

No. 23-12155

**UNITED STATES COURT OF APPEALS
FOR THE ELEVENTH CIRCUIT**

August Dekker et al.,
Plaintiffs-Appellees,

v.

Secretary, Florida Agency for Health Care Administration et al.,
Defendants-Appellants.

U.S. District Court for the Northern District of Florida, No. 4:22-cv-325
(Hinkle, J.)

APPELLANTS' APPENDIX – VOLUME IV OF XXI

Part 1 of 2

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INDEX TO APPENDIX

Volume	Tab	Title
1	Dkt	Docket Sheet
1	Doc.1	Complaint
1-3	Doc.11	Motion for Preliminary Injunction
3-4	Doc.49	Redacted Defendants' Response in Opposition to Motion for Preliminary Injunction
4-7	Doc 49-1	Redacted Appendix to Defendants' Response in Opposition to Motion for Preliminary Injunction
7-8	Doc.58	Reply to Defendants' Response in Opposition to Motion for Preliminary Injunction
8	Doc.60	Notice of Scrivener's Error and Filing of Supplemental Declaration to Correct Error re: Motion for Preliminary Injunction
8	Doc.64	Order Denying Preliminary Injunction
8	Doc.65	Answer to Complaint
8	Doc.108	Preliminary Injunction Motion Hearing Transcript
8	Doc.118	Order Allowing Mr. Weida's Deposition
8-9	Doc.120	Motion for Summary Judgment
9	Doc.120-27	Attachment to Motion for Summary Judgment: Dr. Edmiston Expert Report
9	Doc.120-36	Attachment to Motion for Summary Judgment: Dr. Edmiston Deposition
9	Doc.233	Amended Complaint
9-12	Doc.235	Plaintiffs' Deposition Designations
12	Doc.246	Final Order
12	Doc.247	Clerk's Judgment
12-13	Doc.248	Notice of Appeal
13-14	Doc.221	Trial Transcript, Day One
14-15	Doc.224	Trial Transcript, Day Two
15-16	Doc.225	Trial Transcript, Day Three
16-17	Doc.229	Trial Transcript, Day Four
17	Doc.232	Trial Transcript, Day Five
17-18	Doc.234	Trial Transcript, Day Six
18	Doc.241	Trial Transcript, Day Seven
18	Doc.193-1, DX1	U.S. Health and Human Services Notice and Guidance on Care

18	Doc.193-2, DX2	U.S. Health and Human Services Fact Sheet on Gender-Affirming Care
18	Doc.193-3, DX3	U.S. Department of Justice Letter to State Attorneys General
18	Doc.193-8, DX8	Sweden's Care of Children and Adolescents with Gender Dysphoria, Summary of National Guidelines
18-19	Doc.193-9, DX9	Finland's Recommendation of the Council for Choices in Health Care in Finland
19	Doc.193-10, DX10	The Cass Review, Independent Review of Gender Identity Services for Children and Young People
19-20	Doc.193-11, DX11	National Institute for Health and Care Excellence, Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria
20	Doc.193-12, DX12	National Institute for Health and Care Excellence, Evidence Review: Gender-Affirming Hormones for Children and Adolescents with Gender Dysphoria
20	Doc.193-13, DX13	France's Academie Nationale de Medecine Press Release
20	Doc.193-14, DX14	The Royal Australian and New Zealand College of Psychiatrists' Position Statement on Gender-Affirming Care
20-21	Doc.193-16, DX16	WPATH Standards of Care, Version 8
21	Doc.193-17, DX17	WPATH Standards-of-Care-Revision Team Criteria
21	Doc.193-24, DX24	Endocrine Society Guidelines on Treatments for Gender Dysphoria

Dated: October 13, 2023

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breasts to treat a psychological condition. *See supra*. The efficacy of mastectomies to treat breast cancer says absolutely nothing about the efficacy of mastectomies to treat gender dysphoria. And as Dr. Laidlaw explains in his expert declaration, accepting a false equivalency between a treatment approved for a specific malady and gender dysphoria would run roughshod over warnings from the Food and Drug Administration, among others, on off-label use of medication. App.799-800.

Indeed, material attached to Plaintiffs' motion supports the State's position on the issue. In a 2022 peer-reviewed paper on the use of puberty blockers, academics from Australia, Idaho, Oregon, and California criticized other researchers for "mislead[ing] clinicians unfamiliar with the literature into prescribing puberty blockers to [gender dysphoric] youth with confidence, when the only clinical stance supported by the evidence is that of extreme caution." Doc.11-1 at 115 (Clayton, *et al.*, 2022). The authors said that "research in this field is rapidly evolving," *id.*, with unscrupulous researchers "trumpet[ing]" "positive outcomes of medical interventions in abstracts" but hiding "their profound limitations" "behind the paywall." *Id.* at 117. It follows that off-label use of drugs like puberty blockers should be closely scrutinized in this "rapidly evolving" field. *Id.* at 115.

III. Irreparable Harm, the Equities, and the Public Interest: Refocusing on the Patients and the Science.

A. As this Court is well-aware, the State is irreparably harmed "when it cannot effectuate its laws," particularly those intended to protect its citizens. *Maryland v. King*,

567 U.S. 1301, 1303 (2012) (Roberts, C.J., in chambers). Yet it’s unclear what, if any, harm Plaintiffs will suffer.

Broadly speaking, most of those with gender dysphoria revert to their birth sex. Many suffer co-morbidities that must be disentangled from the condition at issue (gender dysphoria). Plaintiffs, however, seek a broad, statewide injunction. That’s contrary to this Court’s duty to carefully and narrowly craft injunctive relief. *See generally Ga. Advoc. Off.*, 4 F.4th at 1209.

Plaintiffs also provide no medical records for examination. And Plaintiffs provide no evidence—none—from treating physicians for any of the four individuals who now sue. *See Doe v. Snyder*, 28 F.4th 103, 112 (9th Cir. 2022) (“Relatedly, and significantly, [the plaintiff] failed to provide a declaration from any psychiatrist or medical doctor who is treating him that attested to the necessity and suitability of the surgery in his particular case.”). Dr. Laidlaw has, however, reviewed the Medicaid file for each of the four Plaintiffs.

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- Dr. Cantor responds to Dr. Karasic’s and Dr. Olson-Kennedy’s declarations, which, according to Dr. Cantor, “fail to provide any meaningfully full accounting of the science” and “instead cit[e] and address[] only selective pieces, with language insinuating the presence of evidence that does not exist.” App.383. In particular, Dr. Cantor rebuts Dr. Karasic’s representations of mental health improvement for transitioners, and rebuts Dr. Olson-Kennedy’s claim that affirmation does not increase the probability of unnecessary transition and unnecessary medical risks. App.379-80.
- Dr. Donovan responds to Dr. Karasic’s statement that the State’s actions amount to forced detransitioning. Dr. Donovan criticizes Dr. Karasic for “fail[ing] to see that those pathways upon which he has set patients for ‘gender affirming care’ should have included protocols for the ‘detransitioning’ that patients are already voluntarily seeking in increasing numbers.” App.639.
- Dr. Nangia, a pediatric psychiatrist who has “treated over a thousand patients with gender dysphoria,” states that “children under the age of eighteen should not receive” “puberty blockers, hormone and hormone antagonists, and sex reassignment surgeries” because of their inability “to make very serious medical choices that” will “affect their overall health and self concept for the rest of their lives.” App.614, 632.
- Dr. Zanga and Dr. Kaliebe show that the medical trade groups don’t speak for all physicians struggling to treat patients with gender dysphoria. Dr. Zanga, a fellow at the American Academy of Pediatrics, describes the “undemocratic[]” process by which the organization adopts a policy position. App.744-45. He bluntly states that “[t]here is no review or vote by the remainder of the AAP membership,” and thus the AAP’s policies don’t reflect the views of its members. *Id.* Dr. Kaliebe states that the medical community “has become more tribal, moralizing[,] and more likely to attempt to silence divergent opinions,” which has led to a “suppression of research data, publication bias, and penalizing of divergent viewpoints.” App.843-46.
- Dr. Lappert, Dr. Laidlaw, and Dr. Van Mol state that WPATH’s and the Endocrine Society’s standards of care and guidelines do not reflect

professional consensus and are grounded on biased and low-quality evidence. App.544-45, 566-69, 571-72, 796-801.

- Dr. Laidlaw and Dr. Van Mol state that hormone therapies and surgeries for gender dysphoria can lead to cardiovascular disease, cancer, bone density deficiencies, brain development issues, harms to sexual function, infertility, and permanent sterility. App.527, 823.

In sum, Rule 59G-1.050(7)(a) serves the public interest. From the perspective of the State, which is charged with safeguarding the public's welfare, the rule better accords with the admonition to first do no harm.

IV. Conclusion.

This Court should deny the motion for preliminary injunction. The kind of “extraordinary” and “drastic” relief that Plaintiffs seek is simply not warranted here. *McDonald's Corp.*, 147 F.3d at 1306. The State of Florida has made a measured decision to exclude reimbursement under Medicaid for certain treatments for one medical condition because those treatments threaten to do more harm than good. Neither the law nor the facts provide a basis to undo that decision entrusted to the State.

Respectfully submitted,

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Dated: October 3, 2022

LOCAL RULE CERTIFICATIONS

The undersigned certifies that this memorandum contains 7,989 words, excluding the case style and certifications.

/s/ Mohammad O. Jazil
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CERTIFICATE OF SERVICE

I hereby certify that on October 3, 2022, I electronically filed the foregoing with the Clerk of Court by using CM/ECF, which automatically serves all counsel of record for the parties who have appeared. I hereby certify that a non-redacted response in opposition has been emailed to counsel for Plaintiffs.

/s/ Mohammad O. Jazil
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Doc. 49-1

IN THE UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF FLORIDA
TALLAHASSEE DIVISION

AUGUST DEKKER, et al.,

Plaintiffs,

v.

Case No. 4:22-cv-00325-RH-MAF

SIMONE MARSTILLER, et al.,

Defendants.

**REDACTED DEFENDANTS' APPENDIX TO RESPONSE IN
OPPOSITION TO MOTION FOR PRELIMINARY INJUNCTION**

Given the numerous reports, studies, and attachments referenced in Defendants Secretary Marstiller and the Agency for Health Care Administration's response in opposition, for ease of reference, the Defendants provide this appendix. Appendix cites are referred to as "App." in the response in opposition. Below is a table of contents.

<u>Number</u>	<u>Title</u>	<u>Page</u>
1.	Generally Accepted Professional Medical Standards on the Treatment of Gender Dysphoria	5
1a.	Attachment A to GAPMS Report	53
1b.	Attachment B to GAPMS Report	56
1c.	Attachment C to GAPMS Report (Brignardello-Petersen Report)	59
1d.	Attachment D to GAPMS Report (Cantor Report)	132
1e.	Attachment E to GAPMS Report (Van Meter Report)	204
1f.	Attachment F to GAPMS Report (Lappert Report)	218
1g.	Attachment G to GAPMS Report (Donovan Report)	236
2.	Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition, "DSM-5", Relevant Excerpts	246
3.	Declaration of Matthew Brackett, with Attachments	260

4.	Declaration of Dr. James Cantor, with Attachments	371
5.	Declaration of Dr. Quentin Van Meter, with Attachments	492
6.	Declaration of Dr. Andre Van Mol, with Attachments	520
7.	Declaration of Dr. Patrick Lappert, with Attachments	557
8.	Declaration of Dr. Geeta Nangia, with Attachments	612
9.	Declaration of Dr. G. Kevin Donovan, with Attachments	639
10.	Declaration of Dr. Joseph Zanga, with Attachments	742
11.	Declaration of Dr. Michael K. Laidlaw, with Attachments	770
12.	Declaration of Dr. Kristopher Kaliebe, with Attachments	840
13.	Declaration of C.G.	871
14.	Declaration of Camille Kiefel	878
15.	Declaration of Carol Freitas	885
16.	Declaration of Chloe Cole	892
17.	Declaration of KathyGrace Duncan	900
18.	Declaration of Sydney Wright	905
19.	Declaration of Zoe Hawes	912
20.	Declaration of Yaacov Sheinfeld	919
21.	Declaration of Julie Framingham	925
22.	Declaration of Jeanne Crowley	931

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CERTIFICATE OF SERVICE

I hereby certify that on October 3, 2022, I electronically filed the foregoing with the Clerk of Court by using CM/ECF, which automatically serves all counsel of record for the parties who have appeared.

/s/ Mohammad O. Jazil
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Appendix Attachment

1

Florida Medicaid

Generally Accepted Professional Medical Standards Determination on the Treatment of Gender Dysphoria

June 2022

Ron DeSantis, Governor
Simone Marstiller, Secretary



Contents

Contents	1
Introductory Remarks and Abstract	2
Health Service Summary	4
Literature Review: Introduction	9
Literature Review: Etiology of Gender Dysphoria	10
Literature Review: Desistance of Gender Dysphoria and Puberty Suppression	14
Literature Review: Cross-Sex Hormones as a Treatment for Gender Dysphoria	17
Literature Review: Sex Reassignment Surgery	23
Literature Review: Quality of Available Evidence and Bioethical Questions	27
Coverage Policies of the U.S. and Western Europe	31
Generally Accepted Professional Medical Standards Recommendation	37
Works Cited	39
Attachments	45

Introductory Remarks and Abstract

Generally Accepted Professional Medical Standards

The Secretary of the Florida Agency for Health Care Administration requested that the Division of Florida Medicaid review the treatment of gender dysphoria for a coverage determination pursuant to Rule 59G-1.035, Florida Administrative Code (F.A.C.) (See Attachment A for the Secretary's Letter to Deputy Secretary Tom Wallace). The treatment reviewed within this report included "sex reassignment treatment," which refers to medical services used to obtain the primary and/or secondary physical sexual characteristics of a male or female. As a condition of coverage, sex reassignment treatment must be "consistent with generally accepted professional medical standards (GAPMS) and not experimental or investigational" (Rule 59G-1.035, F.A.C., see Attachment B for the complete rule text).

The determination process requires that "the Deputy Secretary for Medicaid will make the final determination as to whether the health service is consistent with GAPMS and not experimental or investigational" (Rule 59G-1.035, F.A.C.). In making that determination, Rule 59G-1.035, F.A.C., identifies several factors for consideration. Among other things, the rule contemplates the consideration of "recommendations or assessments by clinical or technical experts on the subject or field" (Rule 59G-1.035(4)(f), F.A.C.). Accordingly, this report attaches five assessments from subject-matter experts:

- **Attachment C:** Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.
- **Attachment D:** James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.
- **Attachment E:** Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.
- **Attachment F:** Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.
- **Attachment G:** G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

Abstract

Available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. Studies presenting the benefits to mental health, including those claiming that the services prevent suicide, are either low or very low quality and rely on unreliable methods such as surveys and retrospective analyses, both of which are cross-sectional and highly biased. Rather, the available evidence demonstrates that these treatments cause irreversible physical changes and side effects that can affect long-term health.

Five clinical and technical expert assessments attached to this report recommend against the use of such interventions to treat what is categorized as a mental health disorder (See attachments):

- **Health Care Research:** Brignardello-Petersen and Wiercioch performed a systematic review that graded a multitude of studies. They conclude

that evidence supporting sex reassignment treatments is low or very low quality.

- **Clinical Psychology:** Cantor provided a review of literature on all aspects of the subject, covering therapies, lack of research on suicidality, practice guidelines, and Western European coverage requirements.
- **Plastic Surgery:** Lappert provided an evaluation explaining how surgical interventions are cosmetic with little to no supporting evidence to improve mental health, particularly those altering the chest.
- **Pediatric Endocrinology:** Van Meter explains how children and adolescent brains are in continuous phases of development and how puberty suppression and cross-sex hormones can potentially affect appropriate neural maturation.
- **Bioethics:** Donovan provides additional insight on the bioethics of administering these treatments, asserting that children and adolescents cannot provide truly informed consent.

Following a review of available literature, clinical guidelines, and coverage by other insurers and nations, Florida Medicaid has determined that the research supporting sex reassignment treatment is insufficient to demonstrate efficacy and safety. In addition, numerous studies, including the reports provided by the clinical and technical experts listed above, identify poor methods and the certainty of irreversible physical changes. Considering the weak evidence supporting the use of puberty suppression, cross-sex hormones, and surgical procedures when compared to the stronger research demonstrating the permanent effects they cause, these treatments do not conform to GAPMS and are experimental and investigational.

Health Service Summary

Gender Dysphoria

Frequently used to describe individuals whose gender identity conflicts with their natural-born sex, the term gender dysphoria has a history of evolving definitions during the past decades (Note: This report uses the term “gender” in reference to the construct of male and female identities and the term “sex” when regarding biological characteristics). Prior to the publication of the *Fifth Edition of the Diagnostic and Statistical Manual of Mental Disorders* (DSM-V), the American Psychiatric Association (APA) used the diagnosis of gender identity disorder (GID) to describe individuals who sought to transition to the opposite gender. However, behavioral health clinicians sought a revision after determining that using GID created stigma for those who received the diagnosis. This is despite the APA having adopted GID to replace the previous diagnosis of transsexualism for the exact same reason (APA, 2017).¹

When crafting its new definition and terminology, the APA sought to remove the stigma of classifying as a disorder the questioning of one’s gender identity by focusing instead on the psychological distress that such questioning can evoke. This approach argues that individuals seeking behavioral health and transition services are doing so due to experiencing distress and that gender non-conformity by itself is not a mental health issue. This led to the adoption of gender dysphoria in 2013 when the APA released the DSM-V. In addition to using a new term, the APA also differentiated the diagnosis between children and adolescents and adults, listing different characteristics for the two age groups (APA, 2017).

According to the DSM-V, gender dysphoria is defined as “the distress that may accompany the incongruence between one’s experienced or expressed gender and one’s assigned gender.” As for the criteria to receive the diagnosis, the APA issued stricter criteria for children than adolescents and adults. For the former, the APA states that a child must meet six out of eight behavioral characteristics such as having “a strong desire to be of the other gender or an insistence that one is the other gender” or “a strong preference for cross-gender roles in make-believe or fantasy play.” The criteria for adults and adolescents are less stringent with individuals only having to meet two out of six characteristics that include “a strong desire to be the other gender” or “a strong desire to be rid of one’s primary and/or secondary sexual characteristics.” The APA further notes that these criteria can also apply to young adolescents (DSM-V, 2013).

In 2021, the Merck Manual released a slightly different definition for gender dysphoria, citing that the condition “is characterized by a strong, persistent cross-gender identification associated with anxiety, depression, irritability, and often a wish to live as a gender different from the one associated with the

¹ The concept of gender being part of identity and disconnected from biological sex originated during the mid-twentieth century and was publicized by psychologist John W. Money. His research asserted that gender was a complete social construct and separate from biology, meaning that parents and/or caregivers could imprint on a young child (under three years) the identity of a boy or girl. In 1967, Money’s theories led to a failed experiment on twin boys where physicians surgically transitioned one to appear as a girl. The twin that underwent sex reassignment never fully identified as a female. However, Money never publicly acknowledged this and reported the experiment as a success. Furthermore, he promoted his conclusions across the scientific community, concealing what actually unfolded. As a result, Money’s ideas on gender fluidity served as a basis for performing procedures on children with hermaphroditic features or genital abnormalities. The case reveals how the understanding of a concept (e.g., gender) at any given time can lead to incorrect medical decisions with irreversible consequences (Gaetano, 2015).

sex assigned at birth.” Additionally, the Merck Manual further states that “gender dysphoria is a diagnosis requiring specific criteria but is sometimes used more loosely for people in whom symptoms do not reach a clinical threshold” (Merck Manual, 2021). This definition is largely consistent with the DSM-V but does not emphasize the distress component to the same extent.²

Like other behavioral health diagnoses classified in the DSM-V, gender dysphoria has the following subtypes:

- **Early-Onset Gender Dysphoria:** This subtype begins during childhood and persists through adolescence into adulthood. It can be interrupted by periods where the individual does not experience gender dysphoria signs and may classify as homosexual (DSM-V, 2013).
- **Late-Onset Gender Dysphoria:** Occurring after puberty or during adulthood, this subtype does not begin until late adolescence and can emerge following no previous signs of gender dysphoria. The APA attributes this partially to individuals who did not want to verbalize their desires to transition (DSM-V, 2013).

Further studies have identified additional subtypes of gender dysphoria. In 2018, Lisa Littman introduced the concept of a rapid-onset subtype. Classified as rapid-onset gender dysphoria (ROGD), it features characteristics such as sudden beginnings during or following puberty. However, it differs from the DSM-V definitions because ROGD is associated with other causes such as social influences (e.g., peer groups, authority figures, and media). In other words, adolescents who had no history of displaying typical gender dysphoria characteristics go through a sudden change in identity following intense exposure to peers and/or media that heavily promotes transgender lifestyles (Littman, 2018). While more long-term studies are needed to confirm whether ROGD is a temporary or long-term condition, Littman’s study has initiated discussions regarding potential causes of gender dysphoria as well as introduced a potential subtype.

Additionally, the frequent use of gender dysphoria in clinical and lay discourse has led to a fracturing of the definition. Studies on the topic frequently do not apply the DSM-V’s criteria for the diagnosis and overlook certain key features such as distress. In a 2018 review by Zowie Davy and Michael Toze, the authors evaluated 387 articles that examine gender dysphoria and noted stark departures from the APA’s definition. They further asserted that the APA intended to “reduce pathologization” by establishing a new definition for gender dysphoria in the DSM-V. This in turn would reduce diagnoses, although as Davy and Toze note, the tendency for the literature to diverge from the APA’s definition may result in increased numbers of individuals classified as having gender dysphoria when they do not meet the DSM-V’s criteria (Davy and Toze, 2018). This further raises the question of whether individuals are receiving potentially irreversible treatments for the condition when they might not actually have it.

The current usage of gender dysphoria is the result of discussions spanning across decades as demonstrated in the past editions of the DSM. Until 2013, the APA considered having gender identity issues a mental disorder by itself regardless of the presence of psychological distress. That perspective has since shifted to only consider the adverse psychological effects of questioning one’s gender as a disorder. In addition, the APA considers gender as part of one’s identity, which is not subject to a diagnosis. Whether the APA has shifted its terminology and criteria for gender identity issues due to

² Following the release of the Florida Department of Health’s guidelines for treating gender dysphoria, Merck removed its definition for “gender dysphoria” from the Merck Manual (Fox News, 2022).

emerging clinical data or cultural changes is another question. In 1994, the APA replaced transsexualism with gender identity disorder as part of the “effort to reduce stigma” (APA, 2017). This raises questions about what influences decisions to revise definitions and criteria; is it social trends or medical evidence?

Behavioral Health Issues Co-Occurring with Gender Dysphoria

Because gender dysphoria pertains directly to the distress experienced by an individual who desires to change gender identities, secondary behavioral health issues can co-occur such as depression and anxiety. If left untreated, these conditions can lead to the inability to function in daily activities, social isolation, and even suicidal ideation. Studies do confirm that adolescents and adults with gender dysphoria report higher levels of anxiety, depression, and poor peer relationships than the general population (Kuper et al, 2019). Other associated conditions include substance abuse, eating disorders, and compulsivity. A significant proportion of individuals with gender dysphoria also have autism spectrum disorder (ASD) (Saleem and Rizvi, 2017). Although the number reporting secondary issues is increased, individuals diagnosed with gender dysphoria do not necessarily constitute the entire population that is gender non-conforming (i.e., does not identify with natal sex), and no information is available breaking down the percentage of those who are non-conforming with gender dysphoria and those who are non-conforming with no distress. Additionally, available research raises questions as to whether the distress is secondary to pre-existing behavioral health disorders and not gender dysphoria. This is evident in the number of adolescents who reported anxiety and depression diagnoses prior to transitioning (Saleem and Rizvi, 2017).

Furthermore, conventional treatments for secondary behavioral health issues are available. These include cognitive behavioral therapy, medication, and inpatient services. The APA reports that treatments for these are highly effective with 80% to 90% of individuals diagnosed with depression responding positively (APA, 2020). In addition, a high percentage of adolescents diagnosed with gender dysphoria had received psychiatric treatment for a prior or co-occurring mental health issue. A 2015 study from Finland by Kaltiala-Heino et al noted that 75% of children seeking sex reassignment services had been treated by a behavioral health professional (Kaltiala-Heino et al, 2015).

Diagnosing Gender Dysphoria

Prior to the publication of the DSM-V, diagnosing individuals experiencing gender identity issues followed a different process. Behavioral health clinicians could assign the diagnosis based on gender non-conformance alone. That has changed since 2013. Today, non-conforming to one’s gender is part of personal identity and not a disorder requiring treatment. This change has led professional associations to shift the diagnostic criteria for gender dysphoria to focus on the distress caused by shifting identities (DSM-V, 2013).

For adolescents, the APA identifies “a marked incongruence between one’s experienced/expressed gender and natal sex, of at least 6 months’ duration” as the core component of gender dysphoria (DSM-V, 2013). What the APA does not elucidate is the threshold for “marked.” This raises questions as to whether practitioners exercise uniformity when applying the diagnostic criteria or if they do so subjectively. For example, the WPATH’s *Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People* provides guidance on the processes mental health practitioners should use when assessing for gender dysphoria but offers no benchmarks for meeting diagnostic criteria (WPATH, 2012).

Such processes include evaluating for gender non-conforming behaviors and other co-existing mental disorders like anxiety or depression. This involves not only interviewing the adolescent but also the family in addition to reviewing medical histories. WPATH also asserts that gender dysphoria assessments need to account for peer relationships, academic performance, and provide information of potential treatments. This last component is necessary because it might affect an individual's choices regarding transitioning, particularly if the information does not correspond to the desired outcome (WPATH, 2012).

The diagnosis of gender dysphoria is a relatively recent concept in mental health, being the product of decades of discussion and building upon previous definitions. Instead of treating gender non-conformity as a disorder, behavioral health professionals acknowledge it as part of one's identity and focus on addressing the associated distress. Considering the new criteria, this changes the dynamics of the population who would have qualified for a diagnosis before 2013 and those who would today. Given that desiring to transition into a gender different from natal sex no longer qualifies as a disorder, behavioral health professionals are treating distress and referring adolescents and adults to therapies that are used off-label and pose irreversible effects.

Current Available Treatments for Gender Dysphoria

At present, proposed treatment for gender dysphoria occurs in four stages, beginning with psychological services and ending with sex reassignment surgery. As an individual progresses through each stage, the treatments gradually become more irreversible with surgical changes being permanent. Because of the increasing effects, individuals must have attempted treatment at the previous stage before pursuing the next one (Note: late adolescents and adults have already completed puberty and do not require puberty blockers). Listed in order, the four stages are as follows:

- **Behavioral Health Services:** Psychologists and other mental health professionals are likely the first practitioners individuals with gender dysphoria will encounter. In accordance with clinical guidelines established by the World Professional Association for Transgender Health (WPATH)³, behavioral health professionals are supposed to “find ways to maximize a person's overall psychological well-being, quality of life, and self-fulfillment.” WPATH further discourages services for attempting to change someone's gender identity. Instead, it instructs practitioners to assess for the condition and readiness for puberty blockers or cross-sex hormones while offering guidance to function in a chosen gender. WPATH does assert that the clinicians do need to treat any other underlying mental health issues secondary or co-occurring with gender dysphoria (WPATH, 2012). However, the organization provides conflicting guidance because it also advises practitioners to prescribe cross-sex hormones on demand (Levine, 2018).
- **Puberty Suppression:** Used only on individuals in the earliest stages of puberty (Tanner stage 2), preventing pubertal onset provides additional time to explore gender identities before the physical characteristics of biological sex develop. This treatment is intended to reduce distress and anxiety related to the appearance of adult sexual physical features. To suppress puberty, pediatric endocrinologists inject gonadotropin releasing hormone (Gn-RH) at specific intervals (e.g., 4 weeks or 12 weeks). The Gn-RH suppresses gonadotropin receptors that allow for the

³ The World Professional Association for Transgender Health asserts that it is a professional organization. However, it functions like an advocacy group by allowing open membership to non-clinicians (WPATH, 2022).

development of primary and secondary adult sexual characteristics. Prior to receiving puberty suppression therapy, individuals must have received a diagnosis of gender dysphoria and have undergone a mental health evaluation (Kyriakou et al, 2020).

- **Cross-Sex Hormones:** For adults and late adolescents (16 years or older), the next treatment phase recommended is taking cross-sex hormones (e.g., testosterone or estrogen) to create secondary sex characteristics. In men transitioning into women, these include breast development and widening around the pelvis. Women who transition into men experience deeper voices, redistribution of fat deposits, and growing facial hair. According to the Endocrine Society, late adolescents who qualify for cross-sex hormones must have a confirmed diagnosis of gender dysphoria from a mental health practitioner with experience treating that population. Some physical changes induced by these hormones are irreversible (Endocrine Society, 2017).
- **Sex Reassignment Surgery:** Sometimes referred to as “gender affirming” surgery, this treatment does not consist of just one procedure but several, depending on the desires of the transitioning individual. Primarily, sex reassignment procedures alter the primary and secondary sexual characteristics. Men transitioning into women (trans-females) undergo a penectomy (removal of the penis), orchiectomy (removal of the testes), and vulvoplasty (creation of female genitals). Other procedures trans-females may undergo include breast augmentation and facial feminization. For women that transition into men (trans-males), procedures include mastectomy (removal of the breasts), hysterectomy (removal of the uterus), oophorectomy (removal of the ovaries), and phalloplasty (creation of male genitals). Because of the complexities involved in phalloplasty, many trans-males do not opt for this procedure and limit themselves to mastectomies. Additionally, the effects of sex reassignment surgery, such as infertility, are permanent (WPATH, 2012).

While some clinical organizations assert that they are the standard of care for gender dysphoria, the U.S. Food and Drug Administration (FDA) currently has not approved any medication as clinically indicated for this condition (Unger, 2018). Although puberty blockers and cross-sex hormones are FDA approved, the FDA did not approve them for treating gender dysphoria, meaning that their use for anything other than the clinical indications listed is off-label (American Academy of Pediatrics, 2014). As for surgical procedures, the FDA does not evaluate or approve them, but it does review all surgical devices (FDA, 2021). In addition, the Endocrine Society concedes that its practice guidelines for sex reassignment treatment does *not* constitute a “standard of care” and that its grades for available services are low or very low (Endocrine Society, 2017).⁴

⁴ Disagreement over how to treat gender dysphoria, gender identity disorder, and transsexualism has persisted since sex reassignment surgery first became available in the 1960s. In a 2006 counterargument, Paul McHugh highlights how individuals seeking surgery had other reasons that extended beyond gender identity, including sexual arousal and guilt over homosexuality. In addition, he asserts that undergoing sex reassignment procedures did not improve a patient’s overall behavioral health and that providing a “surgical alteration to the body of these unfortunate people was to collaborate with a mental disorder rather than to treat it” (McHugh, 2006).

Literature Review: Introduction

Currently, an abundance of literature and studies on gender dysphoria is available through academic journals, clinical guidelines, and news articles. Similar to other mental health issues, the material addresses a broad range of topics consisting of available treatments, etiology (i.e., causes), risks, benefits, and side effects. Although most stories reported by the media indicate that treatments such as cross-sex hormones and sex reassignment surgery are the most effective, research reveals that numerous questions still exist. These include what are the long-term health effects of taking cross-sex hormones, what are the real causes of gender dysphoria, and how many individuals that transition will eventually want to revert to their natal sex. Additionally, much of the available research is inconclusive regarding the effectiveness of sex reassignment treatments with multiple studies lacking adequate sample sizes and relying on subjective questionnaires. While much of the scientific literature leans in favor of cross-sex hormones and surgery as options for improving the mental health of individuals with gender dysphoria, it does not conclusively demonstrate that the benefits outweigh the risks involved, either short or long-term. What studies do reveal with certainty is that sex reassignment surgery and cross-sex hormones pose permanent effects that can result in infertility, cardiovascular disease, and disfigurement. All of this indicates that further research is necessary to validate available treatments for gender dysphoria. Thus, physicians, who recommend sex reassignment treatment, are not adhering to an evidence-based medicine approach and are following an eminence-based model.

The following literature review addresses the multiple facets of this condition and presents areas of ongoing debate and persisting questions. Beginning with the condition's etiology and continuing with evaluations of puberty blockers, cross-sex hormones, and surgery, the review explains each area separately and in context of gender dysphoria at large. Additionally, the review provides an analysis on available research on mental health outcomes as well as the condition's persistence into adulthood. Taken as a whole, the available studies demonstrate that existing gender dysphoria research is inconclusive and that current treatments are used to achieve cosmetic benefits while posing risky side effects as well as irreversible changes.

Literature Review: Etiology of Gender Dysphoria

What causes gender dysphoria is an ongoing debate among experts in the scientific and behavioral health fields. Currently, the research indicates that diagnosed individuals have higher proportions of autism spectrum disorder (ASD), history of trauma or abuse, fetal hormone imbalances, and co-existing mental illnesses. Also, experts acknowledge that genetics may factor into gender dysphoria. Another potential cause is social factors such as peer and online media influence. At the moment, none of the studies provides a definite cause and offer only correlations and weakly supported hypotheses. In addition, evidence favoring a biological explanation is highly speculative. However, the research does raise questions about whether treatments with permanent effects are warranted in a population with disproportionately high percentages of ASD, behavioral health problems, and trauma.

In a 2017 literature review by Fatima Saleem and Syed Rizvi, the authors examine gender dysphoria's numerous potential causes and the remaining questions requiring further research. In conclusion, the pair indicate that associations exist between the condition and ASD, schizophrenia, childhood abuse, genetics, and endocrine disruption chemicals but that more research is needed to improve understanding of how these underlying issues factor into a diagnosis. Throughout the review, Saleem and Rizvi identify the following as potential contributing elements to the etiology of gender dysphoria:

- **Neuroanatomical Etiology:** During fetal development, the genitals and brain develop during different periods of a pregnancy, the first and second trimesters respectively. Because the processes are separate, misaligned development is possible where the brain may have features belonging to the opposite sex. The authors identify one study where trans-females presented with a "female-like putamen" (structure at the base of the brain) when undergoing magnetic resonance imaging (MRI) scans.⁵
- **Psychiatric Associations:** Saleem and Rizvi identify multiple studies reporting that individuals with gender dysphoria have high rates of anxiety and depressive disorders with results ranging as high as 70% having a mental health diagnosis. In addition, the pair note that schizophrenia may also influence desires to transition. However, the review does not assess whether the mental health conditions are secondary to gender dysphoria.
- **Autism Spectrum Disorder:** Evidence suggests a significant percentage of individuals diagnosed with gender dysphoria also have ASD. The authors note that the available studies only establish a correlation and do not identify mechanisms for causation.
- **Childhood Abuse:** Like the above causes, Saleem and Rizvi note that those with gender dysphoria tended to experience higher rates of child abuse across all categories, including neglect, emotional, physical, and sexual.
- **Endocrine Disruptors:** Although this cause still requires substantial research, it is a valid hypothesis regarding how phthalates found in plastics can create an imbalance of testosterone in fetuses during gestation, which can potentially lead to gender dysphoria. The authors point to one study that makes this suggestion.

⁵ Research on neuroanatomical etiology for gender dysphoria remains highly speculative due to limitations of brain imaging (Mayer and McHugh, 2016). In addition, neuroscience demonstrates that exposures to certain environments and stimuli as well as behaviors can affect brain changes (Gu, 2014). Furthermore, available research indicates that male and female brains have different physical characteristics but cannot be placed in separate categories due to extensive overlap of white/grey matter and neural connections (Joel et al, 2015).

Saleem and Rizvi's review reveal that gender dysphoria's etiology can have multiple factors, most of which require treatments and therapies not consisting of cross-sex hormones or surgery. (Saleem and Rizvi, 2017).

Out of the research on the condition's etiology, a large portion focuses on the correlation with ASD. One of the more substantial studies by Van der Miesen et al published in 2018 evaluates 573 adolescents and 807 adults diagnosed with ASD and compares them to 1016 adolescents and 846 adults from the general population. The authors' findings note that adolescents and adults with ASD were approximately 2.5 times more likely to indicate a desire of becoming the opposite sex. Although the methodology used to reach this conclusion consisted of surveys where respondents had a choice of answering "never," "sometimes," or "often," the results correspond with those of similar studies. Van der Miesen et al also indicate that most responses favoring a change in gender responded with "sometimes." Additionally, the authors do not state how many in their sample group actually had a gender dysphoria diagnosis. (Van der Miesen et al, 2018).

Another study by Shumer et al from 2016 utilizes a smaller sample size (39 adolescents) referred to an American hospital's gender clinic. Unlike Van der Miesen et al's research, Shumer et al evaluate subjects with a diagnosis of gender dysphoria for possible signs of ASD or Asperger's syndrome. Their findings revealed that 23% of patients presenting at the clinic would likely have one of the two conditions. Possible explanations for the high percentage are the methods used to gather the data. Shumer et al requested a clinical psychologist to administer the Asperger Syndrome Diagnostic Scale to the parents of the sample patients, four of whom already had an ASD diagnosis. The authors conclude that the evidence to support high incidence of gender dysphoria in individuals with ASD is growing and that further research is needed to determine the specific cause (Shumer et al, 2016).

Research indicating a strong correlation between ASD and gender dysphoria is not the only area where new studies are emerging. Discussions about the effects of prenatal testosterone levels are also becoming more prevalent. One such example is Sadr et al's 2020 study that looks at the lengths of the index and ring fingers (2D:4D) of both left and right hands of 203 individuals diagnosed with gender dysphoria. The authors used this method because prenatal testosterone levels can affect the length ratios of 2D:4D. By comparing the ratios of a group with gender dysphoria to a cohort from the general population, Sadr et al could assess for any significant difference. Their results indicated a difference in trans-females who presented with more feminized hands. For trans-males, the difference was less pronounced. The results for both groups were slight, and the meta-analysis that accompanies the study notes no statistically significant differences in multiple groups from across cultures. However, Sadr et al further assert that the evidence strongly suggests elevated prenatal testosterone levels in girls and reduced amounts in boys may contribute to gender dysphoria, requiring additional research (Sadr et al, 2020).

In addition to biological factors and correlations with ASD, researchers are exploring psychological and social factors to assess their role in gender dysphoria etiology. This literature examines a range of potential causative agents, including child abuse, trauma, and peer group influences. One such study by Kozłowska et al from 2021 explores patterns in children with high-risk attachment issues who also had gender dysphoria. The authors wanted to assess whether past incidents of abuse, loss, or trauma are associated with higher rates of persons desiring to transition. As a basis, Kozłowska et al cite John Bowlby's research on childhood brain development, noting that the process is not linear and depends

heavily on lived experiences. The study further acknowledges that biological factors combined with life events serve as the foundation for the next developmental phase and that early poor-quality attachment issues increase the risk for psychological disorders in adolescence and adulthood. Such disorders include mood and affective disorders, suicidal ideations, and self-harm. Kozłowska et al also cite other studies that indicate a high correlation between gender dysphoria and “adverse childhood events” and further assert that the condition “needs to be conceptualized in the context of the child’s lived experience, and the many different ways in which lived experience is biologically embedded to shape the developing brain and to steer each child along their developmental pathway” (Kozłowska et al, 2021).

For their study, Kozłowska et al recruited 70 children diagnosed with gender dysphoria and completed family assessments going back three generations. This in-depth level was necessary to ascertain any and all events that could affect a child’s developmental phases. Additionally, the researchers individually assessed the diagnosed children. To establish comparisons, Kozłowska et al performed assessments on a non-clinical group and a mixed-psychiatric group. Their results demonstrate that children with gender dysphoria have significantly higher rates of attachment issues as well as increased reports of “adverse childhood events” such as trauma (e.g., domestic violence and physical abuse). Furthermore, the authors indicate that a high proportion of families reported “instability, conflict, parental psychiatric disorder, financial stress, maltreatment events, and relational ruptures.” These results led Kozłowska et al to conclude that gender dysphoria can be “associated with developmental pathways – reflected in at-risk patterns of attachment and high rates of unresolved loss and trauma – that are shaped by disruptions to family stability and cohesion.” The study also cites that treatment requires “a comprehensive biopsychosocial assessment with the child and family, followed by therapeutic interventions that address, insofar as possible, the breadth of factors that are interconnected with each particular child’s presentation” (Kozłowska et al, 2021).

This recent study raises questions regarding the medical necessity of gender dysphoria treatments such as puberty blockers and cross-sex hormones for adolescents. If high percentages of children diagnosed with gender dysphoria also have histories of trauma and attachment issues, should conventional behavioral health services be utilized without proposing treatments that pose irreversible effects? Would that approach not provide additional time to address underlying issues before introducing therapies that pose permanent effects (i.e., the watchful waiting approach)?

Aside from the notion that childhood abuse and adversity can potentially cause gender dysphoria, other possible explanations such as social factors (e.g., peer influences and media) may be contributing factors. Research on rapid onset gender dysphoria (ROGD) links this phenomenon to peer and social elements. In an analysis utilizing parent surveys, Lisa Littman asserts that the rapid rise of ROGD is not associated with the traditional patterns of gender dysphoria onset (i.e., evidence of an individual’s gravitation to the opposite sex documented over multiple years) but rather exposure to “social and peer contagion.” Littman uses this term in the context of definitions cited in academic literature, stating that “social contagion is the spread of affect or behaviors through a population” and that “peer contagion is the process where an individual and peer mutually influence each other in a way that promotes emotions and behaviors that can potentially undermine their own development or harm others.” Examples of the latter’s negative effects include depression, eating disorders, and substance abuse. What prompted this study is a sudden increase of parents reporting their daughters declaring themselves to be transgender without any previous signs of gender dysphoria. Littman also indicates

that these parents cite that their daughters became immersed in peer groups and social media that emphasized transgender lifestyles (Littman, 2018).

In addition to identifying characteristics of ROGD, the study examines social media content that provides information to adolescents regarding how to obtain cross-sex hormones through deception of physicians, parents, and behavioral health professionals. Such guidance includes coaching on how to fit a description to correspond to the DSM-V and pressures to implement treatment during youth to avoid a potential lifetime of unhappiness in an undesirable body. Littman further states that “online content may encourage vulnerable individuals to believe that non-specific symptoms and vague feelings should be interpreted as gender dysphoria.” The study also notes that none of the individuals assessed using the parental surveys qualified for a formal diagnosis using the DSM-V criteria (Littman, 2018).

The survey responses revealed similar data to Kozłowska et al’s study with 62.5% of the adolescents having a mental health or neurodevelopmental disorder. Furthermore, the responses indicate a rapid desire to bypass behavioral health options and pursue cross-sex hormones. 28.1% of parents surveyed stated that their adolescents did not want psychiatric treatments. One parent even reported that their daughter stopped taking prescribed anti-depressants and sought advice only from a gender therapist. Littman’s research further reveals that 21.2% of parents responded that their adolescent received a prescription for puberty blockers or cross-sex hormones at their first visit (Littman, 2018). These responses indicate that practitioners do not uniformly follow clinical guidelines when making diagnoses or prescribing treatment.

In the discussion, Littman proposes two hypotheses for the appearance of ROGD. The first states that social and peer contagion is one of the primary causes, and the second asserts that ROGD is a “maladaptive coping mechanism” for adolescents dealing with emotional and social issues. While the surveyed parents did not report early signs of gender dysphoria, a majority noted that their daughters had difficulty in handling negative emotions. Littman concludes that ROGD is distinct from gender dysphoria as described in the DSM-V and that further research is needed to assess whether the condition is short or long-term (Littman, 2018). What the study does not explore, but raises the question, is what proportion of those being treated for gender dysphoria are adolescents with ROGD.

Littman’s study along with the others reveal that the causes of gender dysphoria are still a mystery and could have multiple biological and social elements. Because of this ongoing uncertainty, treatments that pose irreversible effects should not be utilized to address what is still categorized as a mental health issue. That allows adequate opportunity for individuals to receive treatment for co-existing mental disorders, establish their gender dysphoria diagnoses, and understand how cross-sex hormones and surgery will alter the appearance of their bodies as well as long-term health.

Literature Review: Desistance of Gender Dysphoria and Puberty Suppression

The World Professional Association for Transgender Health (WPATH) and the Endocrine Society both endorse the use of gonadotropin releasing hormones (Gn-RH) to suppress puberty in young adolescents who have gender dysphoria. Both organizations state that the treatment is safe and fully reversible. In addition, they state that delaying pubertal onset can provide extra time for adolescents to explore the gender in which they choose to live. The associations further state that puberty suppression is necessary to prevent the development of primary and secondary sexual characteristics that can inhibit successful transitions into adulthood (WPATH, 2012; Endocrine Society, 2017). Of the two groups, WPATH offers clinical criteria an individual should meet to qualify for puberty suppression such as addressing psychological co-morbidities and assessing whether gender dysphoria has intensified (WPATH, 2012).

Neither organization explains that the majority of young adolescents who exhibit signs of gender dysphoria eventually desist and conform to their natal sex and that the puberty suppression can have side effects. Both organizations neglect to mention that using Gn-RH for gender dysphoria by altering the appearance is not an FDA-approved clinical indication. Furthermore, the research used to justify puberty suppression is low or very-low quality and little information is available on long-term effects (Hruz, 2019). Additionally, in his assessment, Quentin Van Meter explained that physical differences between central precocious puberty and natural onset puberty demonstrate that Gn-RH does not have permanent adverse effects for those treated for the former but can for the latter such as insufficient bone-mineral density and neural development (Van Meter, 2022). Also, as recently as May 17, 2022, during a U.S. Senate Committee on Appropriations hearing, Lawrence Tabak, acting director of the National Institutes of Health, responded to Senator Marco Rubio, acknowledging that no long-term studies are available evaluating the effects of puberty blockers when used for gender dysphoria (U.S. Senate Committee on Appropriations, 2022).

Currently, some studies provide weak support for this treatment but leave too many questions as to its effectiveness and medical necessity, especially considering how many children decide against transitioning. In addition, puberty blockers halt development of primary and secondary sexual characteristics and deny opportunities for adolescents to adapt and become comfortable with their natal sex. Instead, puberty blockers can serve as a potential “gateway drug” for cross-sex hormones by denying them the experience of physically maturing (Laidlaw et al, 2018).

A 2013 study by Steensma et al offers data on the percentage of children who opt not to transition after experiencing gender dysphoria. The authors follow 127 adolescents (mean age of 15 during the evaluation period) for four years who had been referred to a Dutch gender dysphoria clinic. Out of this cohort, 47 (37%; 23 boys and 24 girls) continued experiencing the condition and applied for sex reassignment treatment. The other 80 adolescents never returned to the clinic. Because this clinic was the only one that treated gender dysphoria in the Netherlands, Steensma et al assumed that those who did not return no longer desired transitioning. The study indicates one of the key predictors for persisting gender dysphoria was the age of first presentation. Older adolescents that started going to the clinic were more likely to persist, while younger adolescents tended not to follow through. Steensma et al provide further insight into other predicting factors, particularly on how each individual views his or her gender identity. The authors note that adolescents who “wished they were the other sex” were more likely to become desisters and that those who “believed that they were the other sex” persisted

and later sought sex reassignment treatment (Steensma et al, 2013). While the study focuses on factors that contribute to the condition's persistence or desistance, it raises the question as to whether puberty suppression is necessary when age plays such an important role regarding the decision to transition.

WPATH and the Endocrine Society state that the primary reason for initiating pubertal suppression is not to treat a physical condition but to improve the mental health of adolescents with gender dysphoria. However, available research does not yield definitive results that this method is effective at addressing a mental health issue. The "gold standard" for medical studies is the randomized-controlled trial (RCT). Because RCTs utilize large sample sizes, have blind testing groups (i.e, placebos), and use objective controls, they can offer concrete conclusions and shape the array of established treatments. In addition, RCTs require comparisons between cohort outcomes and ensure that participants are randomly assigned to each group. These measures further reduce the potential for bias and subjectivity (Hariton and Locascio, 2018).

Presently, no RCTs that evaluate puberty suppression as a method to treat gender dysphoria are available. Instead, the limited number of published studies on the topic utilize small sample sizes and subjective methods (Hruz, 2019). A 2015 article by Costa et al is one such example. The study asserts that "psychological support and puberty suppression were both associated with an improved global psychological functioning in gender dysphoric adolescents." To reach this conclusion, the authors selected 201 children diagnosed with the condition and divided them into two groups, one to receive psychological support only and the other to get puberty blockers in addition to psychological support. Costa et al did not create a third group that lacked a gender dysphoria diagnosis to serve as a control. To assess whether puberty suppression is an effective treatment, the authors administered two self-assessments (Utrecht Gender Dysphoria Scale and Children's Global Assessment Scale)⁶ to the groups at 6-month intervals during a 12-month period. Because the study relies heavily on self-assessments, the conclusions are likely biased and invalid. Another problem that is also present and common throughout articles supporting puberty suppression is the short-term period of the study. Costa et al's conclusions may not be the same if additional follow-ups occurred three or five years later (Costa et al, 2015). This further raises the question whether low-quality studies like Costa et al's should serve as the basis for clinical guidelines advising clinicians to prescribe drugs for off-label purposes.

Aside from questionable research, information regarding the full physical effects of puberty suppression is incomplete. In a 2020 consensus parameter prepared by Chen et al, 44 experts in neurodevelopment, gender development, and puberty/adolescence reached a conclusion stating that "the effects of pubertal suppression warrant further study." The basis for this was that the "full consequences (both beneficial and adverse) of suppressing endogenous puberty are not yet understood." The participating experts emphasized that the treatment's impact on neurodevelopment in adolescents remains unknown. Chen et al explain that puberty-related hormones play a role in brain development as documented in animal studies and that stopping these hormones also prevents neurodevelopment in addition to sexual maturation. The authors further raise the question whether normal brain development resumes as if it had not been interrupted when puberty suppression ceases. Because this

⁶ Behavioral health practitioners use the Children's Global Assessment Scale (CGAS) to measure child functioning during the evaluation process to determine diagnoses. Available evidence indicates that the CGAS is not effective for evaluating children who experienced trauma and presented with mental health symptoms (Blake et al, 2006).

question remains unanswered, it casts doubt on the veracity of organizations' assertions that puberty suppression is "fully reversible" (Chen et al, 2020).

In addition to the unanswered questions and low-quality research, puberty suppression causes side effects, some of which have the potential to be permanent. According to a 2019 literature review by De Sanctis et al, most side effects associated with Gn-RH are mild, consisting mostly of irritation around injection sites. However, clinicians have linked the drug to long-term conditions such as polycystic ovarian syndrome, obesity, hypertension, and reduced bone mineral density. While reports of these events are low and the authors indicate that Gn-RH is safe for treating central precocious puberty (Note: De Sanctis et al do not consider gender dysphoria in their analysis), the review raises questions about whether off-label use to treat a psychological condition is worth the risks (De Sanctis et al, 2019).

Furthermore, De Sanctis et al cite studies noting increased obesity rates in girls who take Gn-RH but that more research is needed to gauge the consistency. Additionally, the authors note that evidence is strong regarding reduced bone mineral density during puberty suppression but indicate that the literature suggests it is reversible following treatment (De Sanctis et al, 2019). While research leans toward the reversibility of effects on bone mineral density, the quantity of studies available on this subject are limited. Also, no long-term research has been completed on how puberty suppression affects bone growth. This is significant because puberty is when bone mass accumulates the most (Kyriakou et al, 2020). One example of a complication involving bone growth and Gn-RH is slipped capital femoral epiphysis. This condition occurs when the head of the femur (i.e., thighbone) can slip out of the pelvis, which can eventually lead to osteonecrosis (i.e., bone death) of the femoral head. Although the complication is rare, its link to puberty suppression indicates that the "lack of adequate sex hormone exposure" could be a cause (De Sanctis et al, 2019).

The current literature on puberty suppression indicates that using it to treat gender dysphoria is off-label, poses potentially permanent side effects, and has questionable mental health benefits. The limited research and lack of FDA approval for that clinical indication prompt questions about whether medications with physically altering effects should be used to treat a problem that most adolescents who experience it will later overcome by conforming to their natal sex. Additional evidence is required to establish puberty suppression as a standard treatment for gender dysphoria.

Literature Review: Cross-Sex Hormones as a Treatment for Gender Dysphoria

Currently, the debate surrounding the use of cross-sex hormones to treat gender dysphoria revolves around their ability to improve mental health without causing irreversible effects. It is not about whether taking cross-sex hormones can alter someone's appearance. The evidence demonstrating the effectiveness of cross-sex hormones in achieving the secondary sexual characteristics of the opposite sex is abundant. Also, the overall scientific consensus concludes that individuals who take cross-sex hormones will reduce the primary sexual function of his or her natal sex organs. What researchers continue evaluating are the short and long-term effects on mental health, impacts on overall physical health, and how the changes affect the ability to detransition. Of these, benefits to mental health overshadow the other discussions. Prescribers of cross-sex hormones focus so heavily on behavioral health outcomes that they de-emphasize that these drugs cause permanent physical changes and side effects that can lead to premature death (Hruz, 2020). Some clinical guidelines such as WPATH's do not even indicate that some of the changes are irreversible.

Like puberty suppression, the Endocrine Society and WPATH provide guidance on administering cross-sex hormones to individuals with gender dysphoria. Both organizations state that this treatment should not be administered without a confirmed diagnosis of gender dysphoria and only after a full psychosocial assessment. In addition, behavioral health practitioners must ensure that any mental comorbidities are not affecting the individual's desire to transition. WPATH and the Endocrine Society further state that clinicians should administer hormone replacements such as testosterone and Estradiol (estrogen) in gradual phases, where the dose increases over several months. For trans-females, the organizations state that progesterone (anti-androgen) is also necessary to block the effects of naturally produced testosterone (WPATH, 2012; Endocrine Society, 2017). When taking cross-sex hormones, trans-males need increased doses for the first six months. After that, the testosterone's effects are the same on lower doses. Once started, individuals cannot stop taking hormones unless they desire to detransition (Unger, 2016).

Although the two groups provide similar guidance, they vary on statements that can have significant impact on long-term outcomes, particularly regarding age. According to WPATH's standards, 16 years is the general age for initiating cross-sex hormones, but the organization acknowledges that the treatment can occur for younger individuals depending on circumstances (WPATH, 2012). This differs from the Endocrine Society, which states no specific age for appropriateness and explains the disagreements in assigning a number. The group highlights that most adolescents have attained sufficient competence by age 16 but may not have developed adequate abilities to assess risk (Endocrine Society, 2017). This raises the question whether adolescents can make sound decisions regarding their long-term health. Additionally, the varying guidance raises an issue with WPATH not only using age 16 as a standard but also indicating that younger adolescents are capable of making that choice.

WPATH's guidance also does not stress the irreversible nature of cross-sex hormones, citing the treatment as "partially reversible" and not indicating which changes are permanent. Furthermore, parts of WPATH's information are misleading and directly conflict with guidance issued by clinics and other sources. One such example consists of WPATH stating that "hormone therapy *may* (emphasis added) lead to irreversible changes." This statement is misleading in light of existing research, which indicates that multiple physical changes are permanent. In addition, WPATH claims that certain effects of cross-

sex hormones such as clitoral enlargement can last one to two years when it is actually irreversible (UCSF, 2020). WPATH also does not explain the risks to male fertility, noting that lowered sperm count or sterility is “variable.” The University of California at San Francisco (UCSF) provides starkly different information by stating that trans-females should expect to become sterile within a few months of starting cross-sex hormones. UCSF also advises trans-females to consult a sperm bank if they may want to father children after transitioning (WPATH, 2012; UCSF, 2020). Below is a chart that outlines the effects of cross-sex hormones and identifies which ones are reversible or permanent.

Physical Changes Effectuated by Cross-Sex Hormones	
Physical Changes in Trans-Males (Female-to-Male Transitions)	
Physical Change	Reversible or Irreversible
Oily Skin or Acne	Reversible
Facial and Body Hair Growth	Irreversible
Male-Pattern Baldness	Irreversible
Increased Muscle Mass	Reversible
Body Fat Redistribution	Reversible
Ceasing of Menstruation	Reversible
Enlarged Clitoris	Irreversible
Vaginal Atrophy	Reversible
Deepening of Voice	Irreversible
Physical Changes in Trans-Females (Male-to-Female Transitions)	
Body Fat Redistribution	Reversible
Decreased Muscle Mass	Reversible
Skin Softening or Decrease in Oiliness	Reversible
Lower Libido	Reversible
Fewer Spontaneous Erections	Reversible
Male Sexual Dysfunction	Possibly Irreversible
Breast Growth	Irreversible
Decrease in Testicular Size	Reversible
Decrease in Sperm Production or Infertility	Likely Irreversible
Slower Facial and Body Hair Growth	Reversible

Sources: UCSF, 2020; WPATH, 2012; Endocrine Society, 2017⁷

The above chart demonstrates that trans-males and trans-females experience different effects from cross-sex hormones that can cause myriad issues in later life. For example, trans-males who opt to detransition may face challenges related to permanent disfigurement (e.g., facial hair and deepened voices). Trans-females, on the other hand, may not endure the same issues pertaining to visible physical changes but might become despondent over being unable to reproduce. This can occur regardless of whether the transitioning individual is satisfied with sex reassignment. Given that the clinical guidelines do not provide uniform information on the permanent effects of cross-sex hormones, clinicians are unable to make sound recommendations to patients. This treatment can supposedly alleviate symptoms

⁷ This chart consists of conclusions regarding physical changes made by three different clinical organizations. If one organization determined that a physical change was irreversible, that was sufficient to meet the criteria to be listed as “irreversible” in the chart.

of distress. However, cross-sex hormones' permanent effects also have the potential to cause psychological issues.

Arguments favoring cross-sex hormones assert that the desired physical changes can alleviate mental health issues in individuals with gender dysphoria but do not consider that hormones used in this manner, like puberty blockers, are off-label. While the FDA has approved estrogen and testosterone for specific clinical indications (e.g., hypogonadism), it has not cleared these drugs for treating gender dysphoria. Additionally, these arguments do not acknowledge that the U.S. Drug Enforcement Administration (DEA) lists testosterone as a Schedule III controlled substance, meaning that it has a high probability of abuse (DEA, 2022). Furthermore, evidence of psychological benefit from cross-sex hormones is low-quality and relies heavily on self-assessments taken from small sample groups (Hruz, 2020).

A 2019 study by Kuper et al seeks to demonstrate that adolescents desiring cross-sex hormones have elevated rates of depression, anxiety, and challenges with peer relationships. To make their findings, the authors provided questionnaires to 149 adolescents who presented at a gender clinic in Dallas, Texas and concluded that half of the sample group experienced increased psychological issues. One problem with the study is that it relies on parent or self-assessments such as the Youth-Self Report, Body-Image Scale, and the Child Behavior Checklist. While these assessments have strong reliability, the sample is cross-sectional, consisting of gender dysphoric individuals who presented for an initial visit at the clinic. Also, Kuper et al do not directly link these psychological symptoms to gender dysphoria but rather insinuate a strong connection. Without an analysis of the longitudinal histories of the participants, the study cannot demonstrate whether gender dysphoria was a direct cause of the psychological issues, which could possibly result from trauma, abuse, or family dysfunction. Kuper et al's study only presents weak correlation between adolescents who report symptoms of distress and gender dysphoria. While the authors do not claim that the participants' psychological problems caused the condition, they fail to explicitly state that no demonstrable relationship exists and explain that their findings are "broadly consistent with the previous literature" (Kuper et al, 2019).

Additionally, a more comprehensive literature review from 2019 by Nguyen et al evaluates the effect of cross-sex hormones on mental health outcomes. Although the authors argue that the evidence supports the treatment, they do note that available studies use "uncontrolled observational methods" and "rely on self-report." The review also asserts that "future research should focus on applying more robust study designs with large sample sizes, such as controlled prospective cohort studies using clinician-administered ratings and longitudinal designs with appropriately matched control groups." All of these are characteristics of RCTs. While Nguyen et al highlight flaws in the studies in their conclusion, they do not emphasize them in their analysis, opting to focus primarily on results. Another problem with the studies selected for the review is the short-term periods for evaluation. Out of 11 studies Nguyen et al discuss, only one tracks its participants for 24 months. The others only follow their cohorts for 6 or 12 months (Nguyen et al, 2019). Without long-term data to support assertions that cross-sex hormones substantially improve the mental health of individuals with gender dysphoria, the review cannot make definitive conclusions on the treatment's benefits.

Basing their stances on this low-quality evidence, clinical associations such as the American Academy of Pediatrics (AAP) and the American Psychology Association endorse the use of cross-sex hormones as treatments for gender dysphoria. In particular, the AAP discourages use of the term "transition" and

asserts that medical treatments used to obtain secondary characteristics of the opposite sex are “gender affirming.” This decision mirrors the DSM-V’s interpretation of gender being part of identity. The AAP further states that taking cross-sex hormones is an “affirmation and acceptance of who they (i.e., patient) have always been” (AAP, 2018). The American Psychological Association also takes a similar stance in its *Resolution on Gender Identity Change Efforts* by asserting that medical treatments such as puberty suppression, cross-sex hormones, and surgery improve mental health and quality of life and reinforce the notion that transitioning and seeking sex reassignment therapies do not constitute a psychological disorder (American Psychological Association, 2021). Stances like these can substantially influence practitioners and their treatment recommendations. Given that low-quality evidence serves as the basis for supportive positions, this raises questions about whether clinicians can make informed decisions for their patients that will promote the best outcomes.

James Cantor published a critique in 2020 of the AAP’s endorsement of “gender affirming” treatments, arguing that the organization did not base its recommendations on established medical evidence. He asserts that the AAP’s position is based on research that does not support intervention but rather supports “watchful waiting” because most transgender youths desist and identify as their natal sex during puberty. Cantor further argues that the AAP not only disregards evidence but also cites “gender affirming” interventions as the only effective method. To conclude, he states the organization is “advocating for something far in excess of mainstream practice and medical consensus” (Cantor, 2020).

Given those evidentiary problems, those who rely on the AAP’s endorsement as a basis for “gender affirming” treatments are practicing eminence-based medicine as opposed to evidence-based medicine. Eminence-based medicine refers to clinical decisions made by relying on the opinions of prominent health organizations rather than relying on critical appraisals of scientific evidence (Nhi Le, 2016). While it is true that the AAP has more knowledge than a lay person and a degree of credibility in the medical community, the opinions of such organizations are not valid unless they are based on quality evidence.

Research on sex reassignment also does not adequately address the reasons for and prevalence of detransitioning. Although no definite numbers are available regarding the percentage of transgender people who decide to detransition, research indicates that roughly 8% decide to return to their natal sex. The reasons range from treatment side effects to more self-exploration that provided insight on individuals’ gender dysphoria. In a 2020 study by Lisa Littman, 101 people who had detransitioned provided their basis for doing so. Out of the sample group, 96% had taken cross-sex hormones and 33% had sex reassignment surgery. The average age for transitioning was 22 years, and the mean duration for the transition was 4 years. This indicates that even allowing additional time beyond the recommended age of 16 years can still lead to regrets. The study also raises the question as to whether individuals who transitioned at 16 or younger wanted to detransition in greater numbers. The author further offers reasons why these individuals sought cross-sex hormones and surgery, which include having endured trauma (mental or sexual), homophobia (challenged to accept oneself as a homosexual), peer and media influences, and misogyny (applicable only to trans-males). To obtain the results, the participants responded to a survey that asked about their backgrounds (e.g., reasons for transitioning, mental health comorbidities), and motivations for detransitioning. Littman noted that half of the women (former trans-males) had a mental health disorder and/or had experienced trauma within a year of deciding to transition. Men (former trans-females) reported much lower numbers of behavioral health issues and trauma after de-transitioning. Additionally, 77% of men surveyed identified as the opposite gender prior to transition, whereas just 58% of women had (Littman, 2020).

Of the reasons cited for detransitioning, the majority (60%) noted that they became more comfortable with their natal sex. Other reasons included concerns over complications from the treatments, primarily cross-sex hormones, and lack of improved mental health. Other less-cited explanations include concerns about workplace discrimination and worsening physical health. The study also notes that approximately 36% of participants experienced worse mental health symptoms. Based on the findings, Littman concludes that more research is needed in tracking the transgender population to obtain accurate percentages of those who decide to detransition and that men and women reported varying reasons for deciding to transition and later return to their natal sex. The author notes that higher rates of trauma and peer group influences might have contributed to women's decisions, which Littman attributes partially to rapid onset gender dysphoria (Littman, 2020). What the study also indicates is that cross-sex hormones are not a validated treatment for gender dysphoria. Nearly all of the participants had taken them and decided against maintaining the physical changes. Given that the majority of surveyed detransitioners cited that they were comfortable with their biological sex, the study indicates that gender dysphoria is not necessarily a lifelong issue. This necessarily raises doubts about whether cross-hormones, which cause permanent physical damage, is justified.

In addition to the psychological factors, cross-sex hormones pose significant long-term health risks to transitioning individuals. Currently, little information is available given that researchers have not had adequate time to study the effects in this population. However, use of hormones for other conditions has yielded data on how these drugs can affect the body and the cardiovascular system in particular. Because of the high dosages required to achieve physical change and the need to continuously take the drugs, cross-sex hormones can potentially harm quality of life and reduce life expectancy for transitioning individuals. According to Dutra et al, trans-females are three times more likely to die from a cardiovascular event than the general population. In their 2019 literature review, Dutra et al examined the results of over 50 studies evaluating the effects of cross-sex hormones on not only transgender individuals but those with menopause and other endocrine disorders, all of which indicate that use of estrogen or testosterone can increase risks for cardiovascular disease. Throughout their review, Dutra et al cite examples of trans-females having higher triglyceride levels after 24 months of cross-sex hormones and how researchers halted a study on estrogen due to an increase in heart attacks among participants. Another article the authors reference indicates a higher risk for thromboembolisms (i.e., blood clots) in trans-females. For trans-males, Dutra et al explain that research shows significant increased risk for hypertension, high cholesterol, obesity, and heart attacks. One study noted that trans-males have a four times greater risk of heart attack compared to women identifying as their natal sex. Dutra et al conclude that most transgender individuals are younger than 50 and that more studies are needed as this population ages. They do note that available studies indicate that cross-sex hormones pose dangers to long-term cardiovascular health (Dutra et al, 2019).

In sum, the literature reveals that the evidence for cross-sex hormones as a treatment for gender dysphoria is weak and insufficient. Between the permanent effects, off-label use, and consequences to long-term health, cross-sex hormones are a risky option that does not promise a cure but does guarantee irreversible changes to both male and female bodies. Additionally, the inadequate studies serving as the basis for recommendations by clinical associations can lead to providers making poorly informed decisions for their patients. Research asserting that taking cross-sex hormones improves mental health is subjective and short-term. More studies that utilize large sample sizes and appropriate

methods is required before the medical profession should consider cross-sex hormones as one of gender dysphoria's standard treatments.

Literature Review: Sex Reassignment Surgery

The final phase of treatment for gender dysphoria is sex reassignment surgery. This method consists of multiple procedures to alter the appearance of the body to resemble an individual's desired gender. Some procedures apply to the genitals (genital procedures) while others affect facial features and vocal cords (non-genital procedures). While the surgery creates aesthetical aspects, it does not fully transform someone into the opposite biological sex. Transgender persons who undergo the procedures must continue taking cross-sex hormones to maintain secondary sexual characteristics. Additionally, all physical changes are irreversible, and the success rate of a surgery varies depending on the procedure and the population. For example, surgeries for trans-females have much better results than those for trans-males. Complications such as post-operative infections can also arise with the urinary tract system. However, sex reassignment surgery supposedly can provide drastic, if not complete, relief from gender dysphoria (Endocrine Society, 2017). The following is a list of procedures (both genital and non-genital) for trans-females and trans-males that create physical features of the desired sex.

Procedures for Trans-Females

- **Genital Surgeries:** These consist of penectomy (removal of the penis), orchiectomy (removal of the testicles), vaginoplasty (construction of a neo-vagina), clitoroplasty (construction of a clitoris), and vulvoplasty (construction of a vulva and labia). To perform, a surgeon begins by deconstructing the penis and removing the testicles. The penile shaft and glans are repurposed to serve as a neo-vagina and artificial clitoris (Note: These are not actual female genitalia but tissue constructed to resemble female anatomy). If the shaft tissue is insufficient, the surgeon may opt to use a portion of intestine to build a neo-vagina. The scrotum serves as material for fashioning a vulva and labia. In addition to constructing female genitalia, the surgeon reroutes the urethra to align with the neo-vagina. Genital surgeries for trans-females result in permanent sterility (Bizic et al, 2014).
- **Chest Surgery:** To attain full breasts, trans-females can undergo enlargement. The procedure is similar to breast augmentation for women where a surgeon places implants underneath breast tissue. Prior to surgery, trans-females need to take cross-sex hormones for roughly 24 months to increase breast size to get maximum benefit from the procedure (Endocrine Society, 2017).
- **Cosmetic and Voice Surgeries:** Designed to create feminine facial features, fat deposits, and vocal sounds, these procedures are secondary to genital procedures and intended to alter trans-females' appearances to better integrate into society as a member of the desired gender (WPATH, 2012).

Procedures for Trans-Males

- **Mastectomy:** This is the most performed sex reassignment surgery on trans-males because cross-sex hormones and chest-binding garments are often insufficient at diminishing breasts. To remove this secondary sexual characteristic, trans-males can undergo a mastectomy where a surgeon removes breast tissue subcutaneously (i.e., under the skin) and reconstructs the nipples to appear masculine. The procedure can result in significant scarring (Monstrey et al, 2011).
- **Genital Surgeries:** Unlike the procedures for trans-females, genital surgeries for trans-males are more complex and have lower success rates. Consisting of hysterectomy, oophorectomy

(removal of the ovaries), vaginectomy (removal of the vagina), phalloplasty (construction of a penis), and scrotoplasty (construction of prosthetic testicles), a team of surgeons must manufacture a penis using skin from the patient (taken from an appendage) while removing the vagina and creating an extended urethra. The functionality of the artificial penis can vary based on how extensive the construction was. Attaining erections requires additional surgery to implant a prosthesis, and the ability to urinate while standing is often not achieved. Genital procedures for trans-males result in irreversible sterility (Monstrey et al, 2011).

- **Cosmetic Surgeries:** Similar to trans-females, these procedures create masculine facial features, fat deposits, and artificial pectoral muscles. They aid trans-males with socially integrating as their desired gender. Surgery to deepen voices is also available but rarely performed (WPATH, 2012).

Because sex reassignment surgery is irreversible, the criteria for receiving these procedures is the strictest of all gender dysphoria treatments. WPATH and the Endocrine Society suggest rigorous reviews of patient history and prior use of other therapies before approving. Furthermore, the two organizations recommend that only adults (18 years old) undergo sex reassignment surgery.⁸ WPATH and the Endocrine Society also recommend ensuring a strongly documented diagnosis of gender dysphoria, addressing all medical and mental health issues, and at least 12 months of cross-sex hormones for genital surgeries. Although the organizations agree on most criteria, they differ on whether hormones should be taken prior to mastectomies. WPATH asserts that hormones should not be a requirement, whereas the Endocrine Society advises up to 2 years of cross-sex hormones before undergoing the procedure (WPATH, 2012; Endocrine Society, 2017). What this indicates is that trans-males might undergo breast removal without having first pursued all options if their clinician adheres to WPATH's guidelines, which can lead to possible regret over irreversible effects.

As with cross-sex hormones, sex reassignment surgery's irreversible physical changes can potentially show marked mental health improvements and prevent suicidality in people diagnosed with gender dysphoria. In April 2022, the chair of the University of Florida's pediatric endocrinology department, Dr. Michael Haller, advocated for the benefits of "gender affirming" treatments (WUSF, 2020). However, the available evidence calls such statements into question. Recent research assessing both cross-sex hormones and sex reassignment surgery indicate that the effects on "long-term mental health are largely unknown." In studies regarding the benefits of surgery, the results have the same weaknesses as the research for the effectiveness of cross-sex hormones. These include small sample sizes, self-report surveys, and short evaluation periods, all of which are insufficient to justify recommendations for irreversible treatments (Bränström et al, 2020).

Two studies conducted in Sweden provide insight on the effectiveness of sex reassignment surgery in improving the behavioral health of transgender persons. Because Sweden has a nationalized health system that collects data on all residents, this country can serve as a resource to assess service utilization and inpatient admissions. Both studies, one by Dhejne et al from 2011 and another by Bränström et al published in 2020, assessed individuals who had received sex reassignment surgery and examined outcomes over several decades. Dhejne et al's findings indicate that sex reassignment

⁸ Although practice guidelines indicate the minimum age to undergo sex reassignment surgery is 18, available evidence demonstrates that mastectomies have been performed on adolescent girls as young as 13 who experience "chest dysphoria" (Olson-Kennedy et al, 2018).

procedures do not reduce suicidality. The authors explained that individuals who underwent sex reassignment surgery were still more likely to attempt or commit suicide than those in the general population. This study is unique because it monitored the subjects over a long period of time. Dhejne et al note that the transgender persons tracked for the study did not show an elevated suicide risk until ten years after surgery (Dhejne et al, 2011). Given that a high proportion of research follows sex reassignment patients for much shorter timeframes, this evidence indicates that surgery might have little to no effect in preventing suicides in gender dysphoric individuals over the long run.

In addition to having an increased suicide risk, Dhejne et al discuss how individuals who underwent sex reassignment procedures also had higher mortality due to cardiovascular disease. The authors do not list the specific causes but establish the correlation. Given that cross-sex hormones can damage the heart, the increased risk could be related to the drugs and not the surgery. Furthermore, the study explains that the tracked population had higher rates of psychiatric inpatient admissions following sex reassignment. Dhejne et al established this by examining the rates of psychiatric hospitalizations in these individuals prior to surgery and noted higher utilization in the years following the procedures. These results are in comparison to the Swedish population at large. While the study contradicts other research emphasizing improvements in mental health issues, it has its limitations. For example, the sample size is small. Dhejne et al identified only 324 individuals who had undergone sex reassignment surgery between 1973 and 2003. In addition, the authors noted that while the tracked population had increased suicide risks when compared to individuals identifying as their natal sex, the rates could have been much higher if the procedures were not available (Dhejne et al 2011). What this study postulates is that sex reassignment surgery does not necessarily serve as a “cure” to the distress resulting from gender dysphoria and that ongoing behavioral health care may still be required even after a complete transition.

Bränström et al’s study evaluating the Swedish population used a larger sample (1,018 individuals who had received sex reassignment surgery) but tracked them for just a ten-year period (2005 to 2015).⁹ Unlike Dhejne et al, the authors did not track suicides and focused primarily on mood or anxiety disorder treatment utilization. Their results indicate that transgender persons who had undergone surgery utilized psychiatric outpatient services at lower rates and were prescribed medications for behavioral health issues at an annual decrease rate of 8%. Bränström et al also did not limit comparisons to Sweden’s overall population and factored in transgender persons who take cross-sex hormones but have not elected to have surgery. Those results still presented a decrease in outpatient mental health services. However, Bränström et al note that individuals only on cross-sex hormones showed no significant reduction in that category, which calls into question claims regarding effectiveness of cross-sex hormones in ameliorating behavioral issues.

The Bränström et al study prompted numerous responses questioning its methodology. The study lacked a prospective cohort or RCT design, and it did not track all participants for a full ten-year period (Van Mol et al, 2020). These criticisms resulted in a retraction, asserting that Bränström et al’s conclusions were “too strong” and that further analysis by the authors revealed that the new “results demonstrated no advantage of surgery in relation to subsequent mood or anxiety disorder-related

⁹ Although Bränström et al claim to follow individuals for a ten-year period, peer reviews of the research revealed that this was not the case, noting the authors had varying periods of tracking, ranging from one to ten years (Van Mol et al, 2020).

health care visits or prescriptions or hospitalizations following suicide attempts in that comparison” (Kalin, 2020).

There are multiple explanations for why the Bränström et al study reached different results than the Dhejne et al study. For starters, Bränström et al tracked a larger sample group over a later period (2005 to 2015 as opposed to 1973 to 2003) during which gender dysphoria underwent a dramatic shift in definition. Also, Dhejne et al did not see elevated suicides until after ten years, raising the question as to whether sex reassignment surgery has temporary benefits on mental health rather than long-term or permanent benefits. Like the other Swedish study, Bränström et al’s findings are a correlation and do not specifically state that the procedures cause reduced psychiatric service utilization (Bränström et al, 2020).

A 2014 study by Hess et al in Germany evaluated satisfaction with sex reassignment procedures by attempting to survey 254 trans-females on their quality of life, appearance, and functionality as women. Out of the participants selected, only 119 (47%) returned completed questionnaires, which Hess et al indicate is problematic because dissatisfied trans-females might not have wanted to provide input. The results from the collected responses noted that 65.7% of participants reported satisfaction with their lives following surgery and that 90.2% indicated that the procedures fulfilled their expectations for life as women. While these results led Hess et al to conclude that sex reassignment surgery generally benefits individuals with gender dysphoria, the information is limited and raises questions (Hess et al, 2014). Such questions include whether the participants had mental health issues before or after surgery and did their satisfaction wane over time. Hess et al only sent out one questionnaire and not several to ascertain consistency over multiple years. Questions like these raise doubts about the validity of the study. Although Hess et al’s research is just one study, numerous others utilize the same subjective methods to reach their conclusions (Hruz, 2018).

In his assessment, Patrick Lappert contributes additional insight on the appropriate clinical indications for mastectomies, noting that removal of breast tissue is necessary following the diagnosis of breast cancer or as a prophylactic against that disease. He cites that this basis is verifiable through definitive laboratory testing and imaging, making it an objective diagnosis, whereas gender dysphoria has no such empirical methods to assess and depends heavily on the patient’s perspective. Also, Lappert notes that trans-males who make such decisions are doing so on the idea that the procedure will reduce their dysphoria and suicide risk. However, they are making an irreversible choice based on anticipated outcomes supported only by weak evidence, and thus cannot provide informed consent (Lappert, 2022).

The literature is inconclusive on whether sex reassignment surgery can improve mental health for gender dysphoric individuals. Higher quality research is needed to validate this method as an effective treatment. This includes studies that obtain detailed participant histories (e.g., behavioral diagnoses) and track participants for longer periods of time. These are necessary to evaluate the full effects of treatments that cause irreversible physical changes. In addition, sex reassignment procedures can result in severe complications such as infections in trans-females and urethral blockage in trans-males. Health issues related to natal sex can also persist. For example, trans-males who undergo mastectomy can still develop breast cancer and should receive the same recommended screenings (Trum et al, 2015). Until more definitive evidence becomes available, sex reassignment surgery should not qualify as a standard treatment for gender dysphoria.

Literature Review: Quality of Available Evidence and Bioethical Questions

Quality of Available Evidence

Clinical organizations that have endorsed puberty suppression, cross-sex hormones, and sex reassignment surgery frequently state that these treatments have the potential to save lives by preventing suicide and suicidal ideation. The evidence, however, does not support these conclusions. James Cantor notes that actual suicides (defined as killing oneself) are low, occur at higher rates for men, and that interpretations of available research indicate a blurring of numbers between those with gender dysphoria and homosexuals (Cantor, 2022). Although information exists that contradicts certain arguments, media outlets continue to report stories emphasizing the “lifesaving” potential of sex reassignment treatment. A May 2022 story by NBC announced survey results under the headline “Almost half of LGBTQ youths ‘seriously considered suicide in the past year’” (NBC, 2022). This is a significant claim that can have a sensational effect on patients and providers alike, but how strong is the evidence supporting it? Almost all of the data backing this assertion are based on surveys and cross-studies, which tend to yield low-quality results (Hruz, 2018). In addition, how many gender dysphoric individuals are seeing stories in the media and not questioning the narrative? Because research on the effectiveness of treatments is ongoing, a debate persists regarding their use in the adolescent and young-adult populations, and much of it is due to the low-quality studies serving as evidence.

In their assessment, Romina Brignardello-Petersen and Wojtek Wiercioch examined the quality of 61 articles published between 2020 and 2022 (Note: See Attachment A for the full study). They identified research on the effectiveness of puberty blockers, cross-sex hormones, and sex reassignment surgery and assigned a grade (high, moderate, low, or very low) in accordance with the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. Out of the articles reviewed, all with a few exceptions received grades of low or very low quality when demonstrating outcomes regarding improvements in mental health and overall satisfaction with transitioning. For puberty blockers, Brignardello-Petersen and Wiercioch identified low quality evidence for alleviating gender dysphoria and very low quality for reducing suicidal ideation. The authors also had nearly identical findings for cross-sex hormones. However, they noted moderate quality evidence for the likelihood of cardiovascular side effects. Regarding surgery, Brignardello-Petersen and Wiercioch graded articles that examined overall satisfaction and complication rates. None of the studies received grades higher than low quality. These findings led the authors to conclude that “there is great uncertainty about the effects” of sex reassignment treatments and that the “evidence alone is not sufficient to support” using such treatments. Among the studies graded was one the U.S. Department of Health and Human Services cited in its information on “gender affirming” treatments. The authors noted this research had a “critical risk of bias” and was of low quality (Brignardello-Petersen and Wiercioch, 2022).

For his part, James Cantor provided a review of available literature, which addresses studies on etiology, desistance, effectiveness of puberty blockers and cross-sex hormones, suicidal behaviors, and clinical association and international guidelines. Throughout his analysis, Cantor cites weak evidence, poor methodologies (e.g., retrospective versus prospective studies), and lack of professional endorsements in research that indicates the benefits of sex reassignment treatment. Additionally, he notes that improvements in the behavioral health of adolescents who take cross-sex hormones can be attributed to the counseling they receive concurrently and that suicidality is not likely to result from gender

dysphoria but from co-occurring mental disorders. The reasoning behind the third point is based on the blending of suicide and suicidality, which are two distinct concepts. The former refers specifically to killing oneself, and the second regards ideation and threats in attempts to receive help. Cantor specifically notes that actual suicides are highly unlikely among gender dysphoric individuals, particularly trans-males. His other conclusions indicate that young children who experience gender identity issues will most likely desist by puberty, that multiple phenomena can cause the condition, and that Western European health services are not recommending medical intervention for minors. The basis for these statements is the paucity of high to moderate quality evidence on the effectiveness of sex reassignment treatments and numerous studies demonstrating desistance (Cantor, 2022).

Despite the need for stronger studies that provide definitive conclusions, many practitioners stand by the recommendations of the AAP, Endocrine Society, and WPATH. This is evident in a letter submitted to the *Tampa Bay Times*, which was a rebuttal to the Florida Department of Health's (DOH) guidance on treatment for gender dysphoria (Note: The guidance recommends against using puberty blockers, cross-sex hormones, or surgery for minors) (DOH, 2022). The authors, led by six professors at the University of Florida's College of Medicine, state that recommendations by clinical organizations are based on "careful deliberation and examination of the evidence by experts." However, evaluations of these studies show otherwise. Not only does the available research use cross-sectional methods such as surveys, but it provides insufficient evidence based on momentary snapshots regarding mental health benefits. These weak studies are the foundation for the clinical organizations' guidelines that the University of Florida professors tout as a gold standard. In addition, the letter's authors state that DOH's guidance is based on a "non-representative sample of small studies and reviews, editorials, opinion pieces, and commentary" (Tampa Bay Times, 2022). That statement misses the point when it comes to evidence demonstrating whether treatments with irreversible effects are beneficial because the burden of proof is on those advocating for this treatment, not on those acknowledging the need for further research. This raises the question concerning how much academic rigor these professors are applying to practice guidelines released by clinical organizations and whether they also apply the same level of rigor to novel treatments for other conditions (e.g., drugs, medical devices).

Another example of a lack of rigor is a 2019 article by Herman et al from the University of California at Los Angeles (UCLA) that evaluated responses to a 2015 national survey on transgender individuals and suicide. Unlike other studies, this one utilized a large cohort with 28,000 participants from across the U.S. responding. However, the researchers used no screening criteria and did not randomly select individuals. In addition, responses consisted entirely of self-reports with no supporting evidence to even prove a diagnosis of gender dysphoria. Although Herman et al conclude that the U.S. transgender population is at higher risk for suicidal behaviors, the authors' supporting evidence is subjective and serves as a weak basis. Additionally, the survey results do not establish gender dysphoria as a direct cause of suicide or suicidal ideation. The questions required participants to respond about their overall physical and mental health. Out of those that indicated "poor" health, 77.7% reported suicidal thoughts or attempts during the previous year, whereas just 29.1% of participants in "excellent" health had. These percentages indicate that causes beyond gender dysphoria could be affecting suicidal behaviors. Other reasons cited include rejection by family or religious organizations and discrimination. The authors also acknowledge that their findings are broad, not nationally representative, and should serve as a basis for pursuing future research (Herman et al, 2019).

Yet another example is a study published in 2022 by Olson et al tracks 300 young children that identify as transgender over a 5-year period, and asserts low probabilities for detransitioning, while supporting interventions such as puberty blockers. The authors found that children (median age of 8 years) who identified as a gender that differed from their natal sex were unlikely to desist at a rate of 94% and conclude that “transgender youth who socially transitioned at early ages” will continue “to identify that way.” While this appears to contradict earlier studies that demonstrate most young adolescents who change gender identities return to their “assigned gender at birth,” the authors note differences and limitations with the results. For example, Olson et al notes that they did not verify whether the participants met the DSM-V’s diagnostic criteria for gender dysphoria and that the children’s families supported the decisions to transition. Instead, the authors relied on a child’s chosen pronouns to classify as transgender. Also, Olson et al acknowledged that roughly 66% of the sample was biologically male. This is particularly significant considering that the majority of transitioning adolescents in recent years were natal females. Another issue with the study includes the median age at the end of follow-up (13 years), which is when boys begin puberty. Furthermore, the authors cite that the participants received strong parental support regarding the transitions, which constitutes positive reinforcement (Olson et al, 2022). Other research demonstrates that such feedback on social transitioning from parents and peers can prevent desistance following pubertal onset (Zucker, 2019). Despite these limitations, the New York Times announced the study’s publication under the headline “Few Transgender Children Change Their Minds After 5 Years” (New York Times, 2022). Such a title can add to the public’s perception that gender dysphoria requires early medical intervention to address.

Bioethical Questions

The irreversible physical changes and potential side effects of sex reassignment treatment raise significant ethical questions. These questions concern multiple bioethical principles including patient autonomy, informed consent, and beneficence. In a 2019 article, Michael Laidlaw, Michelle Cretella, and Kevin Donovan argue that prescribing puberty blockers or cross-sex hormones on the basis that they will alleviate psychological symptoms should not be the standard of care for children with gender dysphoria. Additionally, the three authors assert that such treatments “constitute an unmonitored, experimental intervention in children without sufficient evidence of efficacy or safety.” The primary ethical question Laidlaw, Cretella, and Donovan pose is whether pushing physical transitioning, particularly without parental consent, violates fully informed consent (Laidlaw et al, 2019).

In accordance with principles of bioethics, several factors must be present to obtain informed consent from a patient. These consist of being able to understand and comprehend the service and potential risks, receiving complete disclosure from the physician, and voluntarily providing consent. Bioethicists generally do not afford the ability of giving informed consent to children who lack the competence to make decisions that pose permanent consequences (Varkey, 2021). Laidlaw, Cretella, and Donovan reinforce this point regarding sex reassignment treatment when they state that “children and adolescents have neither the cognitive nor the emotional maturity to comprehend the consequences of receiving a treatment for which the end result is sterility and organs devoid of sexual function” (Laidlaw et al, 2019). This further raises the question whether clinicians who make such treatment recommendations are providing full disclosure about the irreversible effects and truly obtaining informed consent.

Another issue is the conflict between consumerism and the practitioner's ability to provide appropriate care. Consumerism refers to patients learning about treatments through media/marketing and requesting their health care provider to prescribe it, regardless of medical necessity. Considering that social media is rife with individuals promoting "gender affirmative" drugs and surgeries, children are making self-assessments based on feelings they may not understand and that can lead to deep regret in the future (Littman, 2018). This can contribute to patients applying pressure on their doctors to prescribe medications not proven safe or effective for the condition. Consumerism can also affect bioethical compliance because it constrains clinicians from using their full "knowledge and skills to benefit the patient," which is "tantamount to a form of patient abandonment and therefore is ethically indefensible" (Varkey, 2021).

In his assessment, G. Kevin Donovan explains the bioethical challenges related to sex reassignment treatment, emphasizing the lack of informed consent when administering these services. He asserts that gender dysphoria is largely a self-diagnosis practitioners cannot verify with empirical tests (e.g., labs and imaging) and that providing such treatments is experimental. Because of the lack of consent and off-label use of puberty blockers and cross-sex hormones, Donovan raises the question as to how "experienced and ethical physicians so mislead others or be so misled themselves?" He further attributes this phenomenon to societal and peer pressures that influence self-diagnosis and confirm decisions to transition. As a result, these pressures lead to individuals wanting puberty blockers, cross-sex hormones, and surgery. Donovan goes on to identify several news stories where embracing sex reassignment treatment is a "cult-like" behavior. To conclude, he links these factors back to the failure to obtain informed consent from transgender patients and how that violates basic bioethical principles (Donovan, 2022).

Coverage Policies of the U.S. and Western Europe

U.S. Federal Level Coverage Policies

Medicare: In 2016, the Centers for Medicare and Medicaid Services (CMS) published a decision memo announcing that Medicare Administrative Contractors (MACs) can evaluate sex reassignment surgery coverage on a “case-by-case” basis.¹⁰ CMS specifically noted that the decision memo is not a National Coverage Determination and that “no national policy will be put in place for the Medicare program” (CMS, 2016). This memo was the result of CMS reviewing over 500 studies, reports, and articles to the validity of the procedures. Following its evaluation, CMS determined that “the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding . . . small sample sizes, lack of validated assessment tools, and considerable (number of participants in the studies) lost to follow up.” In 2017, CMS reinforced this position with a policy transmittal that repeated the 2016 memo’s criteria (CMS, 2017).

The basis for Medicare’s decision is that the “clinical evidence is inconclusive” and that “robust” studies are “needed to ensure that patients achieve improved health outcomes.” In its review of available literature, CMS sought to answer whether there is “sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria.” After evaluating 33 studies that met inclusion criteria, CMS’s review concludes that “not enough high-quality evidence” is available “to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively.” Additionally, out of the 33 studies, just 6 provided “useful information” on the procedures’ effectiveness, revealing that their authors “assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies” that “did not demonstrate clinically significant changes or differences in psychometric test results” following sex reassignment surgery (CMS, 2016).

U.S. Department of Defense – Tricare: Tricare does not cover sex reassignment surgery, but it will cover psychological services such as counseling for individuals diagnosed with gender dysphoria and cross-sex hormones when medically necessary (Tricare, 2022).¹¹

U.S. Department of Veterans Affairs: The U.S. Department of Veterans Affairs (VA) does not cover sex reassignment surgery, although it will reimburse for cross-sex hormones and pre- and post-operative care related to transitioning. Because the VA only provides services to veterans of the U.S. armed forces, it cannot offer sex reassignment treatment to children (VA, 2020).¹²

¹⁰ The Centers for Medicare and Medicaid Services is part of the U.S. Department of Health and Human Services. Its primary functions are to administer the entire Medicare system and oversee federal compliance of state Medicaid programs. In addition, CMS sets reimbursement rates and coverage criteria for the Medicare program.

¹¹ Tricare is the insurance program that covers members of the U.S. armed forces and their families. This includes children of all ages.

¹² The U.S. Department of Veterans Affairs oversees the Veterans Health Administration (VHA), which consists of over 1,000 hospitals, clinics, and long-term care facilities. As the largest health care network in the U.S., the VHA provides services to veterans of the U.S. armed forces.

State-Level Coverage Policies

Florida: In April 2022, DOH issued guidance for the treatment of gender dysphoria, recommending that minors not receive puberty blockers, cross-sex hormones, or sex reassignment surgery.¹³ The justification offered for recommending against these treatments is that available evidence is low-quality and that European countries also have similar guidelines. Accordingly, DOH provided the following guidelines:

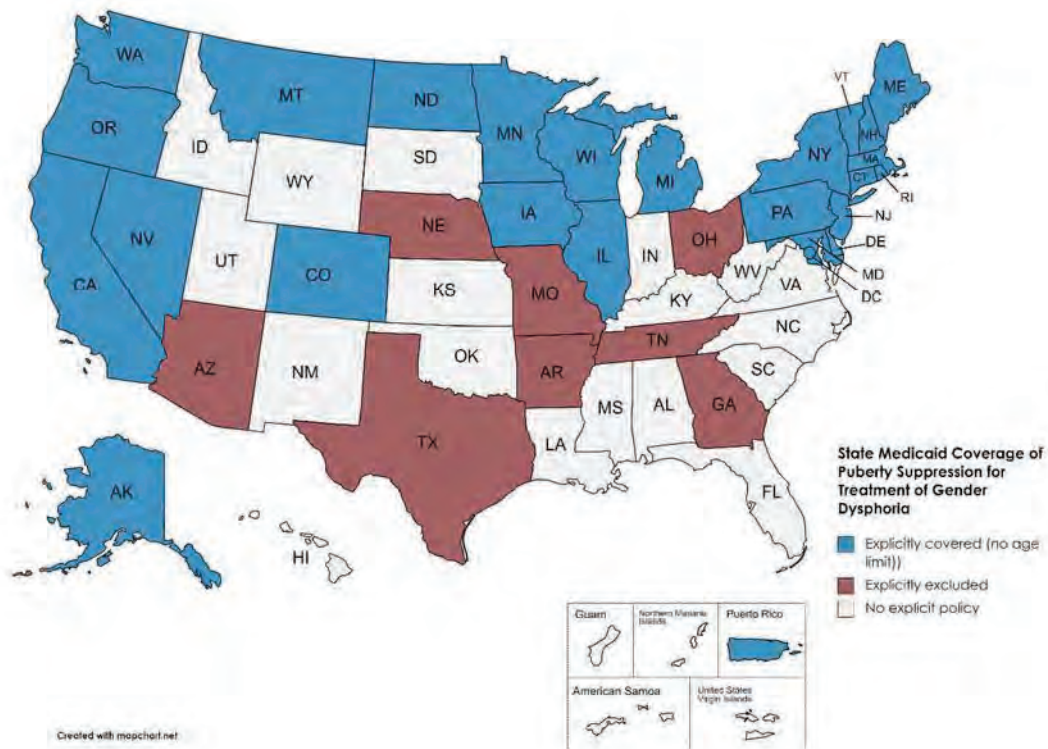
- “Social gender transition should not be a treatment option for children or adolescents.”
- “Anyone under 18 should not be prescribed puberty blockers or hormone therapy.”
- “Gender reassignment surgery should not be a treatment option for children or adolescents.”
- “Children and adolescents should be provided social support by peers and family and seek counseling from a licensed provider.”

In a separate fact sheet released simultaneously with the guidance, DOH further asserts that the evidence cited by the federal government cannot establish sex reassignment treatment’s ability to improve mental health (DOH, 2022).

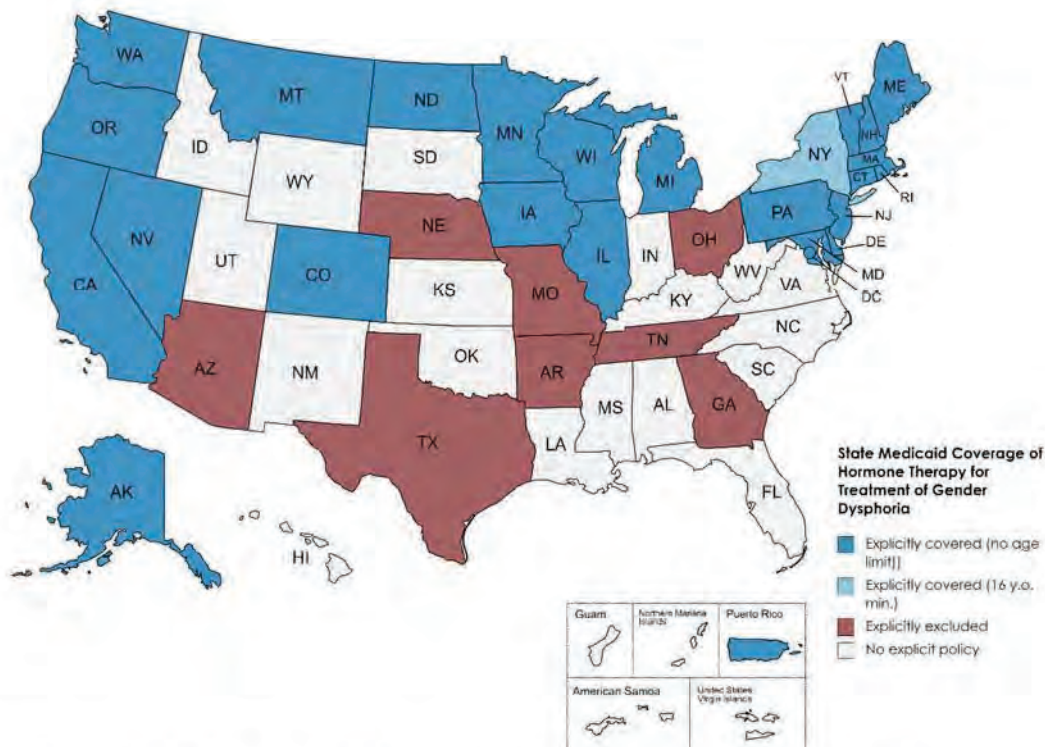
State Medicaid Programs: Because individual states differ in health services offered, Medicaid programs vary in their coverage of sex reassignment treatments. The following maps identify states that cover sex reassignment treatments, states that have no policy, and states that do not cover such treatments.

¹³ Unlike the federal government, the State of Florida delegates responsibilities for Medicaid and health care services to five separate agencies (Agency for Health Care Administration, Department of Health, Department of Children and Families, Department of Elder Affairs, and Agency for Persons with Disabilities). Each agency has its own separate head (secretary or surgeon general), which reports directly to the Executive Office of the Governor. As Florida’s public health agency, DOH oversees all county health departments, medical professional boards, and numerous health and welfare programs (e.g., Early Steps and Women, Infants, and Children). Because it oversees the boards, DOH has authority to release practice guidelines.

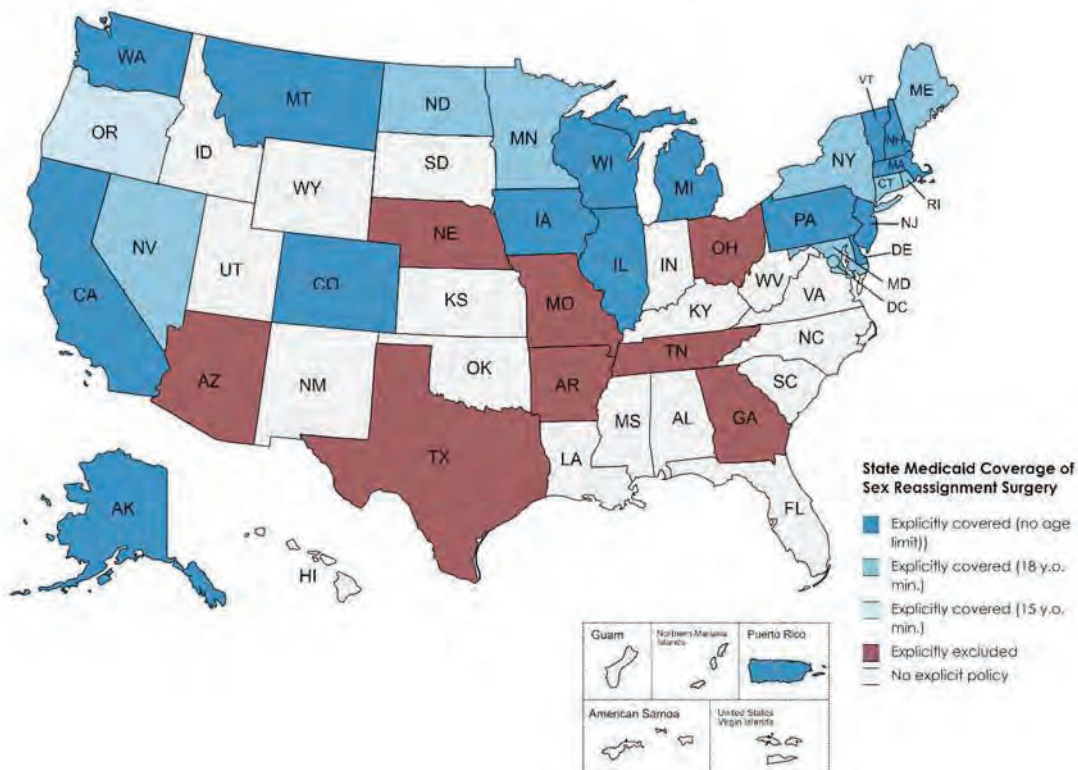
State Medicaid programs with coverage decisions regarding puberty blockers:



State Medicaid programs with coverage decisions regarding cross-sex hormones:



State Medicaid programs with coverage decisions regarding sex reassignment surgery:



Western Europe

Scandinavian countries such as Sweden and Finland have released new guidelines on sex reassignment treatment for children. In 2022, the Swedish National Board of Health stated that “the risks of hormonal interventions for gender dysphoric youth outweigh the potential benefits.” With the exception of youths who exhibited “classic” signs of gender identity issues, adolescents who present with the condition will receive behavioral health services and gender-exploratory therapy (Society for Evidence Based Gender Medicine, 2022).

In Finland, the Palveluvalikoima issued guidelines in 2020 stating that sex reassignment in minors “is an experimental practice” and that “no irreversible treatment should be initiated.” The guidelines further assert that youths diagnosed with gender dysphoria often have co-occurring psychiatric disorders that must be stabilized prior to prescribing any cross-sex hormones or undergoing sex reassignment surgery (Palveluvalikoima, 2020).

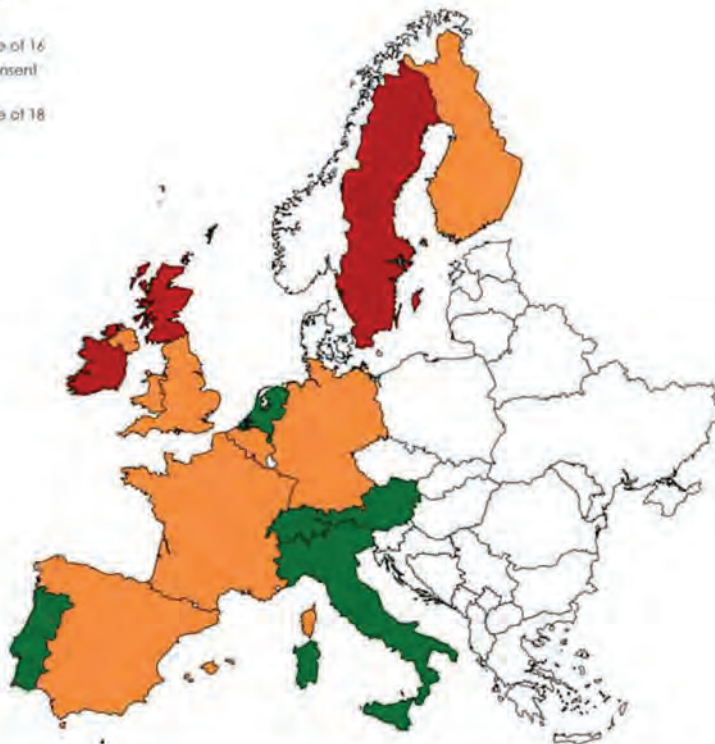
The United Kingdom (U.K.) is also reassessing the use of irreversible treatments for gender dysphoria due the long-term effects on mental and physical health. In 2022, an independent interim report commissioned by the U.K.’s National Health Service (NHS) indicates that additional research and systematic changes are necessary to ensure the safe treatment of gender dysphoric youths. These include reinforcing the diagnosis process to assess all areas of physical and behavioral health, additional training for pediatric endocrinologists, and informing parents about the uncertainties regarding puberty blockers. The interim report is serving as a benchmark until the research is completed for final guidelines (The Cass Report, 2022).

Like state Medicaid programs, health systems across Western Europe also vary in their coverage of sex reassignment treatment.

Western European nations' requirements for cross-sex hormones:

**The Age of Consent for
Hormonal Treatments in
Western Europe**

- Prohibited Under Age of 16
- General Medical Consent Rules Apply*
- Prohibited Under Age of 18

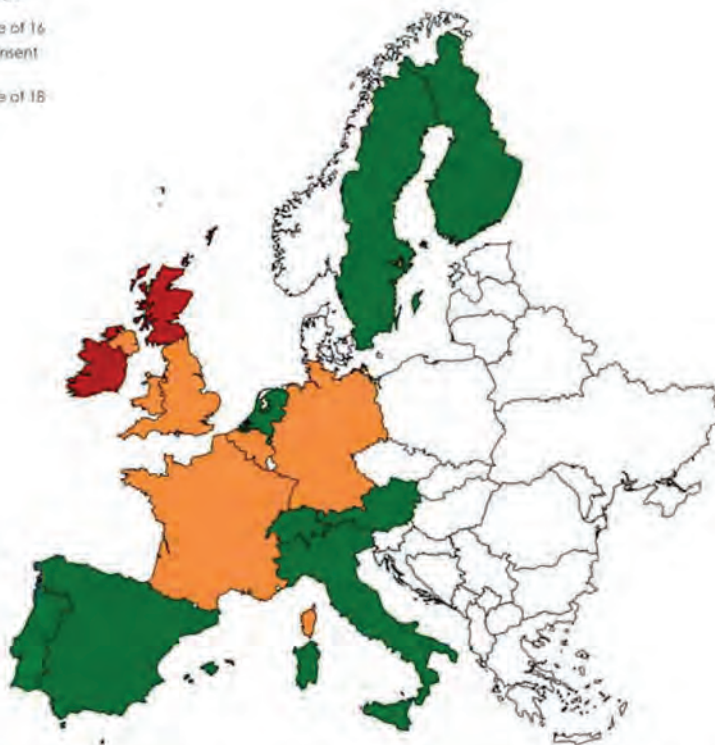


In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Western European nations' requirements for sex reassignment surgery:

The Age of Consent for Surgery in Western Europe

- Prohibited Under Age of 16
- General Medical Consent Rules Apply*
- Prohibited Under Age of 18



In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.

Generally Accepted Professional Medical Standards Recommendation

This report does not recommend sex reassignment treatment as a health service that is consistent with generally accepted professional medical standards. Available evidence indicates that the services are not proven safe or effective treatments for gender dysphoria.

Rationale

The available medical literature provides insufficient evidence that sex reassignment through medical intervention is a safe and effective treatment for gender dysphoria. As this report demonstrates, the evidence favoring "gender affirming" treatments, including evidence regarding suicidality, is either low or very low quality:

- **Puberty Blockers:** Evidence does not prove that puberty blockers are safe for treatment of gender dysphoria. Evidence that they improve mental health and reduce suicidality is low or very low quality.
- **Cross-Sex Hormones:** Evidence suggesting that cross-sex hormones provide benefits to mental health and prevents suicidality is low or very low quality. Rather, evidence shows that cross-sex hormones cause multiple irreversible physical consequences as well as infertility.
- **Sex Reassignment Surgery:** Evidence of improvement in mental health and reduction in suicidality is low or very low quality. Sex reassignment surgery results in irreversible physical changes, including sterility.

While clinical organizations like the AAP endorse the above treatments, none of those organizations relies on high quality evidence. Their eminence in the medical community alone does not validate their views in the absence of quality, supporting evidence. To the contrary, the evidence shows that the above treatments pose irreversible consequences, exacerbate or fail to alleviate existing mental health conditions, and cause infertility or sterility. Given the current state of the evidence, the above treatments do not conform to GAPMS and are experimental and investigational.

Concur

Do not Concur

Comments:



Deputy Secretary for Medicaid (or designee)

6/2/22
Date

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Attachments

Attachment A: Secretary for the Florida Agency for Health Care Administration's Letter to Deputy Secretary Thomas Wallace. 20 April 2022.

Attachment B: Complete text of Rule 59G-1.035, F.A.C.

Attachment C: Romina Brignardello-Petersen, DDS, MSc, PhD and Wojtek Wiercioch, MSc, PhD: *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence*. 16 May 2022.

Attachment D: James Cantor, PhD: *Science of Gender Dysphoria and Transsexualism*. 17 May 2022.

Attachment E: Quentin Van Meter, MD: *Concerns about Affirmation of an Incongruent Gender in a Child or Adolescent*. 17 May 2022.

Attachment F: Patrick Lappert, MD: *Surgical Procedures and Gender Dysphoria*. 17 May 2022.

Attachment G: G. Kevin Donovan, MD: *Medical Experimentation without Informed Consent: An Ethicist's View of Transgender Treatment for Children*. 16 May 2022.

Appendix Attachment

1a

ATTACHMENT A



RON DESANTIS
GOVERNOR

SIMONE MARSTILLER
SECRETARY

April 20, 2022

Tom Wallace
Deputy Secretary for Medicaid
Agency for Health Care Administration
2727 Mahan Drive
Tallahassee, FL 32308

Dear Deputy Secretary Wallace:

On April 20, 2022, the Florida Department of Health released guidance on the treatment of gender dysphoria for children and adolescents.¹ The Florida Medicaid program does not have a policy on whether to cover such treatments for Medicaid recipients diagnosed with gender dysphoria. Please determine, under the process described in Florida Administrative Code Rule 59G-1035, whether such treatments are consistent with generally accepted professional medical standards and not experimental or investigational. Pursuant to Rule 59G-1035(5), I look forward to receiving your final determination.

Sincerely,

A handwritten signature in blue ink that reads "Simone Marstiller". The signature is stylized and includes a large flourish at the end.

Simone Marstiller
Secretary

¹ See <https://www.floridahealth.gov/newsroom/2022/04/20220420-gender-dysphoria-press-release.pr.html> (last visited Apr. 20, 2022).



Appendix Attachment

1b

ATTACHMENT B

59G-1.035 Determining Generally Accepted Professional Medical Standards.

(1) Definitions.

(a) Generally accepted professional medical standards – Standards based on reliable scientific evidence published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations' recommendations.

(b) Health service(s) – Diagnostic tests, therapeutic procedures, or medical devices or technologies.

(c) Relevant – Having a significant and demonstrable bearing on the matter at hand.

(2) Pursuant to the criteria set forth in subparagraph 59G-1.010(166)(a)3., Florida Administrative Code (F.A.C.), the Agency for Health Care Administration (hereafter referred to as Agency) will determine when health services are consistent with generally accepted professional medical standards and are not experimental or investigational.

(3) Health services that are covered under the Florida Medicaid program are described in the respective coverage and limitations handbooks, policies, and fee schedules, which are incorporated by reference in the F.A.C. The public may request a health service be considered for coverage under the Florida Medicaid program by submitting a written request via e-mail to HealthServiceResearch@ahca.myflorida.com. The request must include the name, a brief description, and any additional information that supports coverage of the health service, including sources of reliable evidence as defined in paragraph 59G-1.010(84)(b), F.A.C.

(4) To determine whether the health service is consistent with generally accepted medical standards, the Agency shall consider the following factors:

(a) Evidence-based clinical practice guidelines.

(b) Published reports and articles in the authoritative medical and scientific literature related to the health service (published in peer-reviewed scientific literature generally recognized by the relevant medical community or practitioner specialty associations).

(c) Effectiveness of the health service in improving the individual's prognosis or health outcomes.

(d) Utilization trends.

(e) Coverage policies by other creditable insurance payor sources.

(f) Recommendations or assessments by clinical or technical experts on the subject or field.

(5) Based upon the information collected, a report with recommendations will be submitted to the Deputy Secretary for Medicaid (or designee) for review. The Deputy Secretary for Medicaid (or designee) will make a final determination as to whether the health service is consistent with generally accepted professional medical standards and not experimental or investigational.

(6) In order for the health service to be covered under the Florida Medicaid program, it must also meet all other medical necessity criteria as defined in subsection 59G-1.010(166), F.A.C., and funded through the General Appropriations Act or Chapter 216, F.S.

Rulemaking Authority 409.919 FS. Law Implemented 409.902, 409.906, 409.912, 409.913 FS. History—New 2-26-14, Amended 9-28-15.

Appendix Attachment

1c

ATTACHMENT C

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence

Romina Brignardello-Petersen, DDS, MSc, PhD
Wojtek Wiercioch, MSc, PhD

1. Introduction

We prepared this report to fulfill a request from the Florida Agency for Health Care Administration. This report contains three documents: 1. Main document (this document) summarizing the methodology used and the findings, 2. Methods document, which provides a detailed description of the systematic methodology used to find, prioritize, appraise, and synthesize the evidence, and 3. Results document, which describes the evidence available, the estimates of the effects of gender affirming therapies, and the certainty (also known as quality) of the evidence.

This document is organized in four parts. First, we describe the credentials and expertise of the health research methodologists conducting this evidence evaluation. Second, we summarize the methodology used. Third, we summarize the main findings. Finally, we briefly discuss strengths and limitations of our process and of the evidence.

2. Credentials and expertise

Two experts in health research methodology, who specialize in evidence synthesis to support decision making, prepared this report. Their relevant credentials and expertise are described below.

Dr. Romina Brignardello-Petersen: Assistant Professor at the Department of Health Research Methods, Evidence, and Impact, at McMaster University. Dr. Brignardello-Petersen obtained a DDS degree (University of Chile) in 2007, an MSc degree in Clinical Epidemiology and Health Care Research (University of Toronto) in 2012, and MSc in Biostatistics (University of Chile) in 2015, and a PhD in Clinical Epidemiology and Health Care Research (University of Toronto) in 2016. Dr. Brignardello-Petersen has worked in evidence synthesis projects since 2010, and her research has focused on the methodology for the development of Systematic Reviews and Clinical Practice Guidelines since 2012. Through January 2022, she has published 122 peer reviewed scientific articles (24 as a first author and 9 as a senior author). Dr. Brignardello-Petersen has acted as a research methodologist for several groups and organizations, including the World Health Organization, the Pan-American Health Organization, the American Society of Hematologists, the American College of Rheumatology, and the Society for Evidence Based Gender Medicine, among others. Her research program has been awarded over \$2M CAD from the Canadian Institutes for Health Research. Dr. Brignardello-Petersen has no lived experience as a person or family member of a person with gender dysphoria, and her research interests are not in this area.

Dr. Wojtek Wiercioch: Postdoctoral Research Fellow at the Department of Health Research Methods, Evidence, and Impact, at McMaster University. Dr. Wiercioch obtained an MSc degree (2014, McMaster University) and a PhD degree (2020, McMaster University) in Health Research Methodology. Dr. Wiercioch has worked in evidence syntheses projects since 2011, and his research focuses on evidence synthesis, guideline development methodology, and the guideline development process. Through April

2022, he has published 86 peer-reviewed scientific articles. Dr. Wiercioch has acted as a guideline methodologist for several groups and organizations, including the World Health Organization, the American Society of Hematologists, the Endocrine Society (of America), and the American Association for Thoracic Surgeons, among others. Dr. Wiercioch has no lived experience as a person or family member of a person with gender dysphoria, and his research interests are not in this area.

3. Methods

We conducted an overview of systematic reviews. We used a reproducible approach to search, select, prioritize, appraise, and synthesize the available evidence, following high methodological standards. We describe full details of the methodology in an accompanying document.

In brief, we searched for systematic reviews published in English language in Epistemonikos, OVID Medline, and grey literature sources, through April 30, 2022. We selected systematic reviews which included studies on young individuals with a diagnosis of gender dysphoria, who received puberty blockers, cross-sex hormones, or surgeries; and in which authors reported data regarding outcomes important to patients: gender dysphoria, depression, anxiety, quality of life, suicidal ideation, suicide, adverse effects, and complications. Systematic reviews could have included any type of primary study design.

The two reviewers screened all titles and abstracts, followed by full text of potentially relevant systematic reviews. We then prioritized the most useful systematic review providing evidence for each of the outcomes, using pre-established criteria that considered date of publication, applicability, availability of outcome data, methodological quality of the systematic review, and usefulness of the data synthesis conducted in the systematic review (see methods document for details).

After abstracting data from the systematic reviews, we synthesized the best available evidence for each of the outcomes, and assessed the certainty (also known as quality) of the evidence using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach. We conducted GRADE assessments using the information provided by the systematic review authors (risk of bias of primary studies, characteristics of included studies, results reported by the studies). We present the all the information about outcomes in GRADE summary of findings tables.

In addition, to evaluate the robustness of our conclusions, we systematically searched for and evaluated primary studies answering the questions of interest published after the authors of the included systematic reviews conducted their searches.

4. Results

We included 61 systematic reviews, from which 3 addressed the effects of puberty blockers, 22 addressed the effects of cross-sex hormones, 30 addressed the effects of surgeries, and 6 addressed the effects of more than one of these interventions. After our prioritization exercise, we included information from 2 systematic reviews on puberty blockers, 4 on cross-sex hormones, and 8 on surgeries.

4.1 Puberty blockers

For most outcomes (except suicidality), there is no evidence about the effect of puberty blockers compared to not using puberty blockers. In other words, no studies compared the outcomes between a group of people with gender dysphoria using puberty blockers and another group of people with gender dysphoria not using them. Therefore, it is unknown whether people with gender dysphoria who use puberty blockers experience more improvement in gender dysphoria, depression, anxiety, and quality of life than those with gender dysphoria who do not use them. There is very low certainty about the effects of puberty blockers on suicidal ideation.

The studies included in the systematic review reported outcomes among a group of people with gender dysphoria after receiving puberty blockers. Low certainty evidence suggests that after treatment with puberty blockers, people with gender dysphoria experience a slight increase in gender dysphoria, and an improvement in depression, and anxiety. Low certainty evidence also suggests that a moderate percentage of patients experience adverse effects. The findings must be interpreted considering that these studies did not have a comparison group, and that it is unknown if people with gender dysphoria that do not use puberty blockers experience similar or different outcomes.

4.2 Cross sex hormones

For almost all outcomes (except breast cancer) there is no evidence about the effect of cross sex hormones compared to not using cross sex hormones. In other words, no studies compared the outcomes between a group of people with gender dysphoria using cross sex hormones and another group of people with gender dysphoria not using them. Therefore, it is unknown whether people with gender dysphoria who use cross-sex hormones experience more improvement in gender dysphoria, depression, anxiety, quality of life, and suicidality than those with gender dysphoria who do not use cross-sex hormones. There is low certainty evidence suggesting that cross-sex hormones may not increase the risk of breast cancer.

The studies included in the systematic reviews reported changes in the outcomes among a group of patients with gender dysphoria after the use of cross-sex hormones. Low certainty evidence suggests that after treatment with cross-sex hormones, people with gender dysphoria experience an improvement in gender dysphoria, depression, anxiety, and suicidality. There is very low certainty evidence about the changes in quality of life. There is moderate certainty evidence suggesting a low prevalence of venous thromboembolism after treatment with cross-sex hormones. The findings must be interpreted considering that these studies did not have a comparison group, and that it is unknown if people with gender dysphoria that do not use cross-sex hormones experience similar or different outcomes.

4.3 Surgeries

There were no systematic reviews and studies reporting on gender dysphoria, depression, anxiety, and suicidality. Therefore, the effects of surgeries on these outcomes (when compared to a group of patients with gender dysphoria who do not undergo surgery), or the changes in these outcomes (improvements or deterioration) among patients who undergo any gender-affirming surgery is unknown. Because of the lack of comparative studies, it is also unknown whether people with gender dysphoria who undergo surgeries experience more improvement in quality of life or less regret than those with gender dysphoria who do not undergo any surgeries. There is low certainty evidence suggesting that a low percentage of participants experience regret, and very low certainty evidence about changes in quality of life after surgery.

In assigned females at birth, low certainty evidence suggests that a high percentage of people are satisfied after chest surgery. There is very low certainty evidence, however, about satisfaction after bottom surgery, and about complications after both chest and bottom surgery. In assigned males at birth, low certainty evidence suggests a high percentage of people satisfied and a low percentage of people experiencing regret after vaginoplasty. There is very low certainty, however, about satisfaction with chest surgery and complications and reoperations after bottom surgery.

4.4 Evidence published after the systematic reviews selected

We found 10 relevant studies that were published after the systematic reviews were conducted. This evidence was not sufficient to importantly change the conclusions previously made.

5. Discussion

5.1 Summary of the evidence

In this report, we systematically summarized the best available evidence regarding the effects of puberty blockers, cross-sex hormones, and surgeries in young people with gender dysphoria. We did not find evidence about the effect of these interventions on outcomes important to patients when compared to not receiving the intervention. We found low and very low certainty evidence suggesting improvements in gender dysphoria, depression, anxiety, and quality of life, as well as low rates of adverse events, after treatment with puberty blockers and cross-sex hormones.

5.2 Completeness and applicability

There are several gaps in the evidence regarding the effects of puberty blockers, cross-sex hormones, and surgeries in patients with gender dysphoria. Although we found some evidence for all the outcomes of interest, the evidence is suboptimal; several limitations included the lack of studies with a comparison group, and the risk of bias and imprecision, resulting in low or very low certainty evidence for all outcomes.

The applicability of the evidence may also be limited. Although we only rated down for indirectness when it was considered a serious problem (i.e., in evidence about the effects of surgeries, which was collected from people who were importantly older than the target population in this report), there are also potential applicability issues to consider in the evidence regarding the effects of puberty blockers and cross-sex hormones. It is not clear to what extent the people included in the studies were similar enough to the people seeking these treatment options today. For example, some of the included studies were conducted in people who had a diagnosis of gender dysphoria confirmed with strict criteria, as well as a supportive environment. It is important to take into account to what extent this may compromise the applicability of the results to people who are not in the same situation.

5.3 Strengths and limitations of the process for developing this report

We followed a reproducible process for developing this report. We used the highest methodological standards and the approach to evidence synthesis we generally use when supporting organizations in the development of their guidelines. This approach is based on prioritizing the sources of evidence most likely to be informative (i.e., to identify and use the evidence with the highest certainty level).

To follow the principles for evidence-based decision making, which require using the best available evidence to inform decisions, we summarized the best available evidence. Because knowing the best

available evidence necessitates being aware of all the available evidence, we based this report on systematic reviews of the literature. We chose the most trustworthy and relevant systematic reviews among many published reviews.

One potential limitation of the process is that, due to feasibility concerns, we relied on the information reported by the systematic reviewers. Most of the systematic reviews we used, unfortunately, were judged at moderate or low methodological quality, which may raise concerns about the trustworthiness of the evidence presented in this report. We believe, however, that the results and conclusions of this report would not be importantly different had the systematic reviews been conducted following higher methodological standards. Because there are no randomized controlled trials, well-conducted comparative observational studies, or very large case series (which include a large sample of consecutive patients who are representative of the whole population) addressing the effects of puberty blockers, cross-sex hormones, and surgeries; the certainty of the evidence about the effects of these interventions is likely to continue being low or very low, even if a few more studies are included (as observed after searching for primary studies published after the reviews were conducted) or some data points were reported inaccurately in the systematic reviews.

Also due to feasibility concerns, the scope of this report was limited to outcomes that are important to patients. Although some may question the decision of not including surrogate outcomes for which there is evidence available (e.g. bone density, blood pressure), decision makers should rarely consider these outcomes and should instead focus on outcomes that do matter to people and stakeholders (e.g., fractures, cardiovascular events).

5.4 Implications

The evidence evaluating the effects of puberty blockers, cross-sex hormones, and surgeries in people with gender dysphoria has important limitations. Therefore, decisions regarding their use should carefully consider other relevant factors. At a patient level, these factors include patients' values and preferences (how patients trade off the potential benefit and harms - what outcomes are more important to them), and resources needed to provide the interventions (and the availability of such resources). At a population level, in addition to these factors, it would be important to consider resources needed to implement the interventions, feasibility, acceptability by relevant stakeholders, and equity.

It is important to note that when there is low or very low certainty evidence, it is rarely appropriate to make decisions that will be applied to the majority of the patients (equivalent to strong recommendations). This implies, at the patient level, that shared decision making is a key part of the decision-making process. At a policy level, extensive debate may be needed.

6. Conclusions

Due to the important limitations in the body of evidence, there is great uncertainty about the effects of puberty blockers, cross-sex hormones, and surgeries in young people with gender dysphoria. This evidence alone is not sufficient to support whether using or not using these treatments. We encourage decision makers to be explicit and transparent about which factors play an important role in their decision, and how they are weighed and traded off.

Methods

To ensure completeness and feasibility of the evidence review, we used an approach in which we prioritized the types of studies according to the design that was more likely to provide the best available evidence. First, we searched for systematic reviews of the literature. Second, we appraised all existing systematic reviews to select the most trustworthy (highest methodological quality, most up-to-date, most applicable) from which to draw conclusions. Third, we used the information presented in the systematic reviews to abstract information regarding the effects of the interventions of interest. Fourth, we assessed the certainty of the evidence (also known as quality of the evidence) abstracted from the selected systematic reviews. We planned to search for primary studies if systematic reviews were not found.

Information sources: We searched for existing systematic reviews in:

1. Epistemonikos (<https://www.epistemonikos.org>), an electronic database that focuses on systematic reviews. We used a comprehensive search strategy based on the population, using the terms “gender dysphoria”, “gender identity disorder” and “transgender”. We conducted this search on April 23, 2022.
2. OVID Medline. We used a search strategy based on the population and the interventions of interest, as well as an adaptation of a filter for systematic reviews from the Health Information Research Unit at McMaster University. We conducted this search on April 23, 2022.
3. Grey literature: we conducted a manual search in the websites of specific health agencies: National Institutes for Health and Care Excellence (NICE), Agency for Healthcare Research and Quality (AHRQ), Canada’s Drug and Health Technology Agency (CADTH), and the website from the Society for Evidence-Based Gender Medicine (SEGM). We conducted these searches between April 27-30, 2022.

We used no date limits for the searches, but we did limit to systematic reviews published in English. Search strategies are available in Appendix 1.

Eligibility criteria: We included systematic reviews, which we defined as:

1. Reviews in which the authors searched for studies to include in at least one electronic database, and in which there were eligibility criteria for including studies and a methodology for assessing and synthesizing the evidence, or
2. Reviews in which the authors searched for studies to include in at least one electronic database, and although there was no description of eligibility criteria or methodology, the presentation of the results strongly suggested that the authors used systematic methods (e.g. flow chart depicting study selection, tables with the same information from all included studies, synthesis of data at the outcome level).

We screened systematic reviews using the following criteria for inclusion:

- **Type of participants:** Young individuals (< 25 years old) with a diagnosis of gender dysphoria/gender identity disorder. We included reviews in which authors used any label and diagnostic criteria for this condition. We included reviews in which the participants in the reported studies were older if it was the only evidence available for a specific question. We excluded reviews with mixed populations (i.e. with and without gender dysphoria) in which people without gender dysphoria constituted more than 20% of the total sample.
- **Type of Interventions:** Puberty blockers, cross-sex hormones, gender affirming surgeries. We included any type of puberty blockers and cross-sex hormones, provided with any regimen. We included the following surgeries: phalloplasty, vaginoplasty, and chest surgery (mastectomy or breast implants/augmentation). We only included these when they were performed for the first time (i.e., not revision surgeries).
- **Type of comparison:** When the systematic reviews included comparative studies, the comparator of interest was no intervention. Participants could have received psychotherapy or counselling as a cointervention (in both groups).
- **Type of outcomes:** Gender dysphoria, mental health outcomes (depression and anxiety), quality of life, suicidal ideation, suicide, adverse effects (for puberty blockers and cross-sex hormones only), and satisfaction, complications, reoperation, and regret (for surgeries only). We included any length of follow-up. We excluded surrogate outcomes such as blood pressure, bone mineral density, kidney or liver function test values, etc.
- **Type of studies included in the systematic reviews:** Any clinical study (studies in which the researchers recruited and measured outcomes in humans) regardless of study design. This included randomized clinical trials, comparative observational studies, and case series. Because we could not quantify effect measures, incidence, or prevalence, we excluded case reports.

We excluded systematic reviews published only in abstract format, and those that we could not retrieve in full text (no access through the McMaster University library, or open access online).

Selection process: The two reviewers screened all titles and abstracts independently and in duplicate, followed by screening of full texts of potentially eligible systematic reviews independently and in duplicate, using the systematic review online application Covidence (<https://www.covidence.org>). We solved disagreements by consensus.

To select the most useful systematic reviews among all of those that met the eligibility criteria, we used the following prioritization criteria:

1. **Date of publication:** we prioritized systematic reviews published within the last 3 years (2020-2022)

2. Match between eligibility criteria of the review and the question of interest: we prioritized reviews in which the authors specifically included the population, intervention, comparison, and outcomes of interest for this evidence review
3. Outcome data available: we prioritized systematic reviews in which the authors report outcome data
4. Methodological quality: we used a modified version of the items in AMSTAR 2.¹ We modified the items to ensure assessment of methodological rather than reporting quality (Table 1). We rated each systematic review as having high, moderate, low, or critically low methodological quality, according to the guidance from the developers of the tool.¹ We reached consensus on critical items that determined this rating (Table 1). We prioritized selection of systematic reviews with highest methodological quality.

For surgical interventions, in addition, we prioritized systematic reviews that covered all gender affirming surgeries (instead of focusing on a specific type of surgery).

We selected a systematic review specifically for each of the outcomes of interest. In other words, we chose the best systematic review to inform each outcome. Each systematic review, however, could inform more than one outcome.

Table 1: Items used to rate the methodological quality of the eligible systematic reviews

AMSTAR Item	Modification to measure methodological quality
1. Did the research questions and inclusion criteria for the review include the components of PICO?	Does the review have a clear question and are the eligibility criteria for studies consistent with the question?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?	No modification needed
3. Did the review authors explain their selection of the study designs for inclusion in the review?	No modification needed
4. Did the review authors use a comprehensive literature search strategy?	Did the authors search in at least 2 electronic databases, using a reproducible search strategy?
5. Did the review authors perform study selection in duplicate?	No modification needed
6. Did the review authors perform data extraction in duplicate?	No modification needed
7. Did the review authors provide a list of excluded studies and justify the exclusions?	No modification needed
8. Did the review authors describe the included studies in adequate detail?	No modification needed
9. Did the review authors use a satisfactory technique for assessing the risk of bias (RoB) in individual studies that were included in the review?	No modification needed

10. Did the review authors report on the sources of funding for the studies included in the review?	Did the review authors consider conflicts of interest and how they may have affected the results of the primary studies?
11. If meta-analysis was performed, did the review authors use appropriate methods for statistical combination of results?	Was the synthesis of evidence done appropriately? (outcome level, appropriate meta analysis or narrative synthesis)
12. If meta-analysis was performed, did the review authors assess the potential impact of RoB in individual studies on the results of the meta-analysis or other evidence synthesis?	Did authors use subgroup or sensitivity analysis to assess the effect of risk of bias in meta-analytic results? Likely not applicable to most cases
13. Did the review authors account for RoB in primary studies when interpreting/discussing the results of the review?	Did the review authors incorporate an assessment of risk of bias at the outcome level when drawing conclusions?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?	Did the review authors incorporate an assessment of heterogeneity at the outcome level when drawing conclusions?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?	Did the authors address publication bias? (regardless of whether synthesis was using a meta-analysis or narrative)
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?	Did the authors report conflicts of interest and did they manage any existing conflict of interest appropriately?

Shaded items were items considered critical.

Data abstraction: We abstracted outcome data from each of the systematic reviews. To ensure feasibility, we used the data as reported by the authors of the review and did not re-abstract data from the primary studies. One reviewer abstracted the data and a second reviewer checked the data for accuracy.

Data synthesis: Using the systematic reviews prioritized, we synthesized the evidence at the outcome level. Because of the higher likelihood of it resulting in higher certainty of evidence (details below) for each outcome, when there was comparative data (i.e. comparison of outcomes between an untreated and a treated group) and non-comparative data (i.e. changes from before to after treatment in one group, or only outcomes after treatment), we prioritized comparative data.

We prioritized numerical results (i.e. magnitudes of effect) and reported estimates and their 95% confidence intervals (CIs). When results were not reported in that way, we calculated the estimates and CIs when systematic review authors provided sufficient information. When necessary, we assumed moderate correlation coefficients for the changes between baseline and follow up (coefficient= 0.4). When this information was not available we reported narratively the effect estimates and ranges.

When a specific study reported the same outcome measured by more than one scale, we chose the scale presented first. We highlighted situations when the results obtained with other scales were importantly different.

When the same outcome was reported by more than one study but we could not pool the results, we created narrative syntheses.

Certainty of evidence: For each outcome, we assessed the certainty of the evidence (also known as quality of the evidence) using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) approach.² The certainty of evidence can be rated as high, moderate, low, or very low (Table 2). For effects of interventions, the certainty of the evidence started as high and could be rated down due to serious concerns about risk of bias, inconsistency, indirectness, imprecision, and publication bias. For inferences about the effect of using a treatment versus no treatment, when there was no comparison group, we assessed risk of bias as very serious and rated down the certainty of the evidence 2 levels by default. We used the same principles when assessing the certainty of the evidence in estimates of prevalence or rates, but did not judge risk of bias as resulting in very serious concerns due to lack of a comparison group. For all assessments, we used the information presented by the authors of the systematic review (e.g. assessments of risk of bias of the included studies, effect estimates from studies).

Table 2: GRADE levels of certainty of the evidence

Certainty level	Definition
High ⊕⊕⊕⊕	We are very confident that the true result (effect estimate/ prevalence/ mean, etc.) lies close to that of the estimate of the result
Moderate ⊕⊕⊕○	We are moderately confident in the result: the true result is likely to be close to the estimate of the result, but there is a possibility that it is substantially different
Low ⊕⊕○○	Our confidence in the result is limited: the true result may be substantially different from the estimate of the result
Very low ⊕○○○	We have very little confidence in the result: the true result is likely to be substantially different from the estimate of the result

Presentation of results: We created GRADE Summary of Findings tables in which we describe the evidence available for each of the outcomes, and the certainty of the evidence. These tables contain the following information:

- ⊖ Outcomes: measurement method (including scales, if applicable) and follow-up
- ⊖ Estimates of effect: absolute and relative estimates of effect, and their corresponding 95% CIs.
- ⊖ Number of studies and participants providing evidence for the outcome
- ⊖ GRADE certainty of the evidence, with a link to detailed explanations (provided at the bottom of the table) of why the certainty of the evidence was rated at a specific level
- ⊖ A narrative statement about what happens with the outcome, based on the estimate of effect and certainty of evidence.

Searching for new evidence not included in the systematic reviews: To assess if newer evidence not included in the included systematic reviews would change the conclusions importantly, we searched for and assessed primary studies answering the questions of interest that were published after the authors of such systematic reviews conducted their searches. We defined an important change in conclusions as a change in the certainty of the evidence (from low/ very low/ not available to high/ moderate).

We searched OVID Medline from January 1, 2019 through May 12, 2022, for studies published in English. We included studies if they enrolled young individuals (< 25 years old, with at least 20% of the people being this age) with a diagnosis of gender dysphoria/gender identity disorder, who received puberty blockers, cross-sex hormones, or surgeries; and measured any of the outcomes of interest.

For outcomes that should be evaluated in a comparative manner (e.g., depression, anxiety, etc.), because they are the only type of study design that would change the conclusions importantly, we selected comparative clinical studies (studies in which the researchers recruited and measured outcomes in humans, and compared a group of people who received the intervention with another one who did not receive the intervention). This included randomized clinical trials, and comparative observational studies. For outcomes that can only occur when the treatment is administered, we included non-comparative observational studies (case series). For these to change conclusions, they should have a sufficiently large sample size, and therefore we excluded case series in which the researchers reported information from <100 people.

Two reviewers screened the potentially relevant articles at title and abstract and full text screening stage. We abstracted relevant study characteristics and outcome data, and assessed risk of bias of comparative studies using the most relevant domains of the Risk of Bias for non-Randomized studies of Interventions (ROBINS-I) tool³ (table 3). For non-comparative studies, we used a list of custom items that captured the most important potential risk of bias concerns of case series (table 4). We judged the risk of bias of each study as the highest risk of bias of any of the domains assessed (e.g., one domain judged at critical risk of bias resulted in the study judged at critical risk of bias). We summarized this information at the study and judged whether it would have changed the conclusions importantly if added to the body of evidence from the systematic reviews.

Table 3: Domains used to assess risk of bias of comparative studies

Domain	Low	Critical
Confounding	Adjusted for all relevant confounding factors	No adjustment
Classification of intervention	Intervention recorded prospectively or from medical records	Asked patients to recall whether they received the intervention
Deviation from intended interventions	No cointerventions or cointerventions balanced between the groups	Cointerventions unbalanced between the groups

Missing data	More than 90% of patients who started the study provided outcome data	Less than 50% of patients who started the study provided outcome data
Measurement of outcome	All outcomes measured in the same way in both groups	Outcomes measured differently in both groups

Each domain could be judged at low, moderate, serious, or critical risk of bias. In addition, information could be insufficient to make a judgment. The table describes the criteria used to judge a domain in the extreme categories.

Table 4: Domains used to assess risk of bias of non-comparative studies

Domain	Low	High
Representativeness of the sample	Included all consecutive patients	Highly selected sample based on specific characteristics related with the prognosis after treatment
Classification of the intervention	Intervention recorded prospectively or from medical records	Asked patients to recall whether they received the intervention
Deviation from intended interventions	No cointerventions outside what would be observed in practice (or in a small proportion of patients)	Most patients received co-interventions that could influence the outcomes
Missing data	More than 90% of patients who started the study provided outcome data	Less than 50% of patients who started the study provided outcome data
Measurement of outcome	Outcomes measured prospectively or from medical records	Outcomes reported by the patients and/or needed to recall what happened a long time ago

Each domain could be judged at low, moderate, or high risk of bias. In addition, information could be insufficient to make a judgment. The table describes the criteria used to judge a domain in the extreme categories.

References

1. Shea BJ, Reeves BC, Wells G, et al. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *Bmj* 2017;358:j4008. doi: 10.1136/bmj.j4008 [published Online First: 2017/09/25]
2. Blashem H, Helfand M, Schunemann HJ, et al. GRADE guidelines: 3. Rating the quality of the evidence. *Journal of clinical epidemiology* 2011;64:401-06.
3. Sterne JA, Hernan MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ (Clinical research ed)* 2016;355:i4919. doi: 10.1136/bmj.i4919 [published Online First: 2016/10/14]

Search Strategies

Questions Covered:

PICO questions:

1. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **puberty blockers (gonadotrophin releasing hormone (GnRH) analogues)** compared to no puberty blockers?
2. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **cross-sex hormones** compared to no cross-sex hormones?
3. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of **gender-affirming surgeries** compared to no surgery?

Search Strategies:

Note: Population, puberty blocker, cross-sex hormones search blocks adapted from NICE (2020) evidence reviews. Gender-affirming search block adapted from Wernick *et al.* 2019. Systematic reviews filter adapted from McMaster University Health Information Research Unit (HIRU).

Databases: Medline, Epistemonikos
 Grey Literature: CADTH, AHRQ, SEGM, NICE

Medline

OVERVIEW		
Interface:	Ovid	
Databases:	OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present	
Study Types:	Systematic Reviews	
Search Run:	April 23, 2022	
Search Strategy: search terms [number of results]		
<i>Population</i>		
1	exp "Sexual and Gender Minorities"/	12385
2	Gender Dysphoria/	774
3	Gender Identity/	20481
4	Gender Role/	197
5	"Sexual and Gender Disorders"/	81
6	Transsexualism/	4236
7	Transgender Persons/	5303
8	Health Services for Transgender Persons/	186

- 9 exp Sex Reassignment Procedures/ 1208
- 10 gender identity disorder.mp. 492
- 11 non-binary.mp. 566
- 12 transgender.mp. 9989
- 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. 16428
- 14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)),tw. 13749
- 15 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).tw. 19665
- 16 (genderfluid or genderqueer or agender).mp. 130
- 17 ((correct or chosen) adj3 name).mp. 591
- 18 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).tw. 135313
- 19 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition* or expression*)),tw. 13749
- 20 (male-to-female or m2f or female-to-male or f2m).tw. 148579
- 21 or/1-20 342948

Cross-Sex Hormones

- 22 Hormones/ad, tu, th 4676
- 23 exp Progesterone/ad, tu, th 11265
- 24 exp Estrogens/ad, tu, th 29635
- 25 exp Gonadal Steroid Hormones/ad, tu, th 35375
- 26 (progesteron* or oestrogen* or estrogen*).tw. 223307
- 27 ((cross-sex or crossex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).tw. 1488
- 28 exp Estradiol/ad, tu, th 11197
- 29 exp Testosterone/ad, tu, th 8710
- 30 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).tw. 86509
- 31 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).tw. 100252
- 32 or/22-31 345895

Puberty Blockers

- 33 Gonadotropin-Releasing Hormone/ 28809
- 34 (pubert* adj3 block*).ti,ab. 141
- 35 ((gonadotrophin or gonadotropin) and releasing).ti,ab. 20121
- 36 (GnRH adj2 analog*).ti,ab. 2878
- 37 GnRH*.ti,ab. 24390
- 38 "GnRH agonist*".ti,ab. 4749
- 39 Triptorelin Pamoate/ 1981
- 40 triptorelin.ti,ab. 821
- 41 arvekap.ti,ab. 1

42	("AY 25650" or AY25650).ti,ab.	1	
43	("BIM 21003" or BIM21003).ti,ab.	0	
44	("BN 52014" or BN52014).ti,ab.	0	
45	("CL 118532" or CL118532).ti,ab.	0	
46	Debio.ti,ab.	119	
47	diphereline.ti,ab.	28	
48	moapar.ti,ab.	0	
49	pamorelin.ti,ab.	1	
50	trelstar.ti,ab.	3	
51	triptodur.ti,ab.	1	
52	("WY 42422" or WY42422).ti,ab.	0	
53	("WY 42462" or WY42462).ti,ab.	0	
54	gonapeptyl.ti,ab.	0	
55	decapeptyl.ti,ab.	225	
56	salvacyl.ti,ab.	0	
57	Buserelin/	2137	
58	buserelin.ti,ab.	1395	
59	onist.ti,ab.	0	
60	("hoe 766" or hoe-766 or hoe766).ti,ab.	72	
61	profact.ti,ab.	2	
62	receptal.ti,ab.	31	
63	suprecur.ti,ab.	5	
64	suprefact.ti,ab.	25	
65	tiloryth.ti,ab.	0	
66	histrelin.ti,ab.	78	
67	"LHRH-hydrogel implant".ti,ab.	1	
68	("RL 0903" or RL0903).ti,ab.	1	
69	("SPD 424" or SPD424).ti,ab.	1	
70	goserelin.ti,ab.	1016	
71	Goserelin/	1643	
72	("ici 118630" or ici118630).ti,ab.	51	
73	("ZD-9393" or ZD9393).ti,ab.	0	
74	zoladex.ti,ab.	388	
75	leuprorelin.ti,ab.	525	
76	carcinil.ti,ab.	0	
77	enanton*.ti,ab.	26	
78	ginecrin.ti,ab.	0	
79	leuplin.ti,ab.	15	
80	Leuprolide/	3018	
81	leuprolide.ti,ab.	2004	
82	lucrin.ti,ab.	16	
83	lupron.ti,ab.	183	
84	provren.ti,ab.	0	
85	procrin.ti,ab.	3	
86	("tap 144" or tap144).ti,ab.	41	
87	(a-43818 or a43818).ti,ab.	3	
88	Trenantone.ti,ab.	2	
89	staladex.ti,ab.	0	

90	prostag.	ti,ab.	6	
91	Nafarelin/		327	
92	nafarelin.	ti,ab.	263	
93	("76932-56-4" or "76932564")	.ti,ab.	0	
94	("76932-60-0" or "76932600")	.ti,ab.	0	
95	("86220-42-0" or "86220420")	.ti,ab.	0	
96	("rs 94991 298" or rs94991298)	.ti,ab.	0	
97	synarel.	ti,ab.	13	
98	deslorelin.	ti,ab.	306	
99	gonadorelin.	ti,ab.	237	
100	("33515-09-2" or "33515092")	.ti,ab.	0	
101	("51952-41-1" or "51952411")	.ti,ab.	0	
102	("52699-48-6" or "52699486")	.ti,ab.	0	
103	cetrorelix.	ti,ab.	520	
104	cetrotide.	ti,ab.	52	
105	("NS 75A" or NS75A)	.ti,ab.	0	
106	("NS 75B" or NS75B)	.ti,ab.	0	
107	("SB 075" or SB075)	.ti,ab.	1	
108	("SB 75" or SB75)	.ti,ab.	67	
109	gonadoliberin.	ti,ab.	151	
110	kryptocur.	ti,ab.	7	
111	cetrorelix.	ti,ab.	520	
112	cetrotide.	ti,ab.	52	
113	antagon.	ti,ab.	18	
114	ganirelix.	ti,ab.	160	
115	("ORG 37462" or ORG37462)	.ti,ab.	3	
116	orgalutran.	ti,ab.	26	
117	("RS 26306" or RS26306)	.ti,ab.	5	
118	("AY 24031" or AY24031)	.ti,ab.	0	
119	factrel.	ti,ab.	13	
120	fertagyl.	ti,ab.	12	
121	lutrelef.	ti,ab.	5	
122	lutrepulse.	ti,ab.	3	
123	relefact.	ti,ab.	10	
124	fertiral.	ti,ab.	0	
125	(hoe471 or "hoe 471")	.ti,ab.	6	
126	relisorm.	ti,ab.	4	
127	cystorelin.	ti,ab.	19	
128	dirigestran.	ti,ab.	5	
129	or/33-128		47108	
 <i>Gender-affirming Surgeries</i>				
130	virilization/		2309	
131	(virilism or virili?ation or masculini?ation).	mp.	5657	
132	feminization/		797	
133	femini?ation.	mp.	3420	
134	(vaginoplasty or vaginoplasties).	mp.	1022	

135 exp Vagina/ or *Reconstructive Surgical Procedures/ 78841
136 (vaginoplasty or vaginoplasties).mp. 1022
137 (phalloplasty or phalloplasties).mp. 561
138 exp Penile Prosthesis/ 1636
139 "penile reconstruction".mp. 292
140 (vagina reconstruction or vaginal reconstruction).mp. 549
141 (genitoplasty or genitoplasties).mp. 263
142 transsexualism/su [Surgery] 1007
143 sex reassignment.mp. 1668
144 sex transformation.mp. 42
145 or/130-144 91560

Systematic Review Filter

147 meta-analysis/ 158633
148 (meta anal* or meta-anal* or metaanal*).ti,ab. 231876
149 ((systematic or evidence) adj2 (review* or overview*)).ti,ab. 279806
150 ((pool* or combined) adj2 (data or trials or studies or results)).ab. 65411
151 (search strategy or search criteria or systematic search or study selection or data extraction).ab. 70886
152 (search* adj4 literature).ab. 84593
153 or/146-152 521554

Combine Interventions and Population

154 32 or 129 or 145 459771
155 21 and 154 17838

Limit to Systematic Reviews in English Language

156 153 and 155 295
157 limit 156 to english language 288

Epistemonikos

OVERVIEW	
Interface:	https://www.epistemonikos.org/
Database:	Epistemonikos
Study Types:	Systematic Reviews
Search Run:	April 23, 2022
Search Strategy: search terms [number of results]	
<i>Population</i>	
(title:(title:(gender dysphoria) OR abstract:(gender dysphoria)) OR (title:(gender identity disorder) OR abstract:(gender identity disorder)) OR (title:(transgender) OR abstract:(transgender))) OR abstract:(title:(gender dysphoria) OR abstract:(gender dysphoria)) OR (title:(gender identity disorder) OR abstract:(gender identity disorder)) OR (title:(transgender) OR abstract:(transgender)))	
<i>Limit to Systematic Reviews</i>	
*Limited by publication type "systematic review" [425]	

Canadian Agency for Drugs and Technologies in Health (CADTH)

OVERVIEW	
Interface:	https://www.cadth.ca/
Database:	CADTH
Study Types:	Systematic Reviews, Health Technology Reviews
Search Run:	April 27, 2022
Search Strategy: search terms [number of results]	
<i>"gender dysphoria" [10]</i> <i>Limit to Health Technology Review [2]</i>	
<i>"transgender" [9]</i> <i>Limit to Health Technology Review [5]</i>	
<i>"gender identity disorder" [1]</i>	

Agency for Healthcare Research and Quality (AHRQ)

OVERVIEW	
Interface:	https://search.ahrq.gov/
Database:	AHRQ
Study Types:	Evidence Based Practice (EPC) Centre Reports, Full Research Reports, Health Technology Assessments
Search Run:	April 29, 2022
Search Strategy: search terms [number of results]	
<i>Search titles only: "gender identity disorder" "gender dysphoria" "transgender" [7]</i>	

Society for Evidence-based Gender Medicine (SEGM)

OVERVIEW	
Interface:	https://segm.org/news
Database:	SEGM News
Study Types:	Systematic Reviews
Search Run:	April 30, 2022
Search Strategy: search terms [number of results]	
<i>Find in page: "systematic" [5]</i>	

National Institute for Health and Care Excellence (NICE)

OVERVIEW	
Interface:	https://www.nice.org.uk/
Database:	NICE
Study Types:	Systematic Reviews, Guidelines with Systematic Reviews
Search Run:	April 30, 2022
Search Strategy: search terms [number of results]	
<i>gender dysphoria [1] Limit to Guidance [1]</i>	
<i>transgender [10] Limit to Guidance [7]</i>	

gender identity disorder [9]
Limit to Guidance [8]

Search Strategies – Individual Studies

Questions Covered:

PICO questions:

1. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **puberty blockers (gonadotrophin releasing hormone (GnRH) analogues)** compared to no puberty blockers?
2. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of treatment with **cross-sex hormones** compared to no cross-sex hormones?
3. For children, adolescents, and young adults (<21) with gender dysphoria, what are the effects of **gender-affirming surgeries** compared to no surgery?

Search Strategies:

Note: Population, puberty blocker, cross-sex hormones search blocks adapted from NICE (2020) evidence reviews. Gender-affirming search block adapted from Wernick *et al.* 2019.

Databases: Medline

Medline

OVERVIEW	
Interface:	Ovid
Databases:	OVID Medline Epub Ahead of Print, In-Process & Other Non-Indexed Citations, Ovid MEDLINE(R) Daily and Ovid MEDLINE(R) 1946 to Present
Study Types:	Any
Search Run:	May 12, 2022
Search Strategy: search terms [number of results]	
<i>Population</i>	
1	exp "Sexual and Gender Minorities"/ 12631
2	Gender Dysphoria/ 781
3	Gender Identity/ 20586
4	Gender Role/ 204
5	"Sexual and Gender Disorders"/ 81
6	Transsexualism/ 4259
7	Transgender Persons/ 5371
8	Health Services for Transgender Persons/ 187
9	exp Sex Reassignment Procedures/ 1211
10	gender identity disorder.mp. 492

- 11 non-binary.mp. 574
- 12 transgender.mp. 10079
- 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)).ti,ab. 16546
- 14 ((sex or gender*) adj3 (reassign* or chang* or transform* or transition*)).ti,ab. 9375
- 15 (transgend* or transex* or transsex* or transfem* or transwom* or transma* or transmen* or transperson* or transpeopl*).ti,ab. 19788
- 16 (genderfluid or genderqueer or agender).mp. 132
- 17 ((correct or chosen) adj3 name).mp. 591
- 18 (trans or crossgender* or cross-gender* or crossex* or cross-sex* or genderqueer*).ti,ab. 135744
- 19 (male-to-female or m2f or female-to-male or f2m).ti,ab. 149067
- 20 or/1-19 341083

Cross-sex Hormones

- 21 Hormones/ad, tu, th 4690
- 22 exp Progesterone/ad, tu, th 11270
- 23 exp Estrogens/ad, tu, th 29646
- 24 exp Gonadal Steroid Hormones/ad, tu, th 35401
- 25 (progesteron* or oestrogen* or estrogen*).ti,ab. 223689
- 26 ((cross-sex or crossex or gender-affirm*) and (hormon* or steroid* or therap* or treatment* or prescri* or pharm* or medici* or drug* or intervention* or care)).ti,ab. 1507
- 27 exp Estradiol/ad, tu, th 11200
- 28 exp Testosterone/ad, tu, th 8722
- 29 (testosteron* or sustanon* or tostran or testogel or testim or restandol or andriol or testocaps* or nebido or testavan).ti,ab. 86670
- 30 (oestrad* or estrad* or evorel or ethinyloestrad* or ethinylestrad* or elleste or progynova or zumenon or bedol or femseven or nuvelle).ti,ab. 100411
- 31 or/21-30 346508

Puberty Blockers

- 32 Gonadotropin-Releasing Hormone/ 28845
- 33 (pubert* adj3 block*).ti,ab. 142
- 34 ((gonadotrophin or gonadotropin) and releasing).ti,ab. 20158
- 35 (GnRH adj2 analog*).ti,ab. 2879
- 36 GnRH*.ti,ab. 24437
- 37 "GnRH agonist*".ti,ab. 4763
- 38 Triptorelin Pamoate/ 1983
- 39 triptorelin.ti,ab. 822
- 40 arvekap.ti,ab. 1
- 41 ("AY 25650" or AY25650).ti,ab. 1
- 42 ("BIM 21003" or BIM21003).ti,ab. 0
- 43 ("BN 52014" or BN52014).ti,ab. 0
- 44 ("CL 118532" or CL118532).ti,ab. 0

45	Debio.ti,ab.	119	
46	diphereline.ti,ab.	28	
47	moapar.ti,ab.	0	
48	pamorelin.ti,ab.	1	
49	trelstar.ti,ab.	3	
50	triptodur.ti,ab.	1	
51	("WY 42422" or WY42422).ti,ab.	0	
52	("WY 42462" or WY42462).ti,ab.	0	
53	gonapeptyl.ti,ab.	0	
54	decapeptyl.ti,ab.	225	
55	salvacyl.ti,ab.	0	
56	Buserelin/	2137	
57	buserelin.ti,ab.	1396	
58	onist.ti,ab.	0	
59	("hoe 766" or hoe-766 or hoe766).ti,ab.	72	
60	profact.ti,ab.	2	
61	receptal.ti,ab.	31	
62	suprecur.ti,ab.	5	
63	suprefact.ti,ab.	25	
64	tiloryth.ti,ab.	0	
65	histrelin.ti,ab.	78	
66	"LHRH-hydrogel implant".ti,ab.	1	
67	("RL 0903" or RL0903).ti,ab.	1	
68	("SPD 424" or SPD424).ti,ab.	1	
69	goserelin.ti,ab.	1017	
70	Goserelin/	1644	
71	("ici 118630" or ici118630).ti,ab.	51	
72	("ZD-9393" or ZD9393).ti,ab.	0	
73	zoladex.ti,ab.	388	
74	leuprorelin.ti,ab.	529	
75	carcinil.ti,ab.	0	
76	enanton*.ti,ab.	26	
77	ginecrin.ti,ab.	0	
78	leuplin.ti,ab.	15	
79	Leuprolide/	3018	
80	leuprolide.ti,ab.	2003	
81	lucrin.ti,ab.	16	
82	lupron.ti,ab.	183	
83	provren.ti,ab.	0	
84	procrin.ti,ab.	3	
85	("tap 144" or tap144).ti,ab.	41	
86	(a-43818 or a43818).ti,ab.	3	
87	Trenantone.ti,ab.	2	
88	staladex.ti,ab.	0	
89	prostap.ti,ab.	6	
90	Nafarelin/	327	
91	nafarelin.ti,ab.	263	
92	("76932-56-4" or "76932564").ti,ab.	0	

93	("76932-60-0" or "76932600").ti,ab.	0
94	("86220-42-0" or "86220420").ti,ab.	0
95	("rs 94991 298" or rs94991298).ti,ab.	0
96	synarel.ti,ab.	13
97	deslorelin.ti,ab.	310
98	gonadorelin.ti,ab.	238
99	("33515-09-2" or "33515092").ti,ab.	0
100	("51952-41-1" or "51952411").ti,ab.	0
101	("52699-48-6" or "52699486").ti,ab.	0
102	cetrorelix.ti,ab.	520
103	cetrotide.ti,ab.	52
104	("NS 75A" or NS75A).ti,ab.	0
105	("NS 75B" or NS75B).ti,ab.	0
106	("SB 075" or SB075).ti,ab.	1
107	("SB 75" or SB75).ti,ab.	67
108	gonadoliberin.ti,ab.	152
109	kryptocur.ti,ab.	7
110	cetrorelix.ti,ab.	520
111	cetrotide.ti,ab.	52
112	antagon.ti,ab.	18
113	ganirelix.ti,ab.	161
114	("ORG 37462" or ORG37462).ti,ab.	3
115	orgalutran.ti,ab.	26
116	("RS 26306" or RS26306).ti,ab.	5
117	("AY 24031" or AY24031).ti,ab.	0
118	factrel.ti,ab.	13
119	fertagyl.ti,ab.	12
120	lutrelef.ti,ab.	5
121	lutrepulse.ti,ab.	3
122	relefact.ti,ab.	10
123	fertiral.ti,ab.	0
124	(hoe471 or "hoe 471").ti,ab.	6
125	relisorm.ti,ab.	4
126	cystorelin.ti,ab.	19
127	dirigestran.ti,ab.	5
128	or/32-127	47179
<i>Surgery</i>		
129	virilization/	2309
130	(virilism or virili?ation or masculini?ation).mp.	5664
131	feminization/	798
132	femini?ation.mp.	3425
133	(vaginoplasty or vaginoplasties).mp.	1032
134	(vaginoplasty or vaginoplasties).mp.	1032
135	(phalloplasty or phalloplasties).mp.	561
136	exp Penile Prosthesis/	1642
137	"penile reconstruction".mp.	292

138 (vagina reconstruction or vaginal reconstruction).mp. 550
139 (genitoplasty or genitoplasties).mp. 263
140 transsexualism/su [Surgery] 1007
141 sex reassignment.mp. 1674
142 sex transformation.mp. 42
143 or/129-142 14290

Any intervention AND population

144 31 or 128 or 143 386835
145 20 and 144 16516

Limit to Humans

146 animals/ not humans/ 4972586
147 145 not 146 9281
148 limit 147 to humans 7901

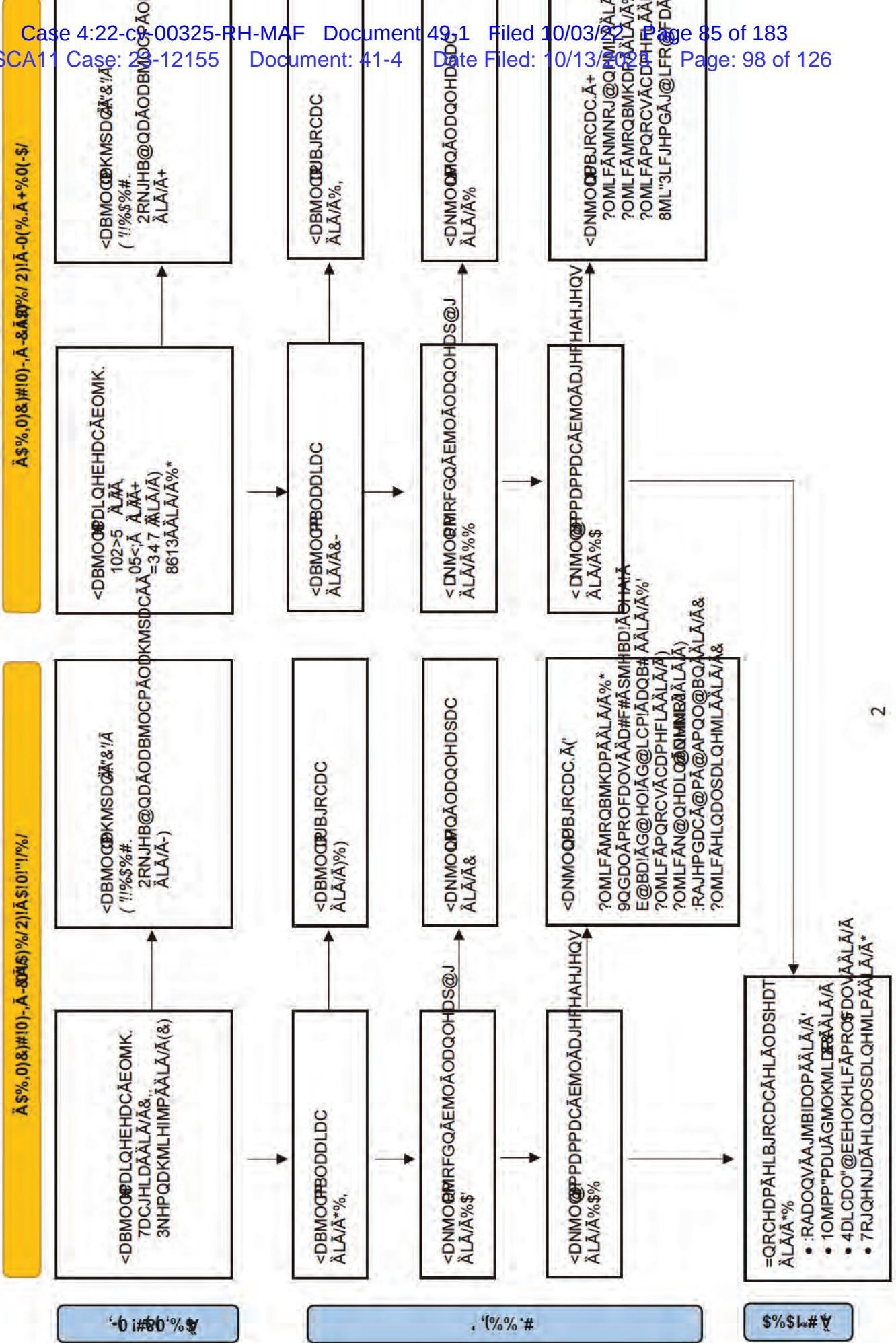
Limit to Publication Year 2019 to Current

149 limit 148 to yr="2019 -Current" 1859

Results

Search results and eligible reviews: After screening 647 records found through our searches, we found 61 eligible systematic reviews. From these, 27 were published between 2020 and 2022 (Figure 1). Overall, 4% (1/27) of the reviews were judged to be of high methodological quality, 15% (4/27) were moderate methodological quality, 37% (10/27) were low methodological quality, and 44% (12/27) were critically low methodological quality.

We provide reasons for excluding systematic reviews in appendix 1.



Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Figure 1: PRISMA flow diagram for the selection of systematic reviews. From: Page MJ, McKenzie JE, Bossuyt PM, Boutron I, Hoffmann TC, Mulrow CD, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. *BMJ* 2021;372:n71. doi: 10.1136/bmj.n71. For more information, visit: <http://www.prisma-statement.org/>

Outcomes:

1. Puberty blockers: We found 4 systematic reviews assessing the effects of puberty blockers published between 2020 and 2022.¹⁻⁴ From these, we judged 2 as having moderate methodological quality, and 2 as having critically low methodological quality. Details of the assessment are provided in Figure 2.

Table 1 summarizes the evidence about the effects of puberty blockers on the outcomes of interest. We used information from 2 systematic reviews.^{2,3} For most outcomes (except suicidality), there is no evidence about the effect of puberty blockers compared to not using puberty blockers. In other words, no studies compared the outcomes between a group of people with gender dysphoria using puberty blockers and another not using them. Therefore, it is unknown whether people with gender dysphoria who use puberty blockers experience more improvement in gender dysphoria, depression, anxiety, and quality of life than those with gender dysphoria who do not use them. There is very low certainty about the effects of puberty blockers on suicidal ideation (see details in Table 1).

Studies, however, reported outcomes among a group of people with gender dysphoria after receiving puberty blockers. The findings are:

- There is low certainty evidence suggesting that treatment with puberty hormones may slightly increase gender dysphoria severity (mean change score in the Utrecht Gender Dysphoria scale, 0.7 points [95% CI, -4.2 to 5.6], range 12-60, with higher scores reflecting more severe gender dysphoria)
- There is low certainty evidence suggesting that treatment with puberty blockers may decrease depression (mean change score in the Beck Depression Inventory, -3.4 [95% CI, -5.7 to -1.0], range 0-63, with higher scores reflecting more severe depression)
- There is low certainty evidence suggesting that treatment with puberty blockers may decrease anxiety (mean change score in the Trait Anxiety Scale, trait subscale, -1.5 [95% CI, -4.7 to -1.8], range 0-80, with higher scores reflecting more severe anxiety)
- There is low certainty evidence suggesting a moderate percentage of patients reporting adverse events after treatment with puberty blockers (see Table 1 for details)
- There is very low certainty evidence about how puberty blockers affect suicidality

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Figure 2: AMSTAR assessment judgements for systematic reviews addressing puberty blockers

Review ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Methodological quality
AHRQ 2021	Yes	Probably no	No	Yes	Probably yes	Probably yes	Yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	MODERATE
NICE 2020a	Yes	Probably no	Probably yes	Yes	Probably yes	Probably yes	Yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	Probably yes	MODERATE
Ramos 2020	Yes	No	No	Probably yes	Probably no	Probably yes	No	Probably no	No	No	No	No	No	No	No	No	CRITICALLY LOW
Rew 2020	Yes	No	No	Probably yes	Probably no	Probably yes	No	Probably no	No	No	No	No	No	No	No	No	CRITICALLY LOW

Figure legend:



Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Table 1: Puberty blockers (gonadotrophin releasing hormone analogues) compared to no puberty blockers in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no puberty blockers	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Gender dysphoria assessed with: difference (effect) in gender dysphoria proportion or severity	Not reported	Not reported			The effects of puberty blockers on gender dysphoria are unknown
Gender dysphoria assessed with: mean change score in the Utrecht Gender Dysphoria Scale (12-60, higher scores reflect more gender dysphoria, 40 points or more indicate a diagnosis of gender dysphoria) (NICE, 2020a) Follow up: mean 1.9 years (range 0.4 to 5.1 years)	NA	NA	41 (1 study)	⊕⊕○○ LOW ¹	The mean gender dysphoria score may increase by 0.7 points after puberty blockers
Depression assessed with: difference (effect) in depression proportion or severity	Not reported	Not reported			The effects of puberty blockers on depression are unknown

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Table 1: Puberty blockers (gonadotrophin releasing hormone analogues) compared to no puberty blockers in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no puberty blockers	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Depression assessed with: mean change score in Beck Depression Inventory-II scale (0-63, higher scores represent more severe depression) (NICE, 2020a) Follow up: mean 1.9 years (range 0.4 to 5.1 years)	NA	NA	41 (1 study)	⊕⊕○○ LOW ¹	The mean depression score may decrease by 3.4 points after puberty blockers
Anxiety assessed with: difference (effect) in anxiety proportion or severity	Not reported	Not reported			The effects of puberty blockers on anxiety are unknown
Anxiety assessed with: mean change score in STAI-Trait scale (0-80, higher scores represent more severe anxiety) (NICE, 2020a) Follow up: mean 1.9 years (range 0.4 to 5.1 years)	NA	NA	41 (1 study)	⊕⊕○○ LOW ¹	The mean anxiety score may decrease by 1.5 points after puberty blockers

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Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no puberty blockers	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Quality of life assessed with: any measure	Not reported				
Suicidal ideation difference (effect) in suicidal ideation (Rew, 2020) Follow-up: cross-sectional survey	Risk / mean with no puberty blockers	The authors report that "compared to youth who did not receive pubertal suppression, those who did showed lower lifetime rates of suicidal ideation".	89 (1 study)	⊕○○○ VERY LOW ²	The effects of puberty blockers on quality of life are unknown We are very uncertain about the effect of puberty blockers on suicidal ideation
Adverse effects assessed with: proportion of patients reporting adverse effects (NICE, 2020a) Follow up: mean 2.3 years (range 0.0 to 11.3 years)	Risk / mean with no puberty blockers	11% ³ (2% to 29%)	27 (1 study)	⊕○○○ LOW ⁴	The proportion of patients reporting adverse effects after treatment with puberty blockers may be 11%

STAI-Trait: Trait Anxiety Scale. Range: 0-80
 CI: Confidence interval
 NA: Not applicable

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Table 1: Puberty blockers (gonadotrophin releasing hormone analogues) compared to no puberty blockers in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: puberty blockers (gonadotrophin releasing hormone analogues)
Comparison: no puberty blockers

Outcomes	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Risk / mean with no puberty blockers	Risk / mean with puberty blockers				

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

- 1.Ā Mean change rated down due to risk of bias and imprecision. According to the systematic review authors, the study had poor methodological quality. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size).
- 2.Ā The authors of Rew 2020 narratively summarized the outcome of Turban *et al.* 2020; a cross-sectional online survey study. According to the systematic review authors, Turban *et al.* did not describe the study participants and the setting in detail and it was unclear whether outcomes were measured in a valid and reliable way. We therefore, downgraded the certainty of evidence by one level from low to very low due to high risk of bias.
- 3.Ā The authors reported 3/27 (11%) participants treated with GnRH developed side effects: 1 participant developed sterile abscesses; they were switched from leuprolide acetate to triptorelin, 1 participant developed leg pains and headaches, which eventually resolved without treatment, 1 participant gained 19 kg within 9 months of initiating GnRH analogues.
- 4.Ā Proportion of adverse effects rated down due to risk of bias and imprecision. According to the systematic review authors, the cohort study Khatchadourian *et al.* 2014 was assessed at high risk of bias due to incomplete reporting of its cohort. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size).

2. \bar{A} Cross-sex hormones: We found 9 systematic reviews assessing the effects of cross-sex hormones published between 2020 and 2022.⁴⁻¹² One of these, however, included both puberty blockers and cross-sex hormones combined in their evidence synthesis as was not prioritized.⁵ From the 8 remaining reviews, we judged 1 as having high methodological quality, 2 as having moderate methodological quality, 2 as having low methodological quality, and 3 as having critically low methodological quality. Details of the assessment are provided in Figure 3. Because of its eligibility criteria related to study design, the systematic review judged at high methodological quality⁷ did not include any studies and therefore we could not use it to inform any outcome.

Table 2 summarizes the evidence about the effects of cross-sex hormones on the outcomes of interest. We used information from 4 systematic reviews.^{6,9,11,12} For most outcomes (all except risk of breast cancer), there is no evidence about the effect of cross-sex hormones compared to not using cross-sex hormones. In other words, no studies compared the outcomes between a group of people with gender dysphoria using cross-sex hormones and another not using it. Therefore, it is unknown whether people with gender dysphoria who use cross-sex hormones experience more improvement in gender dysphoria, depression, anxiety, quality of life, and suicidality than those with gender dysphoria who do not use them. There is low certainty evidence suggesting that cross-sex hormones may not increase or decrease the risk of breast cancer (see details in Table 2).

Studies, however, reported outcomes among a group of people with gender dysphoria after receiving cross-sex hormones. The findings are:

- \bar{A} There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease gender dysphoria severity (mean change score in the Utrecht Gender Dysphoria scale, -42.4 points [95% CI, -44.1 to -40.1], range 12-60, with higher scores reflecting more severe gender dysphoria)
- \bar{A} There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease depression (measured with different scales, see Table 4 for details) and the need for treatment for depression (change in percentage, -39%)
- \bar{A} There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease anxiety (measured with different scales, see Table 4 for details) and the need for treatment for anxiety (change in percentage, -32%)
- \bar{A} There is very low certainty about the change in quality of life after treatment with cross-sex hormones.
- \bar{A} There is low certainty evidence suggesting that treatment with cross-sex hormones may decrease suicidality degree (mean change score in the Ask Suicide-Screening questions scale, -0.84 points [95% CI, -1.30 to -0.44], range 0-4, with higher scores reflecting more severe suicidality) and the percentage of patients with need for treatment due to suicidality/self-harm (change in percentage, -31%). There is very low certainty evidence about the percentage of people with suicidal ideation and suicide attempts after treatment with cross-sex hormones.

- A There is low certainty evidence suggesting a low prevalence of venous thromboembolism after treatment with cross-sex hormones (see Table 2 for details)

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Figure 3: AMSTAR assessment judgements for systematic reviews addressing cross-sex hormones

Review ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Methodological quality
AHRQ 2021	Green	Light Green	Red	Green	Light Green	Light Green	Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	MODERATE
Baker 2021	Green	Light Green	Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Red	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	MODERATE
Fledderus 2020	Light Green	Red	Red	Light Green	Light Green	Green	Red	Light Green	Green	Red	Red	Red	Red	Red	Red	Red	CRITICALLY LOW
Haupt 2020	Green	Light Green	Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	HIGH
Karalexi 2020	Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Red	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	LOW
Kotamarti 2021	Light Green	Red	Red	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Red	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	CRITICALLY LOW
Mattawanon 2021	Light Green	Red	Red	Light Green	Light Green	Light Green	Red	Light Green	Red	Red	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	CRITICALLY LOW
NICE 2021b	Light Green	Light Green	Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	MODERATE
Totaro 2021	Green	Light Green	Red	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	Light Green	LOW

Figure legend:



Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Table 2: Cross-sex hormones compared to no cross-sex hormones in youth (<21 years old) with gender dysphoria

Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no cross-sex hormones	Risk/ mean with cross-sex hormones	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Gender dysphoria assessed with: difference (effect) in gender dysphoria percentage or severity			Not reported			The effects of cross-sex hormones on gender dysphoria are unknown
Gender dysphoria assessed with: mean change score in the Utrecht Gender Dysphoria Scale (12-60, higher scores reflect more gender dysphoria, 40 points or more indicate a diagnosis of gender dysphoria) (NICE, 2020b) Follow up: 1 year	NA	-42.4 (-44.1 to -40.1)	NA	23 (1 study)	⊕⊕○○ LOW ¹	The mean gender dysphoria score may decrease by 42 points after cross-sex hormones
Depression assessed with: difference (effect) in depression percentage or severity			Not reported			The effects of cross-sex hormones on depression are unknown

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Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no cross-sex hormones	Risk/ mean with cross-sex hormones	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Depression assessed with: mean change score in depression scales (higher scores represent more severe depression) (NICE, 2020b) Follow up: 1 year	NA	The mean depression score reduction was 9.6 points when using the BDI-II scale (n=23) and 7.5 when using the CESD-R scale (n=50). The authors report that both reductions were statistically significant ²	NA	73 (2 studies)	⊕⊕○○ LOW ¹	The mean depression score may decrease after cross-sex hormones
Depression assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	NA	The percentage of participants requiring treatment was reduced by 39% (from 54% at baseline), which was statistically significant	NA	52 (1 study)	⊕⊕○○ LOW ¹	The percentage of participants requiring treatment may be reduced by 39% after cross- sex hormones
Anxiety assessed with: difference (effect) in anxiety percentage or severity		Not reported				The effects of cross-sex hormones on anxiety are unknown

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Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no cross-sex hormones	Risk/ mean with cross-sex hormones	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Anxiety assessed with: mean change score in anxiety scales (higher scores represent more severe anxiety) (NICE, 2020b) Follow-up: 1 year	NA	The mean anxiety score reduction was 16.5 points when using the STAI-State scale and 14.5 when using the STAI-Trait scale. The authors report that both reductions were statistically significant	NA	23 (1 study)	⊕⊕○○ LOW ¹	The mean anxiety score may decrease after cross-sex hormones
Anxiety assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	NA	The percentage of participants requiring treatment was reduced by 32% (from 48% at baseline), which was statistically significant	NA	52 (1 study)	⊕⊕○○ LOW ¹	The percentage of participants requiring treatment may be reduced by 32% after cross- sex hormones
Quality of life assessed with: difference (effect) in quality of life improvement	Not reported		Not reported		The effects of cross-sex hormones on quality of life are unknown	

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Intervention: cross-sex hormones

Comparison: no cross-sex hormones

Outcomes	Risk / mean with no cross-sex hormones	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Quality of life assessed with: mean change score in QLES-Q-SF score (higher scores represent better quality of life) (NICE, 2020b) Follow up: 1 year	NA	The mean quality of life score improved, but the differences were not statistically significant. The magnitudes were not reported	NA	50 (1 study)	⊕○○○ VERY LOW ³	We are very uncertain about the quality of life change after cross-sex hormones
Suicide / suicidal ideation assessed with: difference (effect) in suicide or suicidal ideation			Not reported			The effects of cross-sex hormones on suicide/ suicidal ideation are unknown
Suicidality assessed with: change in score from ASQ instrument (higher scores represent greater degree of suicidality) (NICE, 2020b) Mean follow up: 1 year	NA	-0.84 (-1.30 to -0.44)	NA	39 (1 study)	⊕⊕○○ LOW ¹	Suicidality scores may decrease by 0.84 points after cross-sex hormones

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Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no cross-sex hormones	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Suicidal ideation assessed with: percentage of participants with suicidal ideation measured with PHQ-9 (NICE, 2020b) Follow-up: 1 year	NA	NA	50 (1 study)	⊕○○○ VERY LOW ³	We are very uncertain about the change in percentage of patients in suicidal ideation after cross-sex hormones
Suicide attempts assessed with: not reported (NICE, 2020b) Follow up: not reported	NA	NA	130 (1 study)	⊕○○○ VERY LOW ³	We are very uncertain about the percentage of people with suicide attempts after cross-sex hormones
Suicidality/ self-harm assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	NA	NA	52 (1 study)	⊕⊕○○ LOW ¹	The percentage of participants requiring treatment may be reduced by 31% after cross- sex hormones
Venous thromboembolism assessed with: Risk of VTE		Not reported			The effects of cross-sex hormones on the risk of VTE are unknown

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Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Risk / mean with no cross-sex hormones	Anticipated absolute effects* (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Venous thromboembolism assessed with: Prevalence among assigned males at birth (Totaro, 2021) Mean follow up: 4.1 years	NA	20 per 1,000 (10 to 30)	NA	11,542 (18 studies)	⊕⊕⊕⊕ MODERATE ⁴	The prevalence of VTE among assigned males at birth is probably 2% after cross-sex hormones
Venous thromboembolism assessed with: Prevalence among assigned females at birth (Kotamarti, 2021) Mean follow up: 5.7 years	NA	6 per 1,000 (CI not reported) ⁵	NA	4,218 (8 studies)	⊕⊕⊕⊕ MODERATE ⁵	The prevalence of VTE among assigned females at birth is probably 0.6% after cross-sex hormones
Breast cancer assessed with: Risk of breast cancer (Fledderus, 2020) Follow up: not reported	Two studies compare the risk of breast cancer between assigned females at birth using versus not using testosterone, and found no differences (0 vs 1 case [total n= 130], and 1 vs 6 [total n=1579]). A third study compared assigned females at birth with non transgender women and found a lower risk in the former (magnitude not reported)		NA	2,938 (3 studies)	⊕⊕⊕⊕ LOW ⁷	The risk of breast cancer may not increase or decrease due to the use of cross-sex hormones

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Patient or population: youth (<21 years old) with gender dysphoria
Intervention: cross-sex hormones
Comparison: no cross-sex hormones

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no cross-sex hormones	Risk/ mean with cross-sex hormones	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
<p>ASQ: Ask Suicide-Screening Questions. Range: 0-4 BDI-II: Beck Depression Inventory. Range: 0-63 CESD-R: Center for Epidemiological Studies Depression Scale. Range: 0-60 CI: Confidence interval NA: Not applicable PHQ-9: Patient Health Questionnaire (PHQ) Modified for Teens. For suicidal ideation, it is a single question (yes/no) QLES-Q-SF: Quality of Life Enjoyment and Satisfaction Questionnaire. Range: 15-75 STAI: State-Trait Anxiety Inventory. Range: 0-80</p>						

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect
Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect
Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

1. **1.Ā** Mean change rated down due to risk of bias and imprecision. According to the systematic review authors, the studies had poor methodological quality. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size)
2. **2.Ā** Similar results when this outcome was measured using the Patient Health Questionnaire (PHQ) Modified for Teens in one of the same studies
3. **3.Ā** Rated down due to risk of bias, imprecision, and indirectness. According to the systematic review authors, the studies had poor methodological quality. In addition, there are too few participants included, which is not sufficient to make trustworthy inferences (does not meet the optimal information size). Finally, 30% of the participants did not have a diagnosis of gender dysphoria.
4. **4.** Prevalence rated down due to risk of bias. According to the systematic review authors, only 6 out of the 18 studies (representing 16.5% of the weight of the studies) were at low risk of bias.

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

5. A meta-analysis of independent studies reported in this systematic review suggested that the prevalence of VTE in non-transgender females at birth was 1.7% (based on 7 studies and 18,748 persons)
6. Prevalence rated down due to risk of bias. According to the systematic review authors, all studies had at least one domain judged as problematic.
7. Risk rated down 2 levels because of risk of bias. The researchers did not account for confounding in any of the studies.

3.3 Surgeries: We found 15 systematic reviews assessing the effects of gender-affirming surgeries published between 2020 and 2022. We judged 8 as having low methodological quality and 7 as having critically low methodological quality. Details of the assessment are provided in Figure 4. We present the results regarding the effects of surgeries in three parts. First, we describe the effects of all surgeries on mental health outcomes in all patients. Second, we describe the effects of all surgeries on surgical outcomes in assigned females at birth (transgender males). Finally, we describe the effects of all surgeries on surgical outcomes in assigned males at birth (transgender females).

3.1 Effects of surgeries on mental health outcomes: Table 3 summarizes the evidence about the effects of all surgeries on mental health outcomes in all patients. We used information from 2 systematic reviews.^{13 14} There were no systematic reviews and studies reporting on gender dysphoria, depression, anxiety, and suicidality. Therefore, the effects of surgeries on these outcomes (when compared to a group of patients with gender dysphoria who do not undergo surgery), or the changes in these outcomes (improvements or deterioration) among patients who undergo surgeries is unknown.

The systematic reviews addressed quality of life and depression, but none of the included studies included a comparison group. Thus, it is unknown whether people with gender dysphoria who undergo surgeries experience more improvement in quality of life or less regret than those with gender dysphoria who do not undergo surgeries.

Studies, however, reported the following outcomes among a group of people with gender dysphoria after undergoing surgeries. The findings are:

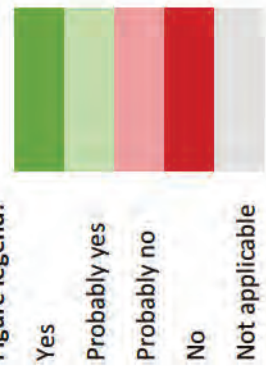
- A** There is low certainty evidence suggesting that the percentage of people who experience regret after surgery is low (1%)
- A** There is very low certainty evidence about how surgeries affect quality of life (see Table 3 for details)

Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Figure 4: AMSTAR assessment judgements for systematic reviews addressing gender-affirming surgery

Review ID	Item 1	Item 2	Item 3	Item 4	Item 5	Item 6	Item 7	Item 8	Item 9	Item 10	Item 11	Item 12	Item 13	Item 14	Item 15	Item 16	Methodological quality
Bustos SS 2021	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Bustos VP 2021	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Bustos VP 2021b	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Dunford 2021	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Eftekhar, 2020	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Falcone 2021	Red	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	CRITICALLY LOW
Hu, 2022	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	CRITICALLY LOW
Huayllani 2021	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	CRITICALLY LOW
Jolly 2021	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Nassiri 2020	Red	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	CRITICALLY LOW
Oles 2022	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Oles 2022b	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	LOW
Salibian 2021	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	CRITICALLY LOW
Sijben 2021	Red	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	CRITICALLY LOW
Tay 2021	Green	Red	Red	Green	Green	Red	Red	Green	Green	Red	Green	Red	Red	Green	Red	Green	CRITICALLY LOW

Figure legend:



Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

Table 3: All surgeries compared to no surgeries in young people (<21 years old) with gender dysphoria

Patient or population: young people (<21 years old) with gender dysphoria



Intervention: surgeries

Comparison: no surgeries

Outcomes: Mental health and regret

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no surgery	Risk/ mean with surgery	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Gender dysphoria assessed with: any measure			Not reported			The effects of surgery on gender dysphoria, the changes in gender dysphoria severity after surgery, and the prevalence of gender dysphoria after surgery are unknown
Depression assessed with: any measure			Not reported			The effects of surgery on depression, the changes in depression severity after surgery, and the prevalence of depression after surgery are unknown
Anxiety assessed with: any measure			Not reported			The effects of surgery on anxiety, the changes in anxiety severity after surgery, and the prevalence of anxiety after surgery are unknown
Suicidality assessed with: any measure			Not reported			The effects of surgery on suicidality, the changes in anxiety severity after surgery, and the prevalence of anxiety after surgery are unknown
Quality of life assessed with: difference (effect) in quality of life			Not reported			The effects of surgery on quality of life are unknown
Quality of life assessed with: change in quality of life			Not reported			The change in quality of life after surgery is unknown

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<p>Quality of life assessed with: mean score in the Short Form-36 Scale (0-100, higher scores reflect better quality of life) (Eftekhar Ardebili, 2020) Follow up: cross-sectional</p>	<p>NA</p>	<p>59.17 (48.59 to 69.74)¹</p>	<p>NA</p>	<p>633 (5 studies)</p> <p> VERY LOW²</p> <p>We are very uncertain about the quality of life after surgeries</p>
<p>Regret assessed with: difference (effect) in percentage of people with regret</p>	<p>Not reported</p>			<p>The effects of surgery on regret are unknown</p>
<p>Regret assessed with: percentage of people with regret (Bustos, 2021) Mean follow up: 4 years</p>	<p>NA</p>	<p>1% (0 to 2%)³</p>	<p>NA</p>	<p>7928 (27 studies)</p> <p> LOW⁴</p> <p>The percentage of people who experience regret is low</p>
<p>CI: Confidence interval NA: Not applicable</p>				
<p>GRADE Working Group grades of evidence High certainty: We are very confident that the true effect lies close to that of the estimate of the effect Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect</p>				

Explanations

1. \bar{A} Similar scores for assigned males at birth and assigned females at birth.
2. \bar{A} Mean score rated down for risk of bias and inconsistency. According to the systematic review authors, all studies had concerns related to risk of bias. In addition, the smaller studies showed better quality of life than the larger study.
3. \bar{A} Similar percentage for assigned males at birth and assigned females at birth, and for different types of surgeries (all pooled percentages below 2%).
4. \bar{A} Percentage rated down due to risk of bias and indirectness. According to the authors, many of the studies had moderate or high risk of bias. The mean age of the participants at the time of surgery was higher than the target population. Because it was considered to not have an important effect on the pooled estimate, we did not rate down for statistical heterogeneity

3.2 Effects of surgeries on assigned females at birth: Table 4 summarizes the evidence about the effects of all surgeries on surgical outcomes among assigned at birth females. We used information from 3 systematic reviews.¹³⁻¹⁷ Due to the nature of the outcomes (i.e. they can only be experienced by people who undergo surgeries), there cannot be studies comparing the outcomes between a group of people with gender dysphoria who undergo surgeries and another who does not.

Studies, therefore, assessed the outcomes among a group of people with gender dysphoria after surgery. The findings are:

- \bar{A} There is low certainty evidence suggesting that the percentage of people who are satisfied after chest surgery is high (92%)
- \bar{A} There is very low certainty evidence about the rate of surgical complications after chest surgery
- \bar{A} There is very low certainty evidence about the percentage of people who are satisfied, and the rate of surgical complications after bottom surgeries (see Table 4 for details)

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Table 4: All surgeries compared to no surgeries in assigned females at birth (<21 years old) with gender dysphoria

Patient or population: assigned females at birth (<21 years old) with gender dysphoria

Intervention: surgeries

Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no surgery	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Chest surgery					
Satisfaction assessed with: percentage of people who reported being satisfied (Bustos VP, 2020b) Range of follow up: 6 weeks to 46 months ¹	NA	NA	733 (14 studies)	⊕⊕○○ LOW ³	The percentage of people who reports being satisfied may be 92%
Surgical complications assessed with: rate of complications across patients (Oles, 2022) Range of follow up: 8 weeks to 1 year	NA	NA	1255 (7 studies)	⊕○○○ VERY LOW ⁴	We are very uncertain about the rate of surgical complications
Reoperation assessed with: rate of reoperation across patients (Oles, 2022) Range of follow up: 8 weeks to 1 year	NA	NA	1214 (6 studies)	⊕○○○ VERY LOW ⁴	We are very uncertain about the rate of reoperation
Bottom surgery					

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Patient or population: assigned females at birth (<21 years old) with gender dysphoria

Intervention: surgeries

Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no surgery	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
<p>Satisfaction assessed with: percentage of people who reported being satisfied (Oles, 2022b) Range of follow up: 6 weeks to 46 months</p>	NA 89.6% (45% to 100%) [§]	NA	1458 (27 studies)	⊕○○○ VERY LOW ⁴	We are very uncertain about the percentage of people who reports being satisfied
<p>Surgical complications- Major assessed with: percentage of people experiencing major complications (Oles, 2022b) follow up: not reported</p>	NA The percentage was - 2.3% (range 0 to 20%) experiencing total flap loss - 19.5% (range 0 to 72%) experiencing prosthesis issues - 24.5% (range 0 to 86%) experiencing urethral issues	NA	3177 (42 studies) [§]	⊕○○○ VERY LOW ⁴	We are very uncertain about the percentage of people who experience major surgical complications
<p>Surgical complications- Minor assessed with: percentage of people experiencing major complications (Oles, 2022b) follow up: not reported</p>	NA The percentage varied from 9.3% (range 0% to 45.5%) experiencing donor site issues, to 2.4% (range -10 to 93%) experiencing urethral issues ⁷	NA	4466 (52 studies) [§]	⊕○○○ VERY LOW ⁴	We are very uncertain about the percentage of people who experience minor surgical complications


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Table 4: All surgeries compared to no surgeries in assigned females at birth (<21 years old) with gender dysphoria

Patient or population: assigned females at birth (<21 years old) with gender dysphoria

Intervention: surgeries

Comparison: no surgeries

Outcomes	Anticipated absolute effects* (95% CI) Risk / mean with no surgery	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
Reoperation assessed with: rate of reoperation across patients (Oles, 2022b) follow up: not reported	NA Range (2.5% to 40%) 27.6%	NA	1624 (15 studies)	 VERY LOW ⁴	We are very uncertain about the percentage of people who undergo reoperations

CI: Confidence interval
 NA: Not applicable

GRADE Working Group grades of evidence

High certainty: We are very confident that the true effect lies close to that of the estimate of the effect

Moderate certainty: 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 certainty: Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect

Very low certainty: We have very little confidence in the effect estimate: The true effect is likely to be substantially different from the estimate of effect

Explanations

1. \bar{A} Studies used different scales to assess satisfaction
2. \bar{A} The percentage was similar when the analysis was done by type of surgery and by follow up time (< 1 year vs 1 year or more). Another systematic review (Oles, 2022) also investigated this outcome, and reported a very similar percentage of satisfaction (91.8%, range 73% to 100%)
3. \bar{A} Percentage of patients satisfied rated down due to risk of bias and indirectness. According to the systematic review authors, several studies were judged at moderate and high risk of bias. In addition, the median of the mean age of patients included in the studies was 28 years
4. \bar{A} Rated down due to risk of bias, inconsistency/ imprecision, and indirectness. Even though the review authors did not assess risk of bias, these studies were included in other systematic reviews in which the authors judged several of them at high risk of bias. The studies report inconsistent results (some high and other low rates). The patients are older than the target population.
5. \bar{A} Results for phalloplasty. Similar results for metoidioplasty (91.3%).

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- 6. People and studies for urethral complications. 2671 people (37 studies) for prosthesis issues, and 1548 people (22 studies) for total flap loss.
- 7. Percentage of wound dehiscence 9.8% (range, 2.9% to 75%), percentage of infection/ partial necrosis 10.3% (range, 0 to 45.8%), percentage of prosthesis issues 14.2% (range, 1.6 to 41.9%), percentage of incontinence 15.3% (range, 5.4% to 59.1%)
- 8. People and studies for infection/ partial necrosis. 2389 people (31 studies) for urethral issues, 1736 people (17 studies) for wound dehiscence, 1080 (10 studies) for prosthesis issues, 1053 people (8 studies) for donor site issues, 131 people (3 studies) for incontinence

CERTIFICATE OF SERVICE

I certify that I e-filed this appendix on ECF, which will email everyone requiring notice.

Dated: October 13, 2023

/s/ Mohammad O. Jazil