, and very low certainty evidence regarding gender dysphoria and other psychological outcomes such as global functioning and suicide attempt. The review also identified high certainty evidence for outcomes of death, necrosis, and excessive scarring after surgery. The numbers of events after mastectomy were estimated to be 0, 10 to 30, and 50 per 1,000 persons for death, necrosis, and excessive scarring, respectively.

[75] Miroshnychenko et al. (2024).

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Miroshnychenko et al. 2025a[76]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	PBs
Outcomes	Gender dysphoria, global function, depression, bone mineral density, progression to CSH.
Included studies	10 studies, 3 comparative observational studies, and 7 before–after design studies.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[77]
Results	The systematic review identified very low certainty of evidence on the outcomes of gender dysphoria, global function, depression, and bone mineral density. There remains considerable uncertainty regarding the effects of PBs in individuals experiencing gender dysphoria.

[76] Miroshnychenko, Roldan, et al. (2025).
[77] Miroshnychenko et al. (2024).

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Miroshnychenko et al. 2025b[78]	
Study population description	Individuals aged <26 years experiencing gender dysphoria
Intervention	CSH
Outcomes	Gender dysphoria, global function, depression, death by suicide, bone mineral density, sexual dysfunction, cardiovascular events.
Included studies	24 studies, including 9 comparative observational studies, 13 before–after studies, and 2 case series.
Risk of bias assessment consideration	Same as Miroshnychenko 2024[79]
Results	This systematic review found very low to low certainty evidence about depression, very low certainty evidence on gender dysphoria, global function, and bone mineral density. The systematic review found moderate to high certainty evidence on the incidence of cardiovascular events after receiving CSH.

[78] Miroshnychenko, Ibrahim, et al. (2025).
[79] Miroshnychenko et al. (2024).

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Ramos et al. 2021[80]	
Study population description	Adolescents with gender incongruity
Intervention	PBs
Outcomes	Gender dysphoria, bone mineral density, side effects.
Included studies	11 studies including 9 observational studies and 2 qualitative studies.
Risk of bias assessment consideration	Study eligibility criteria: The authors used study design as a reason for exclusion (e.g. literature reviews, systematic reviews, reports and case series, guidelines, summaries and comments). "Theme" was described as an exclusion reason at full-text screening, but the associated eligibility criterion was not clear. Identification and selection of studies: Search terms, filters, and strategies were reported. However, search strategy included restrictive terms including "NOT" operators that could be related to outcomes of interest (e.g. depressive disorder), which was probably not appropriate as psychosocial functioning is one of the outcomes summarized. The literature search only identified 108 records, which was low compared to other included reviews. Data collection and study appraisal: The study characteristics were not systematically reported. The authors noted using "Cochrane risk of bias assessment for observational and intervention studies", assessing, "bias of selection, performance, selective reporting, detection, attrition, and other (e.g., inadequate control for key confounders)...", and provided an alphanumeric rating at the study level in Table 1 (e.g. 2B, 2C, 4). There was no legend provided for the meaning of these ratings. It was not clear whether the Cochrane risk of bias tool is referring to ROBINS-I, which does not have these rating categories. At least one of the studies included is a qualitative study, and it was not clear how the risk of bias tool for observational and intervention studies would apply to the qualitative study. There was no mention of whether the assessment was conducted independently, in duplicate. Synthesis and findings: The authors included a narrative synthesis at the study-level highlighting results or conclusions from individual studies. The synthesis was not organized by outcome, and there was high risk of bias for selectively including study results in the narrative synthesis. The authors did not address heterogeneity in the synthesis, rather in the limitations it was noted, "Studies found are heterogeneous (different definitions, population and evaluation techniques) and sometimes based on small sample size, restricting statistical power." Risk of bias in the review: The concerns identified were not addressed.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results by individual studies. There was no certainty of evidence assessment, but according to the review authors, the use of GnRHa seems to be well tolerated by the studied population, prevent the irreversible phenotypic changes, and “contribute to the mental health.”

[80] Ramos et al. (2021).

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Rew et al. 2021[81]	
Study population description	Transgender and gender diverse youth
Intervention	PBs
Outcomes	Anthropomorphic measurements, sexual characteristics, mental health functioning, depression, emotional and behaviour problems, suicide, and side effects.
Included studies	9 studies including 6 observational studies, 1 cross-sectional study, and 2 case reports.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criterion for outcomes was vague by being specified as studies needing to "identify risks and/or benefits associated with the use of these medications." Identification and selection of studies: The literature search only identified 151 records after de-duplication, which was low compared to other included reviews. The study selection approach was not described. Screening involved multiple reviewers but there was no detailed reporting of calibration or adjudication. Data collection and study appraisal: A data extraction form was developed, but approach to data extraction was not described. Synthesis and findings: Narrative synthesis was justified due to design heterogeneity. Some of the included studies reported the same outcomes (e.g., body composition), but the synthesis (Table 2) was presented at the study-level instead of at the outcome-level, and the summary in the main text was collated under 'risks/adverse outcomes' and 'positive outcomes'. Risk of bias in the review: The interpretation of findings did not address the concerns identified in the process. While the risk of bias was described for the studies, it was not described in relation to the outcomes and findings.
Results	This systematic review did not conduct evidence synthesis by outcome, rather narratively described results. This systematic review listed studies reporting positive outcomes and adverse effects. For example, “positive outcomes were decreased suicidality in adulthood, improved affect and psychological functioning, and improved social life. Adverse factors associated with use were changes in body composition, slow growth, decreased height velocity, decreased bone turnover, cost of drugs, and lack of insurance coverage.” There was no certainty of evidence assessment, and the interpretation did not take into consideration of the strengths and limitations of the evidence.

[81] Rew et al. (2021).

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Taylor et al. 2024a[82]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	PBs
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including puberty progression, hormone levels, menstrual suppression, height/growth, body composition, bone geometry, etc.).
Included studies	50 studies, including 11 cohorts, 8 cross-sectional and 31 before-after studies. The descriptive evidence synthesis included 1 high quality cross-sectional study, and 25 moderate observational studies.
Risk of bias assessment consideration	Study eligibility criteria: There was a registered review protocol for the review titled "The epidemiology, management and outcomes of children with gender-related distress/gender dysphoria: a systematic review", including puberty blockers. The eligibility criteria described in the report were clear. Identification and selection of studies: The major issue was that literature search was updated until April 2022, while the review was submitted for publication in November 2023, and published in April 2024. Databases searched comprehensively and search dates reported. One overarching search was conducted for all relevant efforts (including the other reviews e.g., on cross-sex hormones, psychotherapy, social transition). Data collection and study appraisal: There were duplicate efforts for data collection and study appraisal. The risk of bias tool (adapted version of Newcastle-Ottawa Scale) was acceptable. Synthesis and findings: There was no meta-analysis. Narrative synthesis by outcomes was conducted. Variation in design and measures described qualitatively; Limitations of studies and evidence quality were discussed, though no GRADE certainty of evidence was conducted. This review accounted for biases from primary studies by synthesizing only moderate or high-quality studies. Risk of bias in the review: The authors interpreted findings cautiously, highlighting limited strength of evidence. The review also discussed the studies that published after the literature search date. The conclusions were consistent with limitations.
Results	This systematic review did not identify high-quality studies with appropriate designs (only 1 “high-quality” cross-sectional study). Of the 11 cohort studies, only five were rated as moderate in quality. The evidence on the effects of PBs in adolescents with gender dysphoria or incongruence regarding its impact on gender dysphoria, mental or psychosocial health, or cognitive development was limited. Evidence also suggests that bone health and height may be adversely affected during treatment. Recently published studies which were not included in this systematic review align with the findings of this systematic review.

[82] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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Taylor et al. 2024b[83]	
Study population description	Adolescents with gender dysphoria or gender incongruence
Intervention	CSH
Outcomes	Gender dysphoria and body satisfaction, psychological health (including depression, anxiety, anger, etc.), psychosocial outcomes (including quality of life, peer-relation, etc.), cognitive/neurodevelopmental outcomes, physical health outcomes (including bone health, cardiovascular health, and physiological parameters), side effects, and puberty suppression (including induced puberty progression, hormone levels, menstrual suppression, height/growth, body composition/shape, bone geometry, etc.), and fertility.
Included studies	53 studies including 12 cohort, 9 cross-sectional, 32 pre–post studies. This systematic review included 1 high quality cohort study.
Risk of bias assessment consideration	Same as Taylor 2024a.[84]
Results	High-quality research on the outcomes of hormone interventions in adolescents with gender dysphoria or incongruence is lacking, and few studies include long-term follow-up. There is uncertainty regarding their effects on gender-related outcomes, body satisfaction, psychosocial health, cognitive development, or fertility, and the impacts on height, growth, cardiometabolic health, and bone health. The review authors identified "moderate quality" studies[85] mental health may be improved during treatment.

[83] Taylor, Mitchell, Hall, Langton, et al. (2024).
[84] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[85] This review had identified "moderate quality" observational studies. Including "moderate-quality observational studies" is not equivalent to "moderate quality (certainty) evidence." According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).

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Thompson et al. 2023[86]	
Study population description	Adolescents with gender dysphoria
Intervention	Psychosocial only PBs CSH Surgeries
Outcomes	Psychosocial only: mental health. PBs: blood pressure, biochemistry and hematological measurements, anthropometric, bone density and physical changes, mental health. CSH: biochemical and hematological, anthropometric, bone density and physical changes, and mental health. Surgeries: mental health.
Included studies	19 studies, including 13 retrospective studies and no randomized controlled trial.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: There was no literature search for unpublished literature. Reference list of included studies was checked. But the inclusion criteria also excluded the possibility of searching grey literature. Data collection and study appraisal: Data were comprehensive and tabulated; overlapping samples were identified. All outcome domains from included studies were described, but synthesis was limited to narrative integration. Risk of bias was assessed using Crowe Critical Appraisal Tool, this tool may lack specificity. For example, with this tool, many papers scored lower on was the issue of consent— but many studies were retrospective in nature and the consent process was waived. Synthesis and findings: Narrative synthesis was used by outcomes. However, the syntheses for outcomes were conducted combining both puberty blockers and cross-sex hormones, which may not be appropriate. Heterogeneity was discussed narratively but no subgroup or sensitivity analysis was performed. This review described risk of bias, however, did not account for the limitations of studies in the synthesis. Risk of bias in the review: The interpretation of evidence did not address the concerns identified.
Results	No certainty of evidence assessment was conducted. Most changes to health parameters were inconclusive, “except an observed decrease in bone density z-scores with PBs.” “Some improvements were observed in global functioning and depressive symptoms once treatment was started.”

[86] Thompson et al. (2023).

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Zepf et al. 2024[87]	
Study population description	Children/adolescents with gender dysphoria
Intervention	PBs CSH
Outcomes	PBs: gender dysphoria, mental health, quality of life, body image, psychosocial effects, health care utilization, satisfaction with surgery following PBs, and treatment discontinuation. Cross-sex hormone: body image, psychosocial outcomes, treatment discontinuation, and bone metabolism.
Included studies	This systematic review was an update on the systematic review efforts by NICE (National Institute for Health and Care Excellence) – which aimed to "inform Dr Hilary Cass' independent review into gender identity services for children and young people." This updated further included two observational studies on CSH.
Risk of bias assessment consideration	Study eligibility criteria: The eligibility criteria were clear. Identification and selection of studies: Five databases were searched; strategy was comprehensive. Screening process was not fully described. Data collection and study appraisal: It is unclear if a structured risk of bias tool was applied. Synthesis and findings: The authors synthesize the results from all studies. They do not describe methods for data analysis. The studies seemed heterogeneous enough that summarizing them narratively is appropriate. Limitations were discussed in detail, including inconsistency and weak study designs. Risk of bias in the review: The authors considered the limitations of the evidence when interpreting the results.
Results	This systematic review concluded that the evidence on the effectiveness of PBs and/or CSH in children and adolescents with gender dysphoria remains inadequate.

[87] Zepf et al. (2024).

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5 Evidence synthesis: Puberty Blockers

This overview identified nine SRs on the treatment effects of PBs. Across all primary studies included in these SRs, there were no eligible randomized controlled trials. These SRs frequently used the labels based on study design, such as “cohort,” to describe the study design for included studies. However, these labels may be confusing due to the variations in study design with the same label. To address this concern, the researchers from McMaster University used labels such as “comparative observational studies” and “before-after study.” This overview found that across all primary studies in the nine SRs on PBs, only six were observational studies with parallel control groups comparing PBs with no PBs among children or adolescents with GD.[88] The sample sizes in these studies were small: three studies included fewer than 100 participants, ranging from 60 to 438 across these six comparative observational studies. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of PBs.

5.1 Included SRs on PBs

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria

[88] Becker-Hebly et al. (2021); Costa et al. (2015); Grimstad et al. (2021); Jensen et al. (2019); McGregor et al. (2024); Tordoff et al. (2022).

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and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025a

Miroshnychenko, A., Roldan, Y., Ibrahim, S., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Puberty blockers for gender dysphoria in youth: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327909

Ramos 2021

Ramos, G. G. F., Mengai, A. C. S., Daltro, C. A. T., Cutrim, P. T., Zlotnik, E., & Beck, A. P. A. (2021). Systematic review: Puberty suppression with gnrh analogues in adolescents with gender incongruity. *Journal of endocrinological investigation*, *44*(6), 1151-1158.

Rew 2021

Rew, L., Young, C. C., Monge, M., & Bogucka, R. (2021). Review: Puberty blockers for transgender and gender diverse youth-a critical review of the literature. *Child and adolescent mental health*, *26*(1), 3-14.

Taylor 2024a

Taylor, J., Mitchell, A., Hall, R., Heathcote, C., Langton, T., Fraser, L., . . . Hewitt, C. E. (2024). Interventions to suppress puberty in adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s33-s47.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

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Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

5.2 Low risk of bias SRs

Four English language SRs were classified at low risk of bias.[89] Only SRs with low risk of bias were summarized to assess outcomes.

Of the four low risk of bias SRs, the eligibility criteria and number of included studies varied. Notably, the systematic review by Taylor and colleagues[90] included most studies: 50 studies including 11 cohorts, 8 cross-sectional, and 31 before-after studies. This SR synthesized only study results from high or moderate quality studies. Dopp 2024[91] included 49 studies including 25 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 7 cohort studies, 8 case reports, and 1 qualitative study (case reports and qualitative studies are inadequate to provide quantitative information on treatment effects). In contrast, Ludvigsson 2023[92] included 21 studies, and Miroshnychenko 2025a[93] included 10 studies (including 3 comparative observational studies and 7 before–after design).

[89] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[90] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[91] Dopp et al. (2024).
[92] Ludvigsson et al. (2023).
[93] Miroshnychenko, Roldan, et al. (2025).

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Only seven studies were included in all four low risk of bias SRs, including two comparative cohorts (one in Germany,[94] one in the UK[95]), as well as the five before-after studies reported in Canada,[96] Netherlands,[97] and UK.[98])

5.3 Outcome 1. Gender dysphoria

A total of four low risk of bias SRs assessed the impact of PBs on GD.[99] Dopp 2024[100] included the most studies, though these included case reports and a qualitative study, which have limited value in estimating treatment effects. This systematic review narratively described that PBs lead to improved GD, without details on its methods for evidence synthesis. In contrast, the other three SRs reported no change in GD associated with PBs.

The interpretation of these results requires caution regarding the certainty of evidence. All three SRs using the GRADE methodology to assess certainty of evidence concluded the certainty of evidence was very low.[101] Taylor 2024a did not formally assess the certainty of evidence but found that "no high-quality studies using an appropriate design were identified, … no conclusions can be drawn," [102] which is equivalent to very low certainty evidence.

In summary, this overview concludes that the certainty of evidence is very low, and no conclusion could be drawn on the impact of PBs on GD.

5.4 Outcome 2. Mental health and wellbeing

A total of four SRs assessed the impact of PBs on mental health, using varying measures of mental health such as global function, suicidality, depression, anxiety, and

[94] Becker-Hebly et al. (2021).
[95] Costa et al. (2015).
[96] Navabi et al. (2021).
[97] Klink et al. (2015); Schagen et al. (2016).
[98] Carmichael et al. (2021); Joseph et al. (2019).
[99] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[100] Dopp et al. (2024).
[101] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025).
[102] Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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quality of life.[103] Similar to the reviews on the GD outcome, Dopp 2024[104] included more studies than the three other SRs because it included case reports and a qualitative study. It narratively described that PBs lead to improved mental health, though the certainty of evidence was assessed as very low. The remaining three SRs reported either no change or small changes in mental health associated with PBs. The certainty of evidence was very low or "uncertain."

In summary, this overview concludes that no conclusion could be drawn on the impact of PBs on mental health due to very low certainty evidence.

5.5 Outcome 3. Pubertal development

Two SRs assessed the impact of PBs on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[105] SRs showed that the use of PBs is consistently associated with reductions in pubertal development. This overview assessed the certainty of evidence as high due to the observed very large effects.[106]

In summary, this overview finds high certainty evidence showing PBs lead to expected physiological effects on pubertal development.

5.6 Outcome 4. Need for or progression to further treatment

Only one systematic review assessed the impact of PBs on proceeding with CSH. Miroshnychenko and colleagues[107] included 2 case series and estimated that 92% of children or adolescents with GD proceeded with CSH, suggesting a high proportion of adolescents receiving PBs proceed to CSH. However, due to concerns related to risk of bias, the certainty of evidence regarding the causal role that PBs play in this progression is very low.

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[103] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[104] Dopp et al. (2024).
[105] Dopp et al. (2024); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[106] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to the very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011).
[107] Miroshnychenko, Roldan, et al. (2025).

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5.7 Outcome 5. Safety

A total of four low risk of bias SRs reported the safety outcomes for PBs in children or adolescents with GD.[108] Outcomes included overall risk of adverse events, bone health, fertility, anthropometric measures, body composition, growth, and other measures. Dopp 2024[109] included the largest number of eligible studies. The SRs reported side effects including mild headaches or hot flushes, moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems. The certainty of evidence on the overall risk of adverse events was very low.

The SRs found no evidence on the long-term safety of PBs.

All four SRs assessed bone health, and the evidence was based primarily on before-after studies. The most frequently reported outcome for bone health was bone mineral density decreases relative to reference values (z score). All SRs reported that bone density is compromised during puberty blocker treatment. Specifically, Miroshnycheko and colleagues[110] reported decreases in bone mineral density for hip, lumbar spine, and femoral neck. There was disagreement across SRs on certainty of evidence assessment, which was low according to Ludvigsson 2023[111] (due to risk of bias and imprecision concerns) but very low according to Dopp 2024[112] and Miroshnycheko 2025a.[113] Taylor 2024a[114] did not formally assess the certainty of evidence but concluded that multiple studies found that bone density is compromised. This overview of SRs assessed the certainty of evidence on bone health as low. This was due to the risk of bias in evidence based on observational studies.[115] In summary, this overview concludes there is low certainty evidence that PBs lead to compromised bone density.

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[108] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Roldan, et al. (2025); Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[109] Dopp et al. (2024).
[110] Miroshnychenko, Roldan, et al. (2025).
[111] Ludvigsson et al. (2023).
[112] Dopp et al. (2024).
[113] Miroshnychenko, Roldan, et al. (2025).
[114] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[115] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty, due to risk of bias concerns arising from unbalanced prognostic factors and uncontrolled confounding (lack of randomization). There is no further downgrade of evidence by this overview. The certainty of evidence is low.

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Only one systematic review reported on fertility outcomes. Based on two case reports of fertility preservation, Dopp et al[116] concluded that there was very low certainty evidence on the risk of infertility after PBs. This overview has not identified empirical evidence on fertility outcomes from included SRs. However, based on high certainty evidence in this overview on PBs' effects on pubertal development and the consideration of fertility preservation in clinical practice, adolescents receiving PBs who then proceed with CSH probably experience infertility, though the impact may depend on natal sex and stage of pubertal development when starting PBs.

Two SRs[117] reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low, or uncertain. This overview concludes that the certainty of evidence for these outcomes is very low.

5.8 Outcome 6. Regret

Only one SR assessed regret after PBs and reported high satisfaction ratings and low rates of regret. The certainty of evidence was very low, and no conclusions can be reached on the regret rate after PBs.

5.9 Evidence gap

Important gaps remain in both the range and quality of outcomes assessed across the existing literature. Many primary studies were not designed to adequately measure or report on outcomes related to puberty blocker use. For example, only a small number of primary studies included in the SRs assessed the impact of PBs on outcomes such as GD or mental health. Although PBs are frequently described as a "pause button," no studies have systematically examined their role in the decision-making process or the outcomes of those who discontinue treatment.

When outcomes were assessed, the primary focus was on short term psychological or physiological changes, or surrogate outcomes—such as suicidal ideation or bone mineral density—rather than clinically important endpoints like suicide or fractures.

[116] Dopp et al. (2024).
[117] Ludvigsson et al. (2023); Taylor, Mitchell, Hall, Heathcote, et al. (2024).

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There is particularly limited evidence on long-term outcomes related to fertility, growth, and cognitive development.

While studies suggest that a high proportion of youth proceed to cross-sex hormones after puberty suppression,[118] there is minimal evidence on the impact of this combined pathway compared to CSH alone, on long-term outcomes such as surgical outcomes, or on the need for future surgery. Furthermore, no studies have clearly examined the physical or psychosocial trajectories of those who stop PBs without transitioning to CSH. As a result, there is little data on what happens after treatment ends, and the assumption of reversibility of all puberty blocker effects remains largely untested. A further important limitation is that most primary studies did not consider the effects of PBs on males versus females. Overall, the absence of long-term, high-certainty evidence on these critical outcomes (including suicide, fractures, fertility, growth, and cognitive development) leaves substantial uncertainty about the effects of PBs.

5.10 Summary

In summary, this overview identified nine SRs addressing the effects of PBs on GD, mental health, safety, pubertal development, and further treatment decisions. There is high certainty evidence that PBs exert physiological effects such as puberty suppression, and that they probably lead to infertility when adolescents receiving PBs go on to receive CSH. PBs may compromise bone health. A high proportion of youth proceed to CSH from PBs. The evidence is very uncertain regarding the effect on GD, improvement in mental health, and safety.

[118] Miroshnychenko, Roldan, et al. (2025).

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5.11 Evidence mapping: SRs on PBs

Table 5.1. Evidence mapping of the SRs on PBs and the primary studies that these SRs included

	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Achille 2020		Y		Y			Y		
Akgul 2019		Y					Y		
Arcelus 2016							Y		
Arnoldussen 2022		Y							
Barnard 2019		Y							
Becker-Hebly 2021		Y	Y	Y			Y	Y	
Brik 2020		Y							Y
Burke 2020	Y						Y		
Caanen 2017		Y							
Cantu 2020			Y						
Carmichael 2021		Y[128]	Y	Y			Y		
Chen 2016								Y	
Chiniara 2018							Y		

[119] Chew et al. (2018).
[120] Dopp et al. (2024).
[121] Ludvigsson et al. (2023).
[122] Miroshnychenko, Roldan, et al. (2025).
[123] Ramos et al. (2021).
[124] Rew et al. (2021).
[125] Taylor, Mitchell, Hall, Heathcote, et al. (2024).
[126] Thompson et al. (2023).
[127] Zepf et al. (2024).
[128] Another citation, McPherson 2023 was provided for this study. This report was a re-analysis of the data collected by the previous report. However, this citation was not included by any other SRs on PBs or CSH.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Cohen-Kettenis 2011[129]		Y				Y			
Costa 2015	Y	Y	Y	Y	Y		Y	Y	Y
de Nie 2022							Y		
de Vries 2014	Y		Y		Y		Y		
de Vries 2011	Y	Y		Y	Y	Y	Y	Y	Y
Delemarre-van de Waal 2006	Y	Y					Y		
Donaldson 2018		Y							
Ewan 2014		Y							
Fontanari 2020							Y		
Ghelani 2020							Y		
Giovanardi 2019					Y				
Grannis 2021, Grannis 2023, and Olsavsky 2023		Y[130]							
Grimstad 2021a							Y		
Hisle-Gorman 2021		Y	Y				Y		
Jensen 2019								Y	
Joseph 2019		Y	Y	Y			Y	Y	Y
Karakılıç Özturan 2023				Y					
Khatchadourian 2014		Y			Y	Y	Y		Y
Klaver 2020		Y	Y				Y	Y	
Klaver 2018			Y		Y	Y	Y	Y	

[129] Another citation (Cohen-Kettenis, 1998) was provided for this study. However, this citation was not included by any other SRs on PBs or CSH, although it was included by Dopp et al. (2024) for CSH and surgeries.
[130] Dopp et al. (2024) included three citations for one study.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Klink 2015	Y	Y	Y	Y	Y		Y		Y
Klink 2013					Y				
Kuper 2020		Y					Y	Y	
Lavender 2023		Y							
Lee 2020			Y					Y	
Lee 2024		Y							
Littman 2021		Y							
Lopez 2018					Y			Y	
López de Lara 2020		Y							
Lynch 2015							Y		
Martin 2021		Y							
McGregor 2024		Y							
Mejia-Otero 2021							Y		
Moussaoui 2023		Y							
Nahata 2017						Y		Y	
Navabi 2021		Y	Y	Y			Y		
Neyman 2019		Y					Y		
Nokoff 2021			Y				Y		
Olson 2022		Y							
Olson-Kennedy 2021							Y		
Pang 2020		Y							

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
Perl 2021[131]		Y					Y		
Perl 2020[132]		Y	Y				Y	Y	
Pine-Twaddell 2023							Y		
Ristori 2019		Y							
Russell 2021							Y	Y	
Schagen 2016	Y	Y	Y		Y	Y	Y		Y
Schagen 2018							Y		
Schagen 2020		Y	Y	Y			Y	Y	
Schneider 2017		Y				Y			
Schulmeister 2022			Y				Y		
Schwartz 2023		Y							
Segev-Becker 2020							Y		
Staphorsius 2015	Y		Y				Y		Y
Stoffers 2019			Y				Y	Y	
Strang 2022							Y		
Tack 2016		Y					Y	Y	
Tack 2018		Y					Y	Y	
Tack 2017		Y					Y	Y	
Tordoff 2022		Y					Y		
Turban 2020		Y				Y	Y		

[131] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024a included the two citations as two moderate quality before-after studies.
[132] See above note.

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	Chew 2018[119]	Dopp 2024[120]	Ludvigsson 2023[121]	Miroshnychenko 2025a[122]	Ramos 2021[123]	Rew 2021[124]	Taylor 2024a[125]	Thompson 2023[126]	Zepf 2024[127]
van de Grift 2020		Y					Y		
van der Loos 2022		Y							
van der Loos 2023		Y							
van der Loos 2021			Y				Y		
van der Miesen 2020		Y					Y		
Vlot 2017	Y	Y	Y		Y	Y	Y		Y
Vrouenraets 2016		Y			Y				
Waldner 2023							Y		

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5.12 Evidence tables on outcomes for PBs in youth with gender dysphoria

Table 5.2. Summary of evidence on gender dysphoria after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[133]	11 studies	-[134]	PBs lead to improved gender dysphoria. However, reductions in gender dysphoria were measured less consistently than pubertal changes, and almost never in the same study as pubertal changes	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Ludvigsson 2023[135]	2 prospective observational cohort studies	145 participants on hormones, 49 were evaluated	Two of these studies observed no statistically significant change in gender dysphoria	Very low certainty due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[136]	2 before-after studies	59 participants	Standardised mean change: -0.1 (95% confidence interval: -0.4 to 0.19) (higher score indicating greater gender dysphoria)	Very low certainty due to serious inconsistency and very serious imprecision
Taylor 2024a[137]	2 before-after studies[138]	114 participants were treated	Two before-after studies measured gender dysphoria and reported no change before and after receiving treatment	No high-quality studies using an appropriate design were identified, and only four measured gender dysphoria as an outcome. No conclusions can be drawn
Evidence synthesis			No conclusion can be drawn on the impact of PBs on gender dysphoria.	The certainty of evidence is very low.

[133] Dopp et al. (2024).
[134] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[135] Ludvigsson et al. (2023).
[136] Miroshnychenko, Roldan, et al. (2025).
[137] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review only synthesized excluded low quality.
[138] Though four studies reported gender dysphoria, only two moderate quality before-after studies were included in evidence synthesis.

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Table 5.3. Summary of evidence on mental health and well-being after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[139]	21 studies	-[140]	Receipt of PBs was sometimes associated with improvements in mental health symptoms (depression, anxiety, quality of life, general functioning). In samples that started psychosocial supports prior to starting PBs, however, there were generally no changes in mental health outcomes after PBs began. Effects were also found less consistently for decreases in suicidality, potentially due to the outcome being relatively rare (which makes finding effects more difficult), especially in the younger age range seen in many of these studies.	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Ludvigsson 2023[141]	4 observational cohort studies: 1 prospective and 3 retrospective	254 participants on hormones,[142] 113 were evaluated	Improved global function as assessed with the Children's Global Assessment Scale	Very low certainty[143] due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[144]	2 comparative observational studies, and 2 before-after studies	103 participants from 2 comparative observational studies, and 53 participants from 2 before-after studies	Difference in mean change from baseline 7.67 (95% confidence interval: -2 to 17.34) in PBs group compared with no PBs group from comparative observational studies; and Mean change 3.63 (95% confidence interval: 3.17 to 4.09) from before-after studies (higher score indicating greater global function)	Very low certainty due to serious risk of bias, inconsistency and imprecision

[139] Dopp et al. (2024).
[140] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020). One study included by this review, Grannis 2023, was about CSH not PBs.
[141] Ludvigsson et al. (2023).
[142] In two studies, the participants had also received CSH.
[143] Ludvigsson et al. concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[144] Miroshnychenko, Roldan, et al. (2025).

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Taylor 2024a[145]	1 cohort and 2 before-after studies	174 participants were treated	Three before-after studies reported no clinically significant change	No conclusions can be drawn.
Suicidality				
Ludvigsson 2023[146]	1 prospective observational cohort study with mixed treatment (38 subjects with no pharmacological treatment)	42 participants on hormones, 28 were evaluated	No change in suicide ideation	Very low certainty[147] due to very serious risk of bias and very serious imprecision
Taylor 2024a[148]	1 cross-sectional study and 1 before-after study	222 participants were treated	The cross-sectional study reported less self-harm/ suicidality in those treated, although similar to group with no gender dysphoria. The before-after study did not report change over time.	No conclusions can be drawn.
Depression				
Ludvigsson 2023[149]	2 prospective observational cohort studies of which one included mixed treatment	97 participants on hormones, 60 were evaluated	No change in depression	Very low certainty[150] due to very serious risk of bias and very serious imprecision
Miroshnychenko 2025a[151]	1 comparative observational study, and 1 before-after study	26 participants from 1 comparative observational study, and 41 participants from 2 before-after study	The comparative observational study with 26 participants (88% using PBs) reported that PBs did not result in a statistically significant decrease in scores in female to male participants; but resulted in a statistically significant decrease in score in male to female	Very low certainty due to very serious risk of bias, and serious imprecision

[145] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[146] Ludvigsson et al. (2023).
[147] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[148] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[149] Ludvigsson et al. (2023).
[150] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[151] Miroshnychenko, Roldan, et al. (2025).

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			participants; and Mean change -3.36 (95% confidence interval: -3.69 to -3.03) from 1 before-after study (higher score indicating greater depression)	
Taylor 2024a[152]	1 before-after study	70 participants were treated	Reduction in depressive symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Anxiety				
Ludvigsson 2023[153]	2 prospective observational cohort studies	97 participants on hormones, 60 were evaluated	No change in anxiety	Very low certainty[154] due to very serious risk of bias and very serious imprecision
Taylor 2024a[155]	1 before-after study	70 participants were treated	No change in anxiety symptom	A single study, reporting small to moderate improvement. No conclusion can be drawn.
Quality of life				
Ludvigsson 2023[156]	2 prospective observational cohort studies, including one retrospective	98 participants on hormones, 46 were evaluated	One study reported improvement in quality of life most pronounced in subjects receiving puberty-blocking hormones, followed by CSH treatment. A second study reported some improvement in quality of life.	Very low certainty[157] due to very serious risk of bias and very serious imprecision.
Taylor 2024a[158]	1 before-after study	44 participants were treated	No change in quality of life	A single study, reporting no improvement. No conclusion can be drawn.

[152] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[153] Ludvigsson et al. (2023).
[154] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[155] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[156] Ludvigsson et al. (2023).
[157] Ludvigsson et al concluded the review "cannot assess certainty of evidence," while according to the downgrading process in the review, the certainty of evidence was very low.
[158] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Internalising problems				
Taylor 2024a[159]	1 cross-sectional study, and 2 before-after studies	292 participants were treated	No change to small decrease in internalising problems	No high certainty evidence was identified. No conclusion can be drawn.
Externalising problems				
Taylor 2024a[160]	1 cross-sectional study, and 2 before-after studies	292 participants were treated	No change to small decrease in externalising problems	No conclusion can be drawn.
Psychological functioning/psychopathology				
Taylor 2024a[161]	2 before-after studies	114 participants were treated	Two before-after studies reported no change to a small change	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of mental health outcomes by PBs.	The certainty of evidence is very low.

[159] See above note,
[160] See above note.
[161] See above note.

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Table 5.4. Summary of evidence on pubertal development after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Pubertal progression				
Dopp 2024[162]	20 studies	-[163]	Receipt of PBs was consistently associated with reductions in pubertal changes (which were targeted for suppression due to being inconsistent with the youth's gender identity), compared to expected pubertal progress and/or developmental control participants. Various physical and hormonal changes were documented over time, including reductions in endogenous sex-linked hormones, decreased progression (and sometimes regression) of physical sex characteristic development, changes in body hair, changes in height/growth and body fat composition congruent with youths' gender identities, grip strength, vocal register, and cessation of menstruation (both from menstrual suppression treatments and other forms of PBs).	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024a[164]	4 studies including 2 cohort studies and 2 before-after studies	385 participants	In one cohort study, clinical pubertal escape was reported in 2/21 participants. Another cohort study reported that Tanner stage 2/3 treatment resulted in smaller breast size in birth registered females and lower average penile length and fewer testes descended in birth registered males, compared with Tanner stage 4/5 or no GnRH-a.	Four studies showed that PBs exert its expected physiological effects
Hormone level				
Taylor 2024a[165]	9 studies including two cohort studies and seven before-after studies	606 participants were treated	Studies reported decreases in luteinising hormone, follicle-stimulating hormone, oestradiol and testosterone after receiving GnRH-a	Multiple mainly before-after studies showed that PBs exerts its expected physiological effects

[162] Dopp et al. (2024).
[163] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Pang et al. 2020), qualitative studies (e.g., Vrouenraets et al. 2022). One study included by this review, Grannis 2023, was about CSH not PBs.
[164] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[165] See note above.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Menstrual suppression				
Taylor 2024a[166]	3 studies including 1 cohort study and 2 before-after studies	202 participants	All studies reported menstrual suppression	Three studies showed that exert its expected physiological effects
Evidence synthesis			PBs lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of PBs).[167]

[166] See note above.

[167] According to GRADE, the evaluation of certainty of evidence based on observational studies starts as low certainty. There is no further downgrade of evidence for this outcome by this overview. The certainty of evidence is upgraded by two levels due to very large observed effect. See Guyatt, Oxman, Sultan, et al. (2011). These very large effects on pubertal development would otherwise not have been observed without PBs.

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Table 5.5. Summary of evidence on progression to further treatment after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[168]	2 case series	65 participants	Proportion 0.92 (95% confidence interval: 0.53 to 0.99)	Very low certainty due to risk of bias concern (rating down by three levels)
Evidence synthesis			A high proportion of adolescents receiving PBs proceed with cross-sex hormone therapy.	The certainty of evidence is very low.

[168] Miroshnychenko, Roldan, et al. (2025).

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Table 5.6. Summary of evidence on safety outcomes after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Overall risk of adverse events				
Dopp 2024[169]	18 studies	-[170]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication). Over time, few statistically significant changes were observed in a variety of parameters for cardiovascular health (cholesterol, blood pressure, glucose, lipid levels) and liver enzymes; for the parameters that did show some changes (e.g., body mass index, creatinine levels, hemoglobin/hematocrit levels), values typically remained within the expected or healthy range and thus were not clinically significant. Other minor and infrequent side effects or complications included sterile abscess, headaches, mood changes, hot flashes, decreased libido, and breakthrough menstruation.	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024a[171]	3 before-after studies	109 participants	A cohort study of GnRH-a reported side effects including mild headaches or hot flushes (~20%) and moderate/severe headaches or hot flushes, mild fatigue, mood swings, weight gain and sleep problems (<10%). Two other studies assessed other medications and reported headaches and hot flushes as common and an increase in acne in a sample of birth-registered females receiving lynestrenol, and complaints of fatigue in birth-registered males receiving cyproterone acetate	No conclusions can be drawn.

[169] Dopp et al. (2024).
[170] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis 2011, Ristori 2019).
[171] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of PBs.	The certainty of evidence is very low.
Bone density				
Dopp 2024[172]	10 studies		The primary concern noted during treatment with PBs was decreases in bone health metrics (e.g., bone mineral density, bone growth markers). These metrics tended to remain stable during PBs treatment but showed decreases relative to age-based reference ranges; as growth rates are slowed during PBs treatment, age-based reference ranges become less relevant, and the clinical significance of these effects is unclear. Bone mineral density generally showed improvement after youth started CSH and initiated puberty consistent with their gender identity; however, it is unclear what the long-term effects on bone health and related functional outcomes (e.g., risk of fracture) would be when a patient desires long-term PBs treatment without future interventions that would enable its discontinuation.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[173]				
• **Bone density during PBs treatment (g/cm2, g/cm3)**	5 observational cohort studies (4 retrospective and 1 prospective)	363 participants on hormones, 297 were evaluated	Unchanged bone density (Dual-Energy X-ray Absorptiometry measurement)	Low certainty due to serious risk of bias and serious imprecision
• **Bone density during PBs treatment in relation to reference data in the literature (z-score)**	5 observational cohort studies (4 retrospective and 1 prospective)	408 participants on hormones, 292 were evaluated	Decreased increase in bone density over time	Low certainty due to serious risk of bias and serious imprecision

[172] Dopp et al. (2024).
[173] Ludvigsson et al. (2023); This review also assessed the effect on bone density when treatment with PBs was followed by CSH.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025a[174]				
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	2 before-after studies	128 participants	Mean change: -0.71 (95% confidence interval: -1.09 to -0.33)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	5 before-after studies	222 participants	Mean change: -0.72 (95% confidence interval: -0.91 to -0.54)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 20–24 months**	1 before-after study	9 participants	Mean change: -1.3 (95% confidence interval: -1.57 to -1.03)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, short term follow-up assessed with: DXA, z scores scale (−3 to 3).**	2 before-after studies	93 participants	Mean change: -0.7 (95% confidence interval: -1.11 to -0.29)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)

[174] Miroshnychenko, Roldan, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Follow-up: 6 months				
Taylor 2024a	5 before-after studies	331 participants	Five studies found decreases in bone mineral apparent density and z-scores before-after treatment; however, absolute measures generally remained stable or increased/decreased slightly	Multiple studies found that bone density is compromised during PBs treatment
Evidence synthesis			PBs may lead to decreases in bone mineral density (BMD)accumulation that normally occurs during puberty, lowering Z-scores.	The certainty of evidence is low due to evidence based on only observational studies (risk of bias).[175]
Fertility				
Dopp 2024[176]	2 studies	12 participants[177]	Case reports documented healthy, viable oocyte cryopreservation after taking PBs and pausing for at least 3 months	Very low certainty due to very serious risk of bias and very serious indirectness
Evidence synthesis			It is uncertain of PBs alone will result in impaired fertility once PBs are discontinued and puberty resumes. PBs probably lead to infertility if followed by CSH.	No empirical evidence. Inferred based on high certainty evidence on PBs effects on puberty progression.
Anthropometric measures				
Ludvigsson 2023[178]	1 retrospective observational cohort	192 participants on hormones, 192 were evaluated	Increased weight and body mass index	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision

[175] This overview re-evaluates the certainty of evidence because there was disagreement across the SRs. This overview concludes that the certainty of evidence is low because only evidence based on observational studies is available. Evidence based on observational studies without additional risk of bias concerns is assessed as low certainty of evidence, if there is no sufficient justification to upgrade the certainty of evidence.
[176] Dopp et al. (2024).
[177] This systematic review by Dopp et al reported fertility preservation based on case reports, not fertility outcomes.
[178] Ludvigsson et al. (2023).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Ludvigsson 2023[179]	2 prospective observational cohort studies and 1 controlled cross-sectional study	325 participants on hormones, 286 were evaluated	Decreased lean body mass	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[180]	2 before-after studies	152 participants	In both sexes, lean body mass percentage or SD score decreased while fat percentage increased	No conclusions can be drawn.
Blood pressure				
Ludvigsson 2023[181]	1 retrospective observational cohort	15 participants on hormones, 15 were evaluated	Change in blood pressure	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[182]	3 before-after studies	96 participants	Three studies reported no change or small, non-clinically significant change in blood pressure	No conclusions can be drawn.
Metabolic measures				
Ludvigsson 2023[183]	1 retrospective observational cohort study and 1 controlled cross-sectional study	209 participants on hormones, 209 were evaluated	No change in serum lipids or blood pressure Increased insulin level in natal males Decreased insulin sensitivity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[184]	3 before-after studies	127 participants	Three studies reported no change or small change in metabolic measures.	No conclusions can be drawn.
Growth (cm/year)				

[179] Ludvigsson et al. (2023).
[180] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[181] Ludvigsson et al. (2023).
[182] Taylor, Mitchell, Hall, Heathcote, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[183] Ludvigsson et al. (2023).
[184] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Ludvigsson 2023[185]	1 prospective multicentre observational study	55 participants on hormones, 55 were evaluated	Reduced growth velocity	Very low certainty due to very serious risk of bias, serious inconsistency and imprecision
Taylor 2024a[186]	11 studies, including 1 cohort study, and 10 before-after studies	925 participants	The cohort study found a similar height velocity between the GnRH-a group and adolescent controls. Other studies reported no change or small decrease	No high-quality studies using an appropriate design were identified. No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on anthropometric measures, body composition, blood pressure, and growth.	The certainty of evidence is very low for outcomes such as body composition, anthropometric measures, blood pressure, metabolic measures, and growth.
Cognition				
Ludvigsson 2023[187]	1 cross-sectional study	20 participants on hormones, 20 were evaluated	No change in cognition compared with matched controls	Very low certainty due to very serious risk of bias and very serious imprecision
Taylor 2024a[188]	1 cross-sectional study, and 1 before-after study	109 participants	One cross-sectional study measured executive functioning and found no difference between adolescents who were treated for <1 year compared with those not treated, but worse executive functioning in those treated for >1 year compared with those not treated. A before-after study found no differences in features typically associated with autism spectrum condition after treatment	No conclusions can be drawn.
Evidence synthesis			No conclusion can be drawn on the impact of PBs on cognitive outcomes.	The certainty of evidence is very low.

[185] Ludvigsson et al. (2023).
[186] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.
[187] Ludvigsson et al. (2023).
[188] Taylor, Mitchell, Hall, Heathcote, et al. (2024); this review did not include low quality studies in the evidence synthesis.

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Table 5.7. Summary of evidence on regret after PBs

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[189]	14 studies	-[190]	High satisfaction ratings and low rates of regret (3.5% or lower) were documented, and most youth who received that intervention progressed to CSH.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after PBs.	The certainty of evidence is very low.

[189] Dopp et al. (2024).
[190] The number of participants is not calculated because this review included heterogeneous types of studies, including that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Cohen-Kettenis et al. 2011), qualitative studies (e.g., Vrouenraets et al. 2022).

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6 Evidence synthesis: Cross-sex hormones

This overview identified eight SRs on the treatment effects of CSH.[191] Across all primary studies included in the eight SRs, there were no eligible randomized controlled trials. Furthermore, this overview found only eight observational studies with parallel comparison groups comparing CSH to no CSH among children or adolescents GD.[192] Generally, the sample size of these studies was small: five studies included fewer than 100 participants. In summary, the methodology of the current studies was insufficient to properly assess the treatment effects of CSH.

6.1 Included SRs on CSH

Chew 2018

Chew, D., Anderson, J., Williams, K., May, T., & Pang, K. (2018). Hormonal treatment in young people with gender dysphoria: A systematic review. *Pediatrics*, *141*(4).

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Karalexi 2020

Karalexi, M. A., Georgakis, M. K., Dimitriou, N. G., Vichos, T., Katsimpris, A., Petridou, E. T., . . . Papadopoulos, F. C. (2020). Gender-affirming hormone treatment and cognitive function in transgender young adults: A systematic review and meta-analysis. *Psychoneuroendocrinology*, *119*, 104721.

[191] Chew et al. (2018); Dopp et al. (2024); Karalexi et al. (2020); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024); Thompson et al. (2023); Zepf et al. (2024).
[192] Becker-Hebly et al. (2021); Filipov et al. (2023); Grannis et al. (2021), (2023); Grimstad et al. (2021); Hisle-Gorman et al. (2021); Jensen et al. (2019); Tordoff et al. (2022).

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Ludvigsson 2023

Ludvigsson, J. F., Adolfsson, J., Hoistad, M., Rydelius, P. A., Kristrom, B., & Landen, M. (2023). A systematic review of hormone treatment for children with gender dysphoria and recommendations for research. *Acta Paediatrica, International Journal of Paediatrics*, *112*(11), 2279-2292.

Miroshnychenko 2025b

Miroshnychenko, A., Ibrahim, S., Roldan, Y., Kulatunga-Moruzi, C., Montante, S., Couban, R., . . . Brignardello-Petersen, R. (2025). Gender affirming hormone therapy for individuals with gender dysphoria aged <26 years: A systematic review and meta-analysis. *Archives of Disease in Childhood*. https://doi.org/https://dx.doi.org/10.1136/archdischild-2024-327921

Taylor 2024b

Taylor, J., Mitchell, A., Hall, R., Langton, T., Fraser, L., & Hewitt, C. E. (2024). Masculinising and feminising hormone interventions for adolescents experiencing gender dysphoria or incongruence: A systematic review. *Archives of Disease in Childhood*, *109*(Suppl 2), s48-s56.

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

Zepf 2024

Zepf, F. D., Konig, L., Kaiser, A., Ligges, C., Ligges, M., Roessner, V., . . . Holtmann, M. (2024). [beyond nice: Updated systematic review on the current evidence of using puberty blocking pharmacological agents and cross-sex-hormones in minors with gender dysphoria]. *Beyond NICE: Aktualisierte systematische Ubersicht zur Evidenzlage der Pubertatsblockade und Hormongabe bei Minderjahrigen mit Geschlechtsdysphorie.*, *52*(3), 167-187.

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6.2 Low risk of bias systematic reviews

Four English SRs were classified at low risk of bias.[193] Of these reviews, the eligibility criteria and number of included studies varied. Dopp 2024[194] included 56 studies including 26 quasi-experimental studies (nearly all before-after), 8 cross-sectional studies, 10 cohort studies, 11 case reports, and 1 qualitative study. The SR by Taylor and colleagues[195] included 53 studies including 12 cohort, 9 cross-sectional, 32 pre–post studies. This SR excluded results from low quality studies in the evidence synthesis. Ludvigsson 2023[196] included 16 studies and Miroshnychenko 2025b[197] included 24 studies (including 9 comparative observational studies, 13 before–after design, and 2 case series) on CSH. Only four primary studies were included in all four low risk of bias SRs, including one comparative cohort study in Germany,[198] and three before-after studies reported in the US[199] and Netherlands.[200]

6.3 Outcome 1. Gender dysphoria

A total of three SRs assessed the impact of CSH on GD.[201] Dopp 2024[202] included a greater number of studies than three other SRs, though it included case reports and a qualitative study, which inflated the overall number of studies. This systematic review narratively described that therapy with CSH was associated with improved GD and body satisfaction, despite concluding that the certainty of evidence was very low. The other two SRs, based on evidence from observational studies, concluded that the evidence on the effect of CSH on GD and body satisfaction was very uncertain.

In summary, the certainty of evidence is very low, and no conclusion can be drawn on the impact of CSH on GD.

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[193] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[194] Dopp et al. (2024).
[195] Taylor, Mitchell, Hall, Langton, et al. (2024).
[196] Ludvigsson et al. (2023).
[197] Miroshnychenko, Ibrahim, et al. (2025).
[198] Becker-Hebly et al. (2021).
[199] Cantu et al. (2020).
[200] Schagen et al. (2020); Vlot et al. (2017).
[201] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[202] Dopp et al. (2024).

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6.4 Outcome 2. Mental health and well-being

Three SRs assessed the impact of CSH on mental health, including global function, suicidality, depression, anxiety, and other symptoms.[203] Like the SRs on GD, Dopp 2024[204] included more studies than the other SRs because it included case reports and a qualitative study. This systematic review narratively described that CSH leads to improved mental health, though the certainty of evidence was assessed as very low. Three SRs reported either no change or small changes in mental health associated with CSH. The certainty of evidence was very low or uncertain. In summary, no conclusion could be drawn on the impact of CSH on mental health due to very low certainty evidence.

For suicidality, the risk of death by suicide among hormonally-treated youth was estimated to be 6 per 1,000 according to Miroshnychenko and colleagues,[205] though the certainty of evidence was very low. According to the review by Taylor and colleagues,[206] two before-after studies reported reduced treatment needs or lower levels of suicidality and self-harm. Two other cross-sectional studies reported mixed findings: one found that adolescents receiving hormones were less likely to have seriously considered or attempted suicide compared to those not receiving hormones, while another found no difference between groups among birth-registered females. It is uncertain whether CSH leads to lower risk of suicide.

In summary, this overview finds the certainty of evidence on mental health and well-being is very low, and no conclusions can be drawn.

6.5 Outcome 3. Pubertal development

Two SRs assessed the impact of CSH on pubertal development, including pubertal progression, hormone level, and menstrual suppression.[207] SRs showed that the use of cross-sex hormone is consistently associated with physical changes. This overview

[203] Dopp et al. (2024); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[204] Dopp et al. (2024).
[205] Miroshnychenko, Ibrahim, et al. (2025).
[206] Taylor, Mitchell, Hall, Langton, et al. (2024).
[207] Dopp et al. (2024); Taylor, Mitchell, Hall, Langton, et al. (2024).

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assessed the certainty of evidence as high due to the observed very large effects.[208] One example of a very large effect pertains to menstrual suppression, which is expected to be rare without CSH. Taylor and colleagues[209] reported that menstrual suppression occurred in most participants on the basis of three before-after studies. In summary, there is high certainty evidence that CSH exerts physiological effects.

6.6 Outcome 4. Safety

Four SRs reported on safety outcomes for CSH in children or adolescents with GD. These included overall risk of adverse events, cardiovascular events, bone health, fertility, sexual dysfunction, body composition, growth, and other measures.[210] Dopp 2024[211] reported that side effects and complications were limited, and these side effects did not have a major impact on treatment. Taylor 2024b[212] listed adverse event types. In birth-registered females, reported adverse events included acne, mood changes, elevated red blood markers, increased appetite, headaches, hot flashes, fatigue, hair loss, and a slight increase in metrorrhagia. In birth-registered males, adverse events included breast tenderness, elevated liver enzymes, mood swings, and increased appetite. The certainty of evidence on the overall risk of adverse events was very low.

There is limited evidence on the long-term safety of CSH among children or adolescents with GD. Based on evidence from retrospective case series, Miroshnychenko 2025b[213] reported that the risk of cardiovascular events after CSH was estimated to be 0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months. The certainty of evidence was estimated to be moderate to high, because the SR authors contemplated that a comparison group was not needed to estimate the risk of cardiovascular events following cross-sex hormone.

All four SRs assessed bone health. The evidence was primarily based on before-after studies. The most frequently reported outcome for bone health was bone mineral

[208] Guyatt, Oxman, Sultan, et al. (2011).
[209] Taylor, Mitchell, Hall, Langton, et al. (2024).
[210] Dopp et al. (2024); Ludvigsson et al. (2023); Miroshnychenko, Ibrahim, et al. (2025); Taylor, Mitchell, Hall, Langton, et al. (2024).
[211] Dopp et al. (2024).
[212] Taylor, Mitchell, Hall, Langton, et al. (2024).
[213] Miroshnychenko, Ibrahim, et al. (2025).

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density decreases relative to reference values (z score). Dopp 2024[214] and Ludvigsson 2023[215] reported that bone density may recover after discontinuation of PBs and initiation of CSH. Miroshnycheko and colleagues[216] reported no changes in bone mineral density for hip, lumbar spine, and femoral neck. Taylor 2024b[217] reported conflicting results from four before-after studies: two studies reported an increase in absolute bone density measures and standard deviation (SD) scores at follow-up, with one focusing exclusively on birth-registered females. In contrast, two other studies found no change in bone density or bone biomarkers, though these involved small sample sizes. There was disagreement across SRs on certainty of evidence assessment, which was very low according to Dopp 2024[218] and Miroshnycheko 2025b,[219] but low according to Ludvigsson 2023.[220] Taylor 2024b[221] did not formally assess the certainty of evidence but concluded the evidence was very uncertain. This overview assessed the certainty of evidence for bone health as very low, considering serious risk of bias in included studies, inconsistent findings in included primary studies, and imprecision of evidence (it is unclear whether the difference in bone density is clinically meaningful).

Two SRs reported on fertility outcomes. Dopp et al[222] reported cases describing successful cryopreservation of healthy, viable oocytes, embryos, and semen, often after pausing hormone therapy. According to Taylor et al,[223] 1 cohort study reported mature spermatozoa observed in patients starting treatment at Tanner stage 4 or higher, but immature germ cells present in all patients treated earlier in puberty. This overview concludes that the evidence is very low for the impact of CSH on fertility.

[214] Dopp et al. (2024).
[215] Ludvigsson et al. (2023).
[216] Miroshnychenko, Ibrahim, et al. (2025).
[217] Taylor, Mitchell, Hall, Langton, et al. (2024).
[218] Dopp et al. (2024).
[219] Miroshnychenko, Ibrahim, et al. (2025).
[220] Ludvigsson et al. (2023).
[221] Taylor, Mitchell, Hall, Langton, et al. (2024).
[222] Dopp et al. (2024).
[223] Taylor, Mitchell, Hall, Langton, et al. (2024).

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Miroshnychenko 2025b[224] included 1 before-after study, reporting no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at 6 months or 12 months of follow-up. The certainty of evidence on sexual dysfunction was assessed as very low.

Taylor 2024b[225] also reported other outcomes such as anthropometric measures, body composition, blood pressure, etc., and found either no change or small changes. The certainty of evidence was judged to be very low or uncertain. Similarly, Ludvigsson et al[226] included three retrospective longitudinal studies assessing CSH in children without prior PBs treatment. Due to small sample sizes and differing outcomes measured (e.g., lipid levels, hemoglobin, blood pressure, metrorrhagia), the studies had low external validity. No overall conclusions could be drawn.

In summary, this overview concludes that the certainty of evidence for these outcomes is very low.

6.7 Outcome 5. Regret

Only one review assessed regret after CSH and reported high satisfaction ratings and low rates of regret.[227] The certainty of evidence was very low. This overview concludes that the evidence is uncertain, and no conclusion can be drawn on regret rate.

6.8 Evidence gap

Important evidence gaps exist for the effects of CSH. Many studies were not specifically designed to capture the full range of long-term outcomes and have largely concentrated on short-term psychological or physiological changes. Key outcomes such as GD, mental health, and quality of life have been inconsistently measured and, when reported, often are derived from small, observational studies with limited follow-up periods. Critically important long-term outcomes remain poorly understood. Sexual dysfunction, despite being highly relevant to long-term well-being, has been infrequently

[224] Miroshnychenko, Ibrahim, et al. (2025).
[225] Taylor, Mitchell, Hall, Langton, et al. (2024).
[226] Ludvigsson et al. (2023).
[227] Dopp et al. (2024).

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assessed. Although a few studies have reported cardiovascular event rates, long-term follow-up is still needed to evaluate cumulative risk.

Evidence on fertility is also sparse, with little data on whether reproductive effects vary by age at treatment initiation and whether these effects are reversible. Furthermore, the compounded effects of sequential treatment with PBs followed by CSH—such as their impact on bone health recovery, final adult height, or likelihood of requiring surgical interventions—have not been investigated adequately. A lack of primary studies that separately evaluate the effects of estrogen in males and testosterone in females is a significant limitation, as hormone-sex interactions may meaningfully influence outcomes.

6.9 Summary

In summary, this overview identified eight SRs addressing the effects of CSH among children or adolescents with GD. There is high certainty evidence that CSH exerts physiological effects. The evidence is very uncertain regarding effects on GD, mental health, or safety (such as impacts on fertility and bone health).

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6.10 Evidence mapping: SRs on CSH

Table 6.1. Evidence mapping of the SRs on CSHs and the primary studies that these SRs included

	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Achille 2020		Y			Y	Y		Y
Aldridge 2021					Y			
Allen 2019		Y				Y		Y
Amir 2020		Y						
Arcelus 2016						Y		
Arnoldussen 2022		Y						
Ascha 2022					Y			
Barnard 2019		Y						
Becker-Hebly 2021		Y		Y	Y	Y	Y	
Beking 2020						Y		
Bodlund 1996		Y						
Burke 2016	Y	Y	Y			Y		
Burke 2020						Y		
Caanen 2017		Y						
Campbell 2023		Y						

[228] Chew et al. (2018).
[229] Dopp et al. (2024).
[230] Ludvigsson et al. (2023)
[231] Miroshnychenko, Ibrahim, et al. (2025).
[232] Taylor, Mitchell, Hall, Langton, et al. (2024).
[233] Thompson et al. (2023).
[234] Zepf et al. (2024).

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Cantu 2020		Y		Y	Y	Y		
Chen 2023		Y			Y			
Chen 2016							Y	
Chiniara 2018						Y		
Cohen-Kettenis 2011[235]		Y						
de Nie 2022		Y				Y		
de Vries 2014	Y	Y		Y		Y		
de Vries 2011							Y	
Delemarre-van de Waal 2006		Y				Y		
Donaldson 2018		Y						
Filipov 2023					Y			
Fontanari 2020					Y	Y		
Foster 2021					Y			
Friedman 2000			Y					
Gale 2021		Y						
Gómez-Gil 2009			Y					
Grannis 2021[236]		Y				Y		Y
Grannis 2023[237]		Y			Y			

[235] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and surgeries.
[236] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 42 for Grannis 2021. The study population may overlap.
[237] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 82 for Grannis 2023. This report was an update to Grannis 2021. The study population may overlap.

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Green 2022		Y			Y	Y		
Grimstad 2021a		Y				Y		
Grimstad 2021b						Y		
Gupta 2023		Y						
Hannema 2017						Y		
Haraldsen 2005			Y		Y			
Hisle-Gorman 2021		Y		Y		Y		
Insogna 2020		Y						
Jarin 2017	Y	Y		Y		Y		
Jensen 2019						Y	Y	
Kaltiala 2020		Y			Y	Y		Y
Khatchadourian 2014		Y				Y		Y
Klaver 2020		Y		Y		Y	Y	Y
Klaver 2018				Y		Y	Y	
Klink 2015	Y	Y		Y		Y		Y
Kuper 2020		Y				Y	Y	Y
Laurenzano 2021		Y				Y		
Lavender 2023		Y						
Lee 2024		Y						
Lierman 2017		Y						
Littman 2021		Y						
López de Lara 2020		Y				Y		Y
Madsen 2021						Y		

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Martin 2021		Y						
Mehringer 2021		Y						
Miles 2006			Y					
Miles 1998			Y					
Millington 2022						Y		
Millington 2021						Y		
Millington 2019						Y		
Morningstar 2023								Y
Mullins 2021		Y		Y		Y		
Nokoff 2020						Y		
Nota 2019					Y			
Olsavsky 2023		Y[238]			Y			
Olson 2014	Y	Y				Y		
Olson 2022		Y						
Olson-Kennedy 2018a		Y				Y		
Perl 2021[239]		Y				Y		
Perl 2020[240]		Y		Y		Y	Y	
Pyra 2020					Y			
Ristori 2019		Y						

[238] Dopp 2024 included three citations for one study, Grannis 2021, Grannis 2023, and Olsavsky 2023. The sample size was 75 for Olsavsky 2023. This report was a cross-sectional analysis of recruited participants.
[239] Dopp 2024 included two citations for one study, Perl 2021 (19 participants) and Perl 2020 (15 participants). The study population may overlap. Taylor 2024b included the two citations as two moderate quality before-after studies.
[240] See above note.

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
Schagen 2016		Y						
Schagen 2018						Y		
Schagen 2020		Y		Y	Y	Y	Y	
Schöning 2010			Y					
Segev-Becker 2020						Y		
Sequeira 2019						Y		
Slabbekoorn 1999			Y					
Stanley 2018		Y						
Stoffers 2019		Y		Y		Y	Y	Y
Strang 2022						Y		
Tack 2016	Y	Y		Y		Y	Y	
Tack 2017	Y	Y				Y	Y	
Tordoff 2022		Y			Y	Y		
Turan 2018					Y			
Turban 2018		Y						
Turban 2022		Y				Y		
Valentine 2021						Y		
van de Grift 2020						Y		
van der Loos 2022		Y						
van der Loos 2023		Y						
van der Loos 2021				Y		Y		
van Dijk 2019					Y			
van Goozen 2002			Y					

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	Chew 2018[228]	Dopp 2024[229]	Karalexi 2020	Ludvigsson 2023[230]	Miroshnychenko 2025b[231]	Taylor 2024b[232]	Thompson 2023[233]	Zepf 2024[234]
van Goozen 1994			Y					
van Kesteren 1996					Y			
Vlot 2017	Y	Y		Y	Y	Y		Y
Wiepjes 2019					Y			
Wiepjes 2017					Y			

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6.11 Evidence tables on outcomes for CSH in youth with gender dysphoria

Table 6.2. Summary of evidence on gender dysphoria after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[241]	8 studies	-[242]	CSH was associated with reduced gender dysphoria and improved body satisfaction in adolescents and young adults with gender dysphoria. Effect sizes for gender dysphoria and body dissatisfaction were the largest observed for any intervention.	Very low certainty due to very serious risk of bias, very serious imprecision, and serious indirectness
Miroshnychenko 2025b[243]	1 comparative observational study and 1 before-after study	146 participants from 1 comparative study and 36 from 1 before-after study	Mean difference: -0.4 (95% confidence interval: -0.24 to 0.16) from 1 comparative study and Standardised mean change 0.26 lower (1.64 lower to 1.13 higher) from 1 before-after study (higher score indicating higher levels of gender dysphoria)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision
Taylor 2024b[244]	1 before-after study	23 participants from the before-after study	The pre–post study reported a reduction in dysphoria with no participants in clinical range at follow-up.	There was insufficient evidence regarding changes to gender dysphoria
Evidence synthesis			No conclusion can be drawn on the impact of gender dysphoria by CSH.	The certainty of evidence is very low.

[241] Dopp et al. (2024).
[242] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (e.g., Ristori et al, 2019).
[243] Miroshnychenko, Ibrahim, et al. (2025).
[244] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Table 6.3. Summary of evidence on mental health and well-being after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[245]	21 studies	-[246]	CSH was associated with improved mental health outcomes in adolescents and young adults with gender dysphoria. The majority of reported outcomes showed statistical significance, and nearly all of those indicated clinical significance as well (measured by effect size or compared to norms). Benefits were most consistent for depression and general functioning or well-being, and sometimes also seen for reductions in outcomes like suicidality, anxiety, and substance use (although these less consistently showed statistically significant changes).	Very low certainty due to very serious risk of bias, serious imprecision, inconsistency, and indirectness
Miroshnychenko 2025b[247]	2 prospective observational cohort studies; 2 before-after studies	125 from 2 prospective observational cohort studies; 73 participants from 2 before-after studies	Standardised mean difference: 0.87 higher (95% confidence interval: 0.25 lower to 2 higher) from 2 prospective observational cohort studies; Standardised mean change 0.25 higher (0.09 higher to 0.4 higher) from 2 before-after studies (higher score indicating better global function)	Very low certainty due to very serious risk of bias, serious imprecision and indirectness

[245] Dopp et al. (2024)

[246] The number of participants is not calculated because this review included heterogeneous types of studies, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. For this outcome of mental health, this systematic review included two reports on the same large cross-sectional study (2015 US Transgender Survey, Lee et al. (2024); Turban et al. (2022)). Cross-sectional studies were of limited value in assessing treatment effects, while the reviewers should not include two studies on the same survey.

[247] Miroshnychenko, Ibrahim, et al. (2025)

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2025b[248]	1 case series study	315 participants	6 per 1000 (1 to 18)	Very low certainty due to very serious risk of bias (rating down by three levels)
Self-harm and suicide				
Taylor 2024b[249]	2 before-after, and 2 cross-sectional studies	99 participants from 2 before-after studies, and 293 participants from 2 cross-sectional studies	Two before-after studies found a reduction in treatment needs for (or lower levels of) suicidality/self-harm, while two cross-sectional studies found conflicting results: those receiving hormones were less likely to have seriously considered/attempted suicide compared with adolescents not receiving hormones, and in birth-registered females there was no difference between groups	Hormone treatment may in the short-term improve psychological health.[250]
Depression				
Miroshnychenko 2025b[251]	2 prospective observational cohort studies; 2 before-after studies	154 from 2 prospective observational cohort studies; 389 participants from 2 before-after studies	Standardised mean difference: 0.3 lower (95% confidence interval: 0.85 lower to 0.25 higher) from 2 prospective observational cohort studies; Standardised mean change 0.41 lower (0.65 lower to 0.17 lower) from 2 before-after studies (higher score indicating worse depression)	Very low certainty due to very serious risk of bias (rating down by three levels) and serious imprecision

[248] Miroshnychenko, Ibrahim, et al. (2025)
[249] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[250] This systematic review concluded that there is “moderate-quality evidence from mainly pre–post studies that hormone treatment may in the short-term improve psychological health”. This review had identified “moderate quality” observational studies. Including “moderate-quality observational studies” is not equivalent to “moderate quality (certainty) evidence.” According to the GRADE methodology, the starting point for evidence from observational studies (including high quality observational studies) is generally low quality. To have moderate certainty, the certainty of evidence needs to be upgraded. See Guyatt, Oxman, Sultan, et al. (2011).
[251] Miroshnychenko, Ibrahim, et al. (2025)

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Taylor 2024b[252]	1 cohort, 1 before-after, and 2 cross-sectional studies	23 participants from 1 cohort, 52 participants from 1 before-after, and 293 participants from 2 cross-sectional studies	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study. A cross-sectional study reported lower levels of depression in adolescents who had received hormones compared with those who had wanted hormones but had not received them.	Hormone treatment may in the short-term improve psychological health.
Anxiety				
Taylor 2024b[253]	1 cohort, 1 before-after, and 1 cross-sectional study	23 participants from 1 cohort, 52 participants from 1 before-after, and 19 participants from 1 cross-sectional study	Studies found a reduction in depression and anxiety at follow-up (cohort) and for birth-registered females receiving hormones compared with females not receiving hormones (cross-sectional), but levels were higher when compared with adolescents not experiencing gender dysphoria/incongruence (cohort). Lower treatment needs for depression and anxiety were reported after treatment in a pre–post study.	Hormone treatment may in the short-term improve psychological health.
Internalising problems				
Taylor 2024b[254]	1 cohort study	23 participants	Emotional symptoms decreased at follow-up and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.

[252] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[253] See above note.
[254] See above note.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Externalising problems				
Taylor 2024b[255]	1 cohort study	23 participants	Conduct problems and hyperactivity decreased and were lower at follow-up compared to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Psychological difficulties				
Taylor 2024b[256]	1 cohort study	23 participants	Difficulties decreased with fewer in borderline/abnormal range at follow-up, and were similar at follow up to adolescents not experiencing gender dysphoria	Hormone treatment may in the short-term improve psychological health.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by CSH.	The certainty of evidence is very low.[257]

[255] See above note.

[256] See above note.

[257] Two systematic reviews assessed reported very low certainty evidence, while another claimed that there was “moderate quality evidence.” This overview assesses the certainty of evidence as very low.

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Table 6.4. Summary of evidence on pubertal development after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Induced physical changes				
Dopp 2024[258]	14 studies	-[259]	CSH was associated with physical changes resulting from increased levels of masculinizing hormones (e.g., deeper voice, increased body hair, changes in muscle mass, menstrual suppression) or feminizing hormones (e.g., decreased body hair, changes in body fat distribution, breast growth), which were targeted for initiation due to being consistent with the gender identity of youth with gender dysphoria.	Low certainty due to serious risk of bias, and serious indirectness
Taylor 2024b[260]	4 before-after studies	187 participants were treated	Two observed an increase in breast volume in birth-registered males after hormones, although objectively breast volume was small, and another reported no change in breast volume in birth-registered females. One study of birth-registered females reported an increase in facial, abdominal, chest and extremities hair, and voice deepening in all participants at follow-up. Another reported no change in Tanner genital stage in birth-registered males, and no change in Tanner pubic hair stage for both	Exogenous hormones increase hormone levels and to varying degrees of induced physical changes, with potential differences depending on birth-registered sex and timing of treatment

[258] Dopp et al. (2024).
[259] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[260] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Hormone level				
Taylor 2024b[261]	15 studies including 2 cohort studies, 12 before-after studies, and 1 cross-sectional study	1519 participants were treated	All pre–post studies and a cohort reporting pre–post data found increased/heightened testosterone and oestradiol in birth-registered females and males	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Menstrual suppression				
Taylor 2024b[262]	3 before-after studies	387 participants were treated	Three pre–post studies reported suppression in most participants	Exogenous hormones increase hormone levels and to varying degrees induced physical changes, with potential differences depending on birth-registered sex and timing of treatment
Evidence synthesis			CSH lead to expected physiological effects	There is high certainty evidence on the physiological effects (High certainty due to very large physiological effects of CSH).[263]

[261] See note above.
[262] Taylor, Mitchell, Hall, Langton, et al. (2024).
[263] According to the GRADE methods, evidence based on observational studies can be upgraded. See Guyatt, Oxman, Sultan, et al. (2011); This overview assessed the certainty of evidence as high, upgraded by two levels due to very large effects on physical changes, hormone level, and menstrual suppression that would otherwise not be observed without CSH.

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Table 6.5. Summary of evidence on safety outcomes after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[264]	19 studies	-[265]	Side effects and complications were limited and did not have a major impact on treatment (e.g., rarely resulted in changed or discontinued medication).[266]	Very low certainty due to very serious risk of bias and serious indirectness
Taylor 2024b[267]	4 studies, including 1 cohort, and 3 before-after studies	17 participants from 1 cohort, and 184 participants from 3 before-after studies	In birth-registered females, three studies noted increased acne; one also reported mood changes, elevated red blood markers, increased appetite, and less commonly, headaches, hot flashes, fatigue, and hair loss. Another study found a slight rise in metrorrhagia after adding testosterone to <6 months of lynestrenol. In birth-registered males, two studies commonly reported breast tenderness. Less common effects included elevated liver enzymes and high oestradiol levels, while mood swings and increased appetite were frequent.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the overall risks of side-effects of CSH.	The certainty of evidence is very low.
Cardiovascular events				
Miroshnychenko 2025b[268]	2 case series studies	5768 participants	0 per 1000 (0 to 10) over 26 months, and 40 per 1000 (30 to 50) over a follow up duration of up to 109 months	Moderate to high certainty

[264] Dopp et al. (2024).
[265] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[266] This systematic review qualitatively described the types of side effects, such as parameters for cardiovascular health, liver enzyme, etc., but did not provide detailed, separate description for these outcomes.
[267] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[268] Miroshnychenko, Ibrahim, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body mass index				
Taylor 2024b[269]	16 studies (1 cohort, 14 before-after studies, and 1 cross-sectional study)	1275 participants	No change overall but some inconsistencies	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			For every 1,000 young people receiving CSH, 40 may experience cardiovascular events in 9 years.	The certainty of evidence is moderate to high.
Bone health				
Dopp 2024[270]	7 studies	-[271]	CSH was associated with improved bone density in adolescents and young adults who experienced decreases in bone density during PBs treatment. Bone density values after CSH returned to pre-treatment levels or fell within the age-based reference range for some participants.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Ludvigsson 2023[272]	3 observational cohort studies (2 retrospective and 1 prospective)	268 participants on hormones, 165 were evaluated	Bone density after 1–3 years (up to 22 years of age) of CSH, which had been preceded by puberty-blocking hormonal treatment in relation to reference data in the literature: After group median five years with CSH, bone density recovered in hip but not in lumbar spine compared to data at start of treatment (z-score)	Low certainty due to serious risk of bias and serious imprecision

[269] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[270] Dopp et al. (2024).
[271] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.
[272] Ludvigsson et al. (2023).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Miroshnychenko 2025b[273]				
• **Bone mineral density, femoral neck, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12 months**	1 before-after study	199 participants	Mean change: 0 (0.01 lower to 0)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, hip, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	1 before-after study	199 participants	Mean change: 0.01 higher (0.01 higher to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
• **Bone mineral density, lumbar spine, long term follow-up assessed with: DXA, z scores scale (−3 to 3). Follow-up: 12–36 months**	2 before-after studies	234 participants	Mean change: 0.01 higher (0 to 0.01 higher)	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
Taylor 2024b[274]	4 before-after studies	244 participants from 4 before-after studies	Two studies reported increased bone density and SD scores at follow-up (one study included birth-registered females only), while two others found no change in bone density or biomarkers, though sample sizes were small.	There is insufficient evidence about the risks of hormone interventions

[273] Miroshnychenko, Ibrahim, et al. (2025).
[274] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Evidence synthesis			No conclusion can be drawn on the impact of CSH on bone health.	The certainty of evidence is very low.
Fertility				
Dopp 2024[275]	7 studies	-[276]	Studies documented healthy, viable oocyte or embryo cryopreservation after taking CSH and pausing for at least 3 months; a case report documented that a transgender young adult man cryopreserved viable oocytes without pausing CSH, and two other case reports documented viable semen cryopreservation after pausing CSH.	Very low certainty due to very serious risk of bias, serious imprecision, and very serious indirectness
Taylor 2024b[277]	1 cohort study	78 participants	Mature spermatozoa only observed in those starting treatment at Tanner stage 4 or higher. Immature germ cells present in all treated in early puberty.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on fertility.	The certainty of evidence is very low.
Sexual dysfunction[278]				
Miroshnychenko 2025b[279]	1 before-after study	193 participants	A linear regression analysis showed no change from baseline in symptoms of vaginal dryness or itch after receiving cross-sex hormone at 6 months or 12 months of follow up.	Very low certainty due to serious risk of bias concern (rating down by 3 levels)
Evidence synthesis			No conclusion can be drawn on the impact of CSH on sexual dysfunction.	The certainty of evidence is very low.

[275] Dopp et al. (2024).
[276] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies. This review assessed fertility preservation outcomes, not fertility outcome.
[277] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[278] Evidence only on natal females.
[279] Miroshnychenko, Ibrahim, et al. (2025).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Cognitive				
Taylor 2024b[280]	4 studies including 2 cohort studies and 2 cross-sectional studies	42 participants from 2 cohort studies and 71 participants from 2 cross-sectional studies	Two cohort studies of birth-registered females explored testosterone's impact on brain activity. One found no performance differences in visuospatial working memory across groups but noted stronger frontal and parietal activation in treated individuals and male controls. The other observed slightly more rightward amygdala lateralisation post-treatment, aligning with patterns in male and female controls. A cross-sectional study also found greater amygdala activation and stronger amygdala–prefrontal connectivity in those on hormones. Another study reported better executive function, cognitive flexibility, and working memory in hormone-treated individuals.	There was insufficient evidence regarding changes to cognitive outcomes
Evidence synthesis			No conclusion can be drawn on the impact of CSH on cognitive outcomes.	The certainty of evidence is very low.
Height/growth				
Taylor 2024b[281]	7 studies including 1 cohort study and 6 before-after studies	43 participants from 1 cohort study and 563 participants from 6 before-after studies	For birth-registered males, two studies reported an increase in height SD score and one no change. Three studies reported an increase in absolute height. For birth-registered females, two studies reported no change in height SD score, and three reported an increase in absolute height. One study reported that birth-registered females who received hormones earlier and for longer, were taller than those who started treatment later.	There is insufficient evidence about the risks of hormone interventions

[280] Taylor, Mitchell, Hall, Langton, et al. (2024); This review did not include low quality studies in the evidence synthesis.
[281] See note above.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Body composition				
Taylor 2024b[282]	2 studies including 1 cohort study and 1 cross-sectional study	28 participants from 1 cohort study and 35 participants from 1 cross-sectional study	Birth-registered females on testosterone had lower body fat and higher lean mass than female controls. Birth-registered males had higher body fat and lower lean mass after hormone treatment than male controls. A pre–post study in birth-registered males found no fat mass change at 2 years, but an increase at 3 years. Fat percentage and lean mass percentage remained stable.	There is insufficient evidence about the risks of hormone interventions
Evidence synthesis			No conclusion can be drawn on the impact of CSH on height/growth or body composition.	The certainty of evidence is very low.

[282] See above note.

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Table 6.6. Summary of evidence on regret after CSH

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[283]	13 studies	-[284]	Findings suggest high levels of satisfaction and low rates of regret with CSH, and most youth who received that intervention did not discontinue it.	Very low certainty due to very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the regret rate after CSH.	The certainty of evidence is very low.

[283] Dopp et al. (2024).
[284] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

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7 Evidence synthesis: surgeries

This overview identified three SRs on surgeries for children or adolescents with GD[285], with most of the evidence considering mastectomy only. Across all primary studies included in the three SRs, there were no eligible randomized controlled trials. Furthermore, this overview found that only two observational studies with parallel control groups comparing surgery with no surgery among youth with GD.[286] Generally, the sample size of these studies was small: one study included 75 participants and another included 136 participants.

7.1 Included SRs on surgeries

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Miroshnychenko 2024

Miroshnychenko, A., Roldan, Y. M., Ibrahim, S., Kulatunga-Moruzi, C., Dahlin, K., Montante, S., . . . Brignardello-Petersen, R. (2024). "Mastectomy for individuals with gender dysphoria below 26 years of age: A systematic review and meta-analysis". *Plast Reconstr Surg*. https://doi.org/10.1097/prs.0000000000011734

Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

[285] Dopp et al. (2024); Miroshnychenko et al. (2024); Thompson et al. (2023).
[286] Becker-Hebly et al. (2021); Olson-Kennedy et al. (2018).

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7.2 Low risk of bias systematic reviews

Of the two low risk of bias SRs,[287] Dopp 2024[288] included 18 studies (6 cross-sectional studies, 7 quasi-experimental studies, 1 cohort study, 3 case reports, and 1 qualitative study), and included all types of surgeries, though most of the included studies were on mastectomy. Miroshnychenko 2024[289] included 39 studies (3 comparative observational, 2 before–after, and 34 case series), and only assessed the effects of mastectomy. Three studies were included by both reviews.[290]

7.3 Outcome 1. Gender dysphoria

Two SRs assessed the impact of surgery on GD. Dopp 2024[291] narratively described that according to 10 studies mastectomy was associated with reduced GD. The certainty of evidence was low. Miroshnychenko and colleagues included 1 comparative observational study with 136 participants and 1 before-after study with 35 participants and concluded that the certainty of evidence was very low. The authors concluded that no conclusion could be drawn on the effect of surgery in improving GD.

In conclusion, this overview finds that the certainty of evidence is very low.

7.4 Outcome 2. Mental health and well-being

The SRs assessed the impact of surgery on mental health, including global functioning, suicidality, non-suicidal self-harm, depression, and quality of life.[292] Dopp 2024[293] reported that adolescents and young adults generally showed improved mental health after surgery, with about half the outcomes showing clinically significant gains (e.g., self-perception, distress, functioning, quality of life). This systematic review acknowledged that most patients had prior interventions or were already high functioning, making it hard to isolate the effects of surgery. The other systematic review[294] reported a lower level of distress measured by Kessler Psychological Distress from one comparative

[287] Dopp et al. (2024); Miroshnychenko et al. (2024).
[288] Dopp et al. (2024).
[289] Miroshnychenko et al. (2024).
[290] Ascha et al. (2022); Marinkovic & Newfield (2017); Tang et al. (2022).
[291] Dopp et al. (2024).
[292] Dopp et al. (2024); Miroshnychenko et al. (2024).
[293] Dopp et al. (2024).
[294] Miroshnychenko et al. (2024).

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observational study. However, both SRs assessed the certainty of evidence as very low. In summary, no conclusion could be drawn on the impact of surgery on global function due to very low certainty evidence.

Miroshnychenko et al[295] reported very low certainty evidence for the effect of mastectomy on outcomes such as quality of life, depression, suicide attempts and death by suicide compared with no mastectomy. Low certainty evidence suggested that mastectomy may be associated with a lower risk of non-suicidal self-injury.

In summary, this overview suggests that it is unclear whether mastectomy leads to benefits in mental health due to very low certainty evidence.

7.5 Outcome 3. Safety

Dopp 2024[296] concluded that side effects after surgeries, such as scarring or issues with function/appearance, were generally limited. Most complications (e.g., fluid buildup, pain, bruising, infection) were minor and resolved naturally or with simple follow-up care. Miroshnychenko and colleagues[297] found high certainty evidence showing no increased risk of death following the surgery as well as high-certainty evidence for necrosis and excessive scarring after surgery.

7.6 Outcome 4. Regret

Both SRs reported a low level of regret,[298] albeit both reviews found the certainty of evidence was very low. The current evidence basis is not sufficient to reach a conclusion on the regret rate after surgery.

7.7 Evidence gap

There are substantial gaps in the evidence on surgeries for adolescents with GD. Most existing studies are case series or small observational designs, with limited or no comparator groups, and thus are unable to isolate the effects of surgery from prior

[295] Miroshnychenko et al. (2024).
[296] Dopp et al. (2024).
[297] Miroshnychenko et al. (2024).
[298] Dopp et al. (2024); Miroshnychenko et al. (2024).

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medical or psychosocial interventions. Outcomes such as GD, mental health, and quality of life are inconsistently reported and often lack validated measures.

Long-term outcomes, including the durability of psychological benefits, sexual function, need for revision surgeries, and satisfaction and well-being into adulthood, remain poorly characterized. Furthermore, while regret is a frequent topic of public discussion, existing studies do not provide robust data on the factors influencing regret. There are also knowledge gaps for other types of surgeries, including genital surgeries

7.8 Summary

In summary, this overview identified three systematic reviews addressing the effects of surgeries among children or adolescents with GD. There is high certainty evidence that mastectomy is associated with predictable surgical complications such as necrosis and scarring. The evidence is very uncertain regarding the effect of surgery on GD, improvement in mental health including suicidality, depression, and long-term outcomes such as sexual function, quality of life, and regret.

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7.9 Evidence mapping: SRs on surgeries

Table 7.1. Evidence mapping of the SRs on surgeries and the primary studies that these SRs included

	Dopp 2024[299]	Miroshnychenko 2024[300]	Thompson 2023[301]
Arnoldussen 2022	Y		
Ascha 2022	Y	Y	
Ayyala 2020		Y	
Becker-Hebly 2021	Y		Y
Berry 2012		Y	
Bodlund 1996	Y		
Boskey 2023	Y		
Bungener 2020	Y		
Bustos 2020		Y	
Caro 2024		Y	
Cohen-Kettenis 2011[302]	Y		
Cohen-Kettenis 1997[303]	Y		
Cuccolo 2019		Y	
de Vries 2014	Y		
Donaldson 2018	Y		
Donato 2017		Y	
Ederer 2023		Y	
Elfering 2020		Y	
Frederick 2017		Y	
Gold 2021		Y	
Jolly 2023		Y	
Junn 2021		Y	
Kääriäinen 2017		Y	

[299] Dopp et al. (2024).
[300] Miroshnychenko et al. (2024).
[301] Thompson et al. (2023).
[302] Another citation, Cohen-Kettenis 1998 was provided for this study. However, this citation (Cohen-Kettenis 1998) was not included by any other SRs on PBs or CSH. Though this study was included by Dopp 2024 for PBs and CSH.
[303] Two other citations were included for this study, Smith 2021 and Smith 2022. Neither citation was included by other reviews on PBs, CSH, or surgeries.

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	Dopp 2024[299]	Miroshnychenko 2024[300]	Thompson 2023[301]
Kamali 2021		Y	
Kaur 2023		Y	
Kelly-Schuette 2022		Y	
Kuper 2020	Y		Y
Lane 2023		Y	
Lang 2021		Y	
Lee 2024	Y		
Littman 2021	Y		
Marinkovic 2017	Y	Y	
McEvenue 2017		Y	
Mehringer 2021	Y		
Naides 2021		Y	
Namba 2009		Y	
Olson-Kennedy 2018a	Y		
Olson-Kennedy 2018b		Y	
Perez-Alvarez 2021		Y	
Robinson 2023		Y	
Rothenberg 2021		Y	
Rothenberg 2018		Y	
Sır 2022		Y	
Skorochod 2023	Y		
Stein 2021		Y	
Stojanovic 2017		Y	
Tan 2023		Y	
Tang 2022	Y	Y	
Top 2017		Y	
van de Grift 2017		Y	
van de Grift 2018		Y	
van de Grift 2016		Y	
Wolf 2021		Y	
Wolter 2018		Y	

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7.10 Evidence tables on outcomes for surgeries in youth with gender dysphoria

Table 7.2. Summary of evidence on gender dysphoria after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Mastectomy				
Dopp 2024[304]	10 studies	-[305]	Mastectomy was associated with reduced gender dysphoria (including specifically chest dysphoria), and related improvements with body satisfaction for primary and sometimes secondary sex characteristics, in natal female adolescents and young adults with gender.	Low certainty due to serious risk of bias and serious indirectness
Miroshnychenko 2024[306]	1 comparative observational study and 1 before-after study	136 participants from 1 comparative observational study and 35 participants from 1 before-after study	Mean difference 26.3 lower (28.84 lower to 23.76 lower) from the comparative observational study; mean change 28 lower (28.33 lower to 27.67 lower) for gender dysphoria related to chest, and mean change 9.1 higher (8.74 higher to 9.46 higher) according to participant reported transgender congruence scale from the before-after study (higher score indicating greater gender dysphoria)	Very low certainty due to serious risk of bias, imprecision, and indirectness
Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty				
Dopp 2024[307]	4 studies	-[308]	Hysterectomy/ovariectomy and/or metoidioplasty or phalloplasty was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal female young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness

[304] Dopp et al. (2024).
[305] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[306] Miroshnychenko et al. (2024).
[307] Dopp et al. (2024).
[308] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Vaginoplasty and/or mammaplasty				
Dopp 2024[309]	5 studies	-[310]	Vaginoplasty "bottom surgery" and/or mammaplasty "top surgery" was associated with reduced gender dysphoria, and related improvements with body satisfaction related to primary and secondary sex characteristics, in natal male adolescents and young adults with gender dysphoria.	Very low certainty due to very serious risk of bias, very serious imprecision and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of surgeries on gender dysphoria.	The certainty of evidence is very low.

[309] Dopp et al. (2024).
[310] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).

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Table 7.3. Summary of evidence on mental health and well-being after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Global function		
Dopp 2024[311]	10 studies	-[312]	Across surgeries, adolescents and young adults with gender dysphoria generally showed improvement in mental health outcomes, with clinically significant effect sizes for about half of reported outcomes; examples of outcomes measured include self-perception, psychological distress, mental health symptoms, global functioning, and quality of life. In cases where improvement was not found, average scores on outcomes were maintained at the same level as pre-surgery. No evidence of mental health harms was found. In most studies, patients had received numerous interventions and/or been required to demonstrate high levels of functioning prior to receiving surgery, which made it difficult to assess mental health outcomes of surgery, and they are considered secondary intervention benefits.	Very low certainty due to very serious risk of bias, very serious imprecision, serious inconsistency and indirectness
Miroshnychenko 2024[313]	1 comparative observational study	299	16.39% participants had mastectomy. A multivariate analysis showed that those who received mastectomy (chest reconstruction surgery) scored an average of -7.13 (CI= -10.25 to -4.02) points lower on the Kessler Psychological Distress.	Very low certainty due to very serious risk of bias and serious indirectness

[311] Dopp et al. (2024).
[312] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), or cross-sectional study (Lee 2024).
[313] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Depression				
Miroshnychenko 2024[314]	1 before-after study[315]	68	mean change 3.16 lower (3.35 lower to 2.97 lower) (higher score indicating greater depression)	Very low certainty due to very serious risk of bias and serious indirectness and imprecision
Suicide attempts				
Miroshnychenko 2024[316]	1 comparative observational study	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.39 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.39 [95% confidence interval 0.11 to 1.45]).	Very low certainty due to very serious risk of bias and serious imprecision
Non-suicidal Self-harm				
Miroshnychenko 2024[317]	1 comparative observational study[318]	299	16.39% participants had mastectomy. Individuals who underwent mastectomy had 0.47 times the odds of non-suicidal self-injury compared to individuals who did not undergo mastectomy (adjusted odds ratio 0.47 [95% confidence interval 0.22 to 0.97])	Low certainty due to very serious risk of bias
Quality of life				
Miroshnychenko 2024[319]	1 before-after study and 1 case series	80 participants from the before-after study and 34 participants from the case series	mean change 5.74 higher (5.29 higher to 6.19 higher lower) (higher score indicating better quality of life)	Very low certainty due to serious risk of bias, indirectness, and imprecision

[314] Miroshnychenko et al. (2024).
[315] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[316] Miroshnychenko et al. (2024).
[317] Miroshnychenko et al. (2024).
[318] The supplementary information of this systematic review reported evidence based on case series, which did not change the certainty of evidence for this outcome.
[319] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Death by suicide				
Miroshnychenko 2024[320]	1 case series	464 participants from the case series	10 per 1,000 (0 to 20)	Very low certainty due to serious very serious risk of bias and serious indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by surgeries.	The certainty of evidence is very low.

[320] Miroshnychenko et al. (2024).

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Table 7.4. Summary of evidence on safety after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[321]	10 studies	-[322]	Across types of surgery, side effects (e.g., scarring, issues with functioning and/or appearance) were limited and primarily would be resolved through improved surgical techniques; concerns about sexual functioning were often noted, but overall sexual functioning tended to improve from pre-surgery. Complications were also generally minor (e.g., blood fluid collection, pain, bruising, infection) and resolved through natural healing or non-invasive follow-up procedures.	Very low certainty due to very serious risk of bias and serious indirectness
Death as a postoperative complication of mastectomy				
Miroshnychenko 2024[323]	5 case series studies	3673	0 per 1,000 (0 to 0)	High certainty evidence
Necrosis (complete and partial nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[324]	8 case series studies	1998	30 per 1,000 (10 to 70)	High certainty evidence
Necrosis (complete nipple/areola/nipple-areola complex/nipple graft necrosis)				
Miroshnychenko 2024[325]	13 case series studies	2236	20 per 1,000 (10 to 30)	High certainty evidence

[321] Dopp et al. (2024).
[322] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that are not typically included a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011).
[323] Miroshnychenko et al. (2024).
[324] Miroshnychenko et al. (2024).
[325] Miroshnychenko et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Excessive Scarring				
Miroshnychenko 2024[326]	12 case series studies	2405	50 per 1,000 (30 to 80)	High certainty evidence
Evidence synthesis			Surgery is generally safe and the risk of dying from surgery is low. There are risks of complications such as necrosis, scarring, sexual function impairment, and other functional impairment.	The evidence for mastectomy is high certainty. The evidence for other surgeries is very low certainty.

[326] Miroshnychenko et al. (2024).

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Table 7.5. Summary of evidence on regret after surgeries

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[327]	9 studies	-[328]	Across types of surgeries, high satisfaction ratings and low rates of regret (<2%) were documented. Comparisons between adolescents and young adults with gender dysphoria suggested rates of regret and satisfaction that were equal or better in youth younger than 18.	Very low certainty due to very serious risk of bias and serious indirectness
Miroshnychenko 2024[329]	4 case series studies	775	10 per 1,000 (0 to 20)	Very low certainty due to very serious risk of bias (rating down for three levels) and serious indirectness
Evidence synthesis			There are cases of regret after surgeries. No conclusion can be drawn on the regret rate after surgery.	The certainty of evidence on regret rate is very low.

[327] Dopp et al. (2024).
[328] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies (Cohen-Kettenis 2011), and qualitative studies (Mehringer 2021).
[329] Miroshnychenko et al. (2024).

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8 Evidence synthesis: psychotherapy

There are five SRs assessing psychotherapy among children or adolescents with GD.[330] Only two were assessed at low risk of bias in the systematic review process.[331]

8.1 Included SRs on psychotherapy

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Expósito-Campos 2023

Expósito-Campos, P., Pérez-Fernández, J. I., & Salaberria, K. (2023). Empirically supported affirmative psychological interventions for transgender and non-binary youth and adults: A systematic review. *Clinical Psychology Review*, *100*, 102229.

Heathcote 2024

Heathcote, C., Taylor, J., Hall, R., Jarvis, S. W., Langton, T., Hewitt, C. E., . . . Fraser, L. (2024). Psychosocial support interventions for children and adolescents experiencing gender dysphoria or incongruence: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s19-s32.

Malpas 2022 – family-based intervention (social and psychological)

Malpas, J., Pellicane, M. J., & Glaeser, E. (2022). Family-based interventions with transgender and gender expansive youth: Systematic review and best practice recommendations. *Transgend Health*, *7*(1), 7-29.

[330] Dopp et al. (2024); Expósito-Campos et al. (2023); Heathcote et al. (2024); Malpas et al. (2022); Thompson et al. (2023).
[331] Dopp et al. (2024); Heathcote et al. (2024).

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Thompson 2023

Thompson, L., Sarovic, D., Wilson, P., Irwin, L., Visnitchi, D., Samfjord, A., . . . Gillberg, C. (2023). A prisma systematic review of adolescent gender dysphoria literature: 3) treatment. *PLOS global public health*, *3*(8), e0001478.

8.2 Low risk of bias systematic reviews

Evidence on the effects of psychotherapy is limited. Dopp 2024[332] included one randomized controlled trial evaluating the effects of "coping-oriented brief videos" on suicidality. There are no other randomized controlled trials. Both SRs found that psychotherapy interventions were delivered through a range of formats, highlighting considerable heterogeneity in delivery. Most were conducted face-to-face or online. Formats for both face-to-face and online interventions varied widely, including individual, group, family-based, and combined approaches. Face-to-face interventions took place in diverse settings, such as specialist gender services, community programs, community mental health clinics, a weekend retreat, and an acute residential treatment program. These heterogeneities limit the generalizability of evidence.

8.3 Outcome 1. Gender dysphoria

There was no evidence on the impact of psychotherapy on GD.

8.4 Outcome 2. Mental health and well-being

Dopp and colleagues[333] reported that peer group interventions were associated with improvements in general mental health functioning, but professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning. The certainty of evidence was very low. Heathcote and colleagues included 10 studies and found that research on psychosocial interventions for children and adolescents with GD is limited. The 10 included studies were generally low in quality and poorly reported. Most lacked clear participant selection criteria, used varied interventions, applied inconsistent outcome measures, and did not include appropriate comparators. This

[332] Dopp et al. (2024).
[333] Dopp et al. (2024).

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systematic review by Heathcote and colleagues[334] underscored a lack of robust research and the use of inadequate methodologies. In summary, the certainty of evidence for benefits of psychotherapy is very low.

8.5 Outcome 3. Safety

Neither systematic review found any indication of harm from psychotherapy.

8.6 Evidence gap

The evidence base for psychotherapy in children and adolescents with GD is marked by substantial gaps. This may be due to the inappropriate conflation of psychotherapy with "conversion therapy." As noted by the Cass Review, "[the] role of psychological therapies in supporting children and young people with gender incongruence or distress has been overshadowed by an unhelpfully polarised debate around conversion practices."[35] There has been very limited evidence on the role of psychotherapy in treating mental health problems co-occurring with GD,[36] including depression, anxiety, eating disorders, self-harm, and suicidality. Studies often did not isolate the effects of psychotherapy from those of other concurrent interventions such as social transition, PBs, or CSH, making it difficult to attribute observed outcomes to psychotherapy alone. There is little understanding of which therapeutic approaches may be more effective for specific subgroups. The lack of robust research was acknowledged by the Cass Review, which noted that "there has been a failure to systematically consider how psychosocial interventions should be used and to research their efficacy."[37]

8.7 Summary

In summary, this overview identified five systematic reviews assessing the effects of psychotherapy among children or adolescents with GD. Only two reviews were rated at low risk of bias. The available evidence on psychotherapy is limited and highly heterogeneous in terms of intervention format, delivery setting, and target population. This overview finds no evidence on the impact of psychotherapy on GD from the SRs.

[334] Heathcote et al. (2024).

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For mental health outcomes, the certainty of evidence is very low. No harms were reported.

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8.8 Evidence tables on outcomes for psychotherapy in youth with gender dysphoria

Table 8.1. Summary of evidence on mental health and well-being after psychotherapy

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Peer group intervention				
Dopp 2024[335]	4 studies	-[336]	Peer group interventions were associated with improvements in general mental health functioning in adolescents and young adults with gender dysphoria; examples of outcomes studied include mental health symptoms, well-being / quality of life, and self-esteem. All studies showed benefits on some reported outcomes, but about half of the reported outcomes did not show significant changes, and in one case the effect was not clinically significant (Austin, Craig, and D'Souza, 2018). Furthermore, a group intervention for youth with autism spectrum disorder and gender dysphoria (Brandsma et al., 2022) was associated with increases in gender dysphoria and showed benefits on only one-third of reported outcomes.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness and inconsistency

[335] Dopp et al. (2024).
[336] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case studies.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Professional psychological support as a precondition for additional interventions for gender dysphoria				
Dopp 2024[337]	2 studies	135 participants	Professional psychosocial support as a precondition for additional interventions was not associated with any improvements on broad measures of mental health symptoms or functioning in adolescents with gender dysphoria who have started puberty. Youth remained in the clinical range on mental health symptom measures post-intervention (compared to norms) and did not show statistically or clinically significant changes over time.	Very low certainty due to very serious risk of bias, and serious indirectness
Depression				
Heathcote 2024[338]	6 studies	n = 226	Four studies found significant reductions in depression levels post-intervention and/or at a later timepoint. Two studies found non-significant differences in depression levels during mid-treatment and/or post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[337] Dopp et al. (2024).
[338] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Anxiety				
Heathcote 2024[339]	3 studies	n = 218	All three studies found significant reductions in anxiety levels post-intervention	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Depression and anxiety combined				
Heathcote 2024[340]	1 study	n = 17	no significant, although marginal, difference from baseline to 6 months	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[339] Heathcote et al. (2024).
[340] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Internalising and externalising symptoms				
Heathcote 2024[341]	1 study	n = 64	Improvement in internalising and externalising symptoms	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Emotional dysregulation				
Heathcote 2024[342]	1 study	n = 35	significant reductions post-intervention and at a later timepoint (1 month)	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[341] Heathcote et al. (2024).
[342] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Suicidality		
Dopp 2024[343]	1 randomized controlled trial	483 LGBTQ+ youth (“lesbian, gay, bisexual, transgender, queer persons or persons with other sexual or gender minority identities”)	A randomized controlled trial found that coping-oriented brief videos ("It Gets Better" project) led to short-term decreases in suicidality and increases in help-seeking intentions with personal contacts in young adults with gender dysphoria, but these benefits were not maintained at 4 weeks post-intervention and were not large enough to represent clinically significant effects.	Very low certainty due to serious risk of bias and indirectness
Heathcote 2024[344]	3 studies	n = 193	Two studies found significant decreases in suicidality scores from baseline to mid-treatment and/or post-intervention, and/or at a later timepoint. One study found no difference in the proportion of patients at high suicide risk before and after the intervention.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[343] Dopp et al. (2024).
[344] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Family support				
Dopp 2024[345]	2 studies	-[346]	Professional psychosocial support in the form of family and/or caregiver therapy was associated with increased family support for youth with gender dysphoria, with small but clinically significant effect sizes; similar effects were also described in one case report.	Very low certainty due to very serious risk of bias and imprecision, and serious indirectness
Psychological change				
Heathcote 2024[347]	5 studies	n = 219	For resilience, self-compassion and self-acceptance, there were significant increases in scores between baseline and post-intervention, and between baseline and 3 months for self-compassion and 6 months for self-acceptance, but the difference was no longer observed for resilience at 3-month follow-up. Participants reported more positive coping and problem-solving and increased confidence. Participants also talked about being more comfortable and accepting of their identity, having a better sense of self and self-worth, and reduced feelings of isolation and distrust towards others.	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.

[345] Dopp et al. (2024).
[346] The sample size was not calculated because one study was an individual case report, and another was a report on parental rating.
[347] Heathcote et al. (2024).

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychosocial change				
Heathcote 2024[348]	5 studies	n = 412	Three studies found significant improvements in quality of life/global functioning/well-being post-intervention and/or at later timepoints. Participants reported having better peer relationships and increased acceptance and/or support from peers (from meeting and forging relationships with others in the same situation).	There is limited research evaluating outcomes of psychosocial interventions for children and adolescents experiencing gender dysphoria/incongruence, and low quality and inadequate reporting of the studies identified. Therefore, firm conclusions about their effects cannot be made.
Evidence synthesis			No conclusion can be drawn on the impact of mental health by psychotherapy.	The certainty of evidence is very low.

[348] Heathcote et al. (2024).

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9 Evidence synthesis: social transition

Two SRs assessed the impact of social transition. Both are assessed at low risk of bias.[349]

9.1 Included SRs on social transition

Dopp 2024

Dopp, A., Peipert, A., Buss, J., De Jesús-Romero, R., Palmer, K., & Lorenzo-Luaces, L. (2024). Interventions for Gender Dysphoria and Related Health Problems in Transgender and Gender-Expansive Youth: A Systematic Review of Benefits and Risks to Inform Practice, Policy, and Research. RAND Corporation; 2024.

Hall 2024

Hall, R., Taylor, J., Hewitt, C. E., Heathcote, C., Jarvis, S. W., Langton, T., . . . Fraser, L. (2024). Impact of social transition in relation to gender for children and adolescents: A systematic review. *Arch Dis Child*, *109*(Suppl 2), s12-s18.

9.2 Outcome 1. Gender dysphoria

Hall 2024[350] reported the impact of social transition on GD based on two observational studies. One study found that children who had socially transitioned were more likely to experience persistence of GD into adolescence compared to those who had not. Another study reported that 92.7% of children who socially transitioned between ages 3 and 12 continued to experience GD an average of 5.4 years later. The systematic review authors did not assess the certainty of evidence, though reported a "lack of robust evidence."

This overview finds the certainty of evidence for effects of social transition on GD is very low.

[349] Dopp et al. (2024); Hall et al. (2024).
[350] Hall et al. (2024).

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9.3 Outcome 2. Mental health and wellbeing

As for mental health outcomes, Dopp 2024[351] reported that social transition among children or adolescents with GD was associated with reduced suicidality and mixed outcomes for depression or mood symptoms. However, associations with other mental health symptoms (e.g., anxiety, substance use, or overall functioning) were inconsistent. The certainty of evidence was very low. The systematic review by Hall 2024[352] highlighted that the evidence on the impact of social transition for children and adolescents with GD is limited and low in quality. Most studies are cross-sectional, US-based, use non-representative samples, and lack appropriate comparator groups. No prospective studies with suitable comparators exist. Furthermore, findings are inconsistent and should be interpreted with caution. For example, some studies suggest benefits from using a chosen name in adolescence, while another found higher rates of suicide attempts and ideation among those who socially transitioned during adolescence compared to those who socially transitioned in adulthood.

In summary, this overview concludes that the certainty of evidence for effects of social transition on mental health and well-being is very low.

9.4 Outcome 3. Regret

There was no evidence on side effects, and Dopp 2024[353] was the only review reporting the regret outcome. Though this systematic review found a low level of regret, the certainty of evidence was assessed as very low.

In conclusion, the evidence is uncertain to determine the regret rate associated with social transition.

9.5 Evidence gap

The impact of social transition on long-term GD, psychological outcomes and well-being, and future treatment decisions such as CSH or surgeries remains poorly understood. Evidence on regret is extremely limited.

[351] Dopp et al. (2024).
[352] Hall et al. (2024).
[353] Dopp et al. (2024).

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Significant evidence gaps remain in the evaluation of social transition as an intervention for children and adolescents with GD. Most available studies are cross-sectional and there are no prospective longitudinal studies with appropriate comparison groups, making it unclear whether observed associations reflect the effects of social transition or other underlying factors. Additionally, studies often did not disentangle the effects of social transition from concurrent interventions such as psychotherapy or medical treatments, further complicating interpretation.

9.6 Summary

In summary, this overview identified two systematic reviews addressing the effects of social transition among children or adolescents with GD. Both reviews were assessed at low risk of bias. The studies reviewed were largely cross-sectional and no high-quality prospective studies with appropriate comparators were identified. This overview finds that the overall certainty of evidence for effects of social transition on children and adolescents with GD is very low, and no reliable conclusions could be drawn regarding the benefits or risks of this intervention.

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9.7 Evidence tables on outcomes for social transition in youth with gender dysphoria

Table 9.1. Summary of evidence on gender dysphoria after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Hall 2024[354]				
Children	2 studies	n = 444	One study found a higher odd of persistence of gender dysphoria/incongruence in adolescence for children who had socially transitioned compared with those who had not socially transitioned. Another study found that 92.7% of those who socially transitioned between ages 3 and 12 continued to experience gender dysphoria/incongruence at the end of the study (on average, 5.4 years after socially transitioning).	There is little evidence of the benefits or harms of social transition in children and adolescents.
Adolescents	1 study	350 participants	Adolescents who preferred to be called by another name compared with no preferred name use reported higher levels of gender distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Evidence synthesis			No conclusion can be drawn on the impact of social transition on gender dysphoria.	The certainty of evidence is very low.[355]

[354] Hall et al. (2024).
[355] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

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Table 9.2. Summary of evidence on mental health and well-being after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
		Suicidality		
Dopp 2024[356]	5 studies	-[357]	Social transition was associated with decreased suicidality in children, adolescents, and young adults with gender dysphoria. The extent to which youth in a sample or subsample were in supportive environments moderated suicidality outcomes in several studies (Campbell, Mann, Rodgers, and Tran, 2023; Turban et al., 2021), such that social transition was associated with greater decreases in suicidality in less supportive environments. An effect size metric was available for about half of reported outcomes, all of which were clinically significant except for the impacts on suicidality in adulthood (Turban et al., 2021) which were statistically but not clinically significant.	Very low certainty due to serious risk of bias, inconsistency, and indirectness
Hall 2024[358]	2 studies	n = 9,840	A cross-sectional study reported that using a chosen name in more contexts was associated with lower suicidal thoughts and behaviors. However, another cross-sectional study[359] found that social transition during adolescence was tied to higher odds of past-year suicidal ideation and lifetime suicide attempts compared to adulthood.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[356] Dopp et al. (2024).
[357] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional studies.
[358] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with those who have not.
[359] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological functioning				
Hall 2024[360]	3 studies	n = 10,077[361]	The studies comparing children experiencing gender dysphoria/incongruence who have socially transitioned with who have not socially transitioned found that the social transition status was not associated with psychological functioning or self-perception.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Non-clinical depression or mood symptoms				
Dopp 2024[362]	6 studies	-[363]	Social transition was associated with a mix of depression or mood symptom outcomes that showed clinically significant decreases and/or showed a lack of statistically significant effects in children, adolescents, and young adults with gender dysphoria. An effect size metric was available for the majority of reported outcomes, all of which were clinically significant or in the nonclinical range (compared to norms or matched samples of cisgender youth) post-intervention.	Very low certainty due to very serious risk of bias and serious indirectness
Depressive and anxiety symptoms				
Hall 2024[364]	2 studies	n = 479	A cross-sectional study reported that adolescents using a preferred name reported fewer depressive symptoms, with no significant difference in anxiety. Another cross-sectional study found that using a chosen name in more social settings was linked to lower depression levels.	There is little evidence of the benefits or harms of social transition in children and adolescents.

[360] Hall et al. (2024); Evidence comparing children with gender dysphoria who have socially-transitioned with those who have not.
[361] One study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 165 socially-transitioned as children.
[362] Dopp et al. (2024).
[363] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[364] Hall et al. (2024); Evidence comparing adolescents with gender dysphoria who have socially-transitioned with who have not

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Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Psychological distress				
Hall 2024[365]	1 study	n = 9,711[366]	A cross-sectional study found no significant link between social transition timing (adolescence vs. adulthood) and severe psychological distress.	There is little evidence of the benefits or harms of social transition in children and adolescents.
Other mental health outcomes				
Dopp 2024[367]	7 studies	-[368]	Social transition did not show consistent associations with other mental health symptoms (beyond depression or mood)—such as anxiety, substance use, or broad measures of mental health symptoms or functioning—in children, adolescents, and young adults with gender dysphoria. Some measures showed a lack of statistically significant change or scores that remained elevated (compared to norms or matched samples of cisgender youth) post-intervention, and/or clinically significant improvements or scores in the nonclinical range. The high level of inconsistency suggests that these outcomes are not a core benefit of social transition. No evidence of mental health harms (e.g., increased symptoms) was found.	Very low certainty due to very serious risk of bias, and serious inconsistency and indirectness
Evidence synthesis			No conclusion can be drawn on the impact of mental health by social transition.	The certainty of evidence is very low. [369]

[365] See above note.
[366] This study (Turban et al. (2021)) reported results from 9,711 socially-transitioned individuals, however, the majority socially-transitioned as adults (n = 8,350), with only 1,196 socially-transitioned as children.
[367] Dopp et al. (2024).
[368] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, cross-sectional study.
[369] Very low certainty due to very serious risk of bias (no prospective longitudinal studies with appropriate comparator group) and serious indirectness concern.

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Table 9.3. Summary of evidence on regret after social transition

Study ID	Included studies (study design)	Number of participants	Conclusion of the review	Certainty of evidence
Dopp 2024[370]	3 studies	-[371] ,	Social transition was found to have a very low rate of detransition to a cisgender identity (3.5%) in children with gender dysphoria, suggesting low rates of regret; data were not available for detransition rates in adolescents or young adults, but rates were lower in older children (Olson et al., 2022). Perspectives among youth who detransitioned were variable, and they did not necessarily regret the transition or reverse all social transition steps (Littman, 2021; Turban, Carswell, and Keuroghlian, 2018).	Very low certainty due to very serious risk of bias, and serious indirectness
Evidence synthesis			There are cases of regret. No conclusion can be drawn on the regret rate after social transition.	The certainty of evidence on regret rate is very low.

[370] Dopp et al. (2024).
[371] The number of participants is not calculated because this review included studies with heterogeneous study types, including studies that were typically not included in a SR assessing treatment effect, for example, individual case report.

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10 Citations for the primary studies included in the SRs on PBs, CSH, and surgeries

Achille 2020

Achille, C., Taggart, T., Eaton, N. R., Osipoff, J., Tafuri, K., Lane, A., . . . Wilson, T. A. (2020). Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: Preliminary results. International Journal of Pediatric Endocrinology, 2020(1), 8. https://doi.org/10.1186/s13633-020-00078-2

Akgul 2019

Akgul, S., Bonny, A. E., Ford, N., Holland-Hall, C., & Chelvakumar, G. (2019). Experiences of gender minority youth with the intrauterine system. J Adolesc Health, 65(1), 32-38. https://doi.org/10.1016/j.jadohealth.2018.11.010

Aldridge 2021

Aldridge, Z., Patel, S., Guo, B., Nixon, E., Pierre Bouman, W., Witcomb, G. L., . . . Arcelus, J. (2021). Long-term effect of gender-affirming hormone treatment on depression and anxiety symptoms in transgender people: A prospective cohort study. Andrology, 9(6), 1808-1816. https://doi.org/https://doi.org/10.1111/andr.12884

Allen 2019

Allen, L. R., Waston, L. B., Egan, A. M., & Moser, C. N. (2019). Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology, 7(3), 302-311. https://doi.org/https://doi.org/10.1037/cpp0000288

Amir 2020

Amir, H., Yaish, I., Samara, N., Hasson, J., Groutz, A., & Azem, F. (2020). Ovarian stimulation outcomes among transgender men compared with fertile cisgender women. J Assist Reprod Genet, 37(10), 2463-2472. https://doi.org/10.1007/s10815-020-01902-7

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Arcelus 2016

Arcelus, J., Claes, L., Witcomb, G. L., Marshall, E., & Bouman, W. P. (2016). Risk factors for non-suicidal self-injury among trans youth. J Sex Med, 13(3), 402-412. https://doi.org/10.1016/j.jsxm.2016.01.003

Arnoldussen 2022

Arnoldussen, M., van der Miesen, A. I. R., Elzinga, W. S., Alberse, A. E., Popma, A., Steensma, T. D., . . . de Vries, A. L. C. (2022). Self-perception of transgender adolescents after gender-affirming treatment: A follow-up study into young adulthood. LGBT Health, 9(4), 238-246. https://doi.org/10.1089/lgbt.2020.0494

Ascha 2022

Ascha, M., Sasson, D. C., Sood, R., Cornelius, J. W., Schauer, J. M., Runge, A., . . . Jordan, S. W. (2022). Top surgery and chest dysphoria among transmasculine and nonbinary adolescents and young adults. JAMA Pediatr, 176(11), 1115-1122. https://doi.org/10.1001/jamapediatrics.2022.3424

Ayyala 2020

Ayyala, H. S., Mukherjee, T. J., Le, T. M., Cohen, W. A., Luthringer, M., & Keith, J. D. (2020). A three-step technique for optimal nipple position in transgender chest masculinization. Aesthet Surg J, 40(11), Np619-np625. https://doi.org/10.1093/asj/sjaa150

Barnard 2019

Barnard, E. P., Dhar, C. P., Rothenberg, S. S., Menke, M. N., Witchel, S. F., Montano, G. T., . . . Valli-Pulaski, H. (2019). Fertility preservation outcomes in adolescent and young adult feminizing transgender patients. Pediatrics, 144(3). https://doi.org/10.1542/peds.2018-3943

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Becker-Hebly 2021

Becker-Hebly, I., Fahrenkrug, S., Campion, F., Richter-Appelt, H., Schulte-Markwort, M., & Barkmann, C. (2021). Psychosocial health in adolescents and young adults with gender dysphoria before and after gender-affirming medical interventions: A descriptive study from the hamburg gender identity service. Eur Child Adolesc Psychiatry, 30(11), 1755-1767. https://doi.org/10.1007/s00787-020-01640-2

Beking 2020

Beking, T., Burke, S. M., Geuze, R. H., Staphorsius, A. S., Bakker, J., Groothuis, A. G. G., . . . Kreukels, B. P. C. (2020). Testosterone effects on functional amygdala lateralization: A study in adolescent transgender boys and cisgender boys and girls. Psychoneuroendocrinology, 111, 104461. https://doi.org/https://doi.org/10.1016/j.psyneuen.2019.104461

Berry 2012

Berry, M. G., Curtis, R., & Davies, D. (2012). Female-to-male transgender chest reconstruction: A large consecutive, single-surgeon experience. J Plast Reconstr Aesthet Surg, 65(6), 711-719. https://doi.org/10.1016/j.bjps.2011.11.053

Bodlund 1996

Bodlund, O., & Kullgren, G. (1996). Transsexualism--general outcome and prognostic factors: A five-year follow-up study of nineteen transsexuals in the process of changing sex. Arch Sex Behav, 25(3), 303-316. https://doi.org/10.1007/bf02438167

Boskey 2023

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Errata to *Treatment for Pediatric Gender Dysphoria: Review of Evidence and Best Practices*

Numerous minor editorial corrections have been made to the originally published version on May 1, 2025 to improve clarity, consistency, and formatting. These include typographical fixes, minor grammatical adjustments, missing bibliography items, and refinements to citations.

The following errata list notes the substantive corrections—that is, changes involving factual clarification, citation accuracy, or correction of misleading or incorrect statements. Page and footnote numbers refer to the current Review document and Appendix 4.

- Appendix 4, Section 1, Figure 1.1 (p. 8): The number of excluded studies was corrected from 3,200 to 3,198. This correction was also made in Section 5.1, Figure 5.1., of the main document.
- Section 4.2.1 (p. 63): The phrase: “recommended that PBs be offered only within a research context until further data are available” was replaced with: “recommended that PBs be offered only as part of a clinical trial until further data are available, and that all potential interventions should be tested within a research context.”
- Section 5.3 (p. 86): The term “irreversible” was corrected to “reversible.”
- Section 6.2.2 (p. 99): “Tordoff et al., 2023” in the section heading was corrected to 2022.
- Section 7.3.5, Footnote 47 (p. 114): The incorrect citation to Shrier (2020) was corrected to Shrier (2021b).
- Section 10.5, Footnote 133 (p. 177): The incorrect amicus curiae brief citation was corrected to Clinical Practice Guideline Experts (2024).
- Section 11.4, Footnote 58 (p. 193): The quotation was previously attributed in part to another source; attribution was corrected to show the entire quotation is from McNamara (2024).

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- Section 12.1 (p. 203): A sentence was corrected to indicate that *Gender-Affirming Psychiatric Care* is a textbook published by the American Psychiatric Association, not a clinical practice guideline.
- Section 12.1 (p. 203): The sentence “Instead, the APA reaffirmed its commitment to existing recommendations without addressing the critiques” and its associated footnote were deleted. The originally-referenced policy was issued by the American Psychological Association, not the American Psychiatric Association.
- Section 14.4, Footnotes 51 and 52 (p. 247): The national origin of treatment recommendations was corrected; the U.K.’s recommendations had been mislabeled as Finland’s, and vice versa.

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