

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.

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Respectfully submitted,

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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  
Mohammad O. Jazil

# Appendix Attachment

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# Florida Medicaid

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

**June 2022**

Ron DeSantis, Governor  
Simone Marstiller, Secretary



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## 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).<sup>1</sup>

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

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<sup>1</sup> 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.<sup>2</sup>

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

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<sup>2</sup> 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)<sup>3</sup>, 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

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<sup>3</sup> 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).<sup>4</sup>

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<sup>4</sup> 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.<sup>5</sup>
- **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.

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<sup>5</sup> 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)<sup>6</sup> 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

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<sup>6</sup> 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, 2017<sup>7</sup>

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

<sup>7</sup> 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.<sup>8</sup> 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

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<sup>8</sup> 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).<sup>9</sup> 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

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<sup>9</sup> 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.<sup>10</sup> 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).<sup>11</sup>

**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).<sup>12</sup>

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<sup>10</sup> 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.

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

<sup>12</sup> 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.<sup>13</sup> 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).

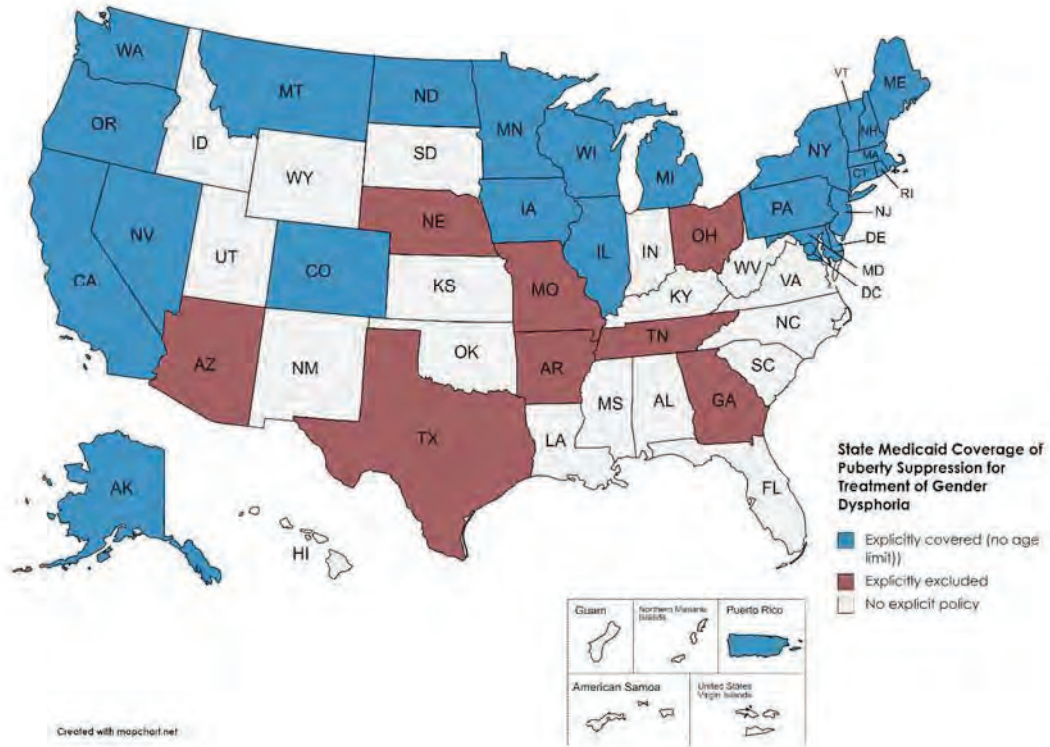
**State Medicaid Programs:** Because individual states differ in health services offered, Medicaid programs vary in their coverage of sex reassignment treatments. The following maps identify states that cover sex reassignment treatments, states that have no policy, and states that do not cover such treatments.

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<sup>13</sup> 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.

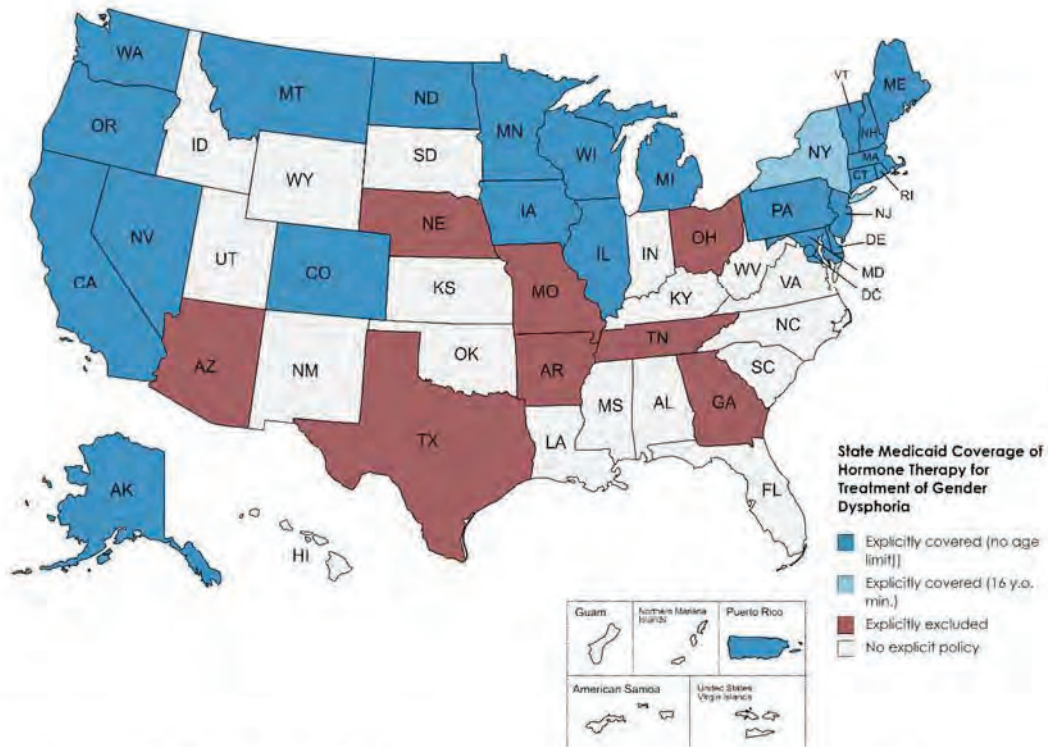


State Medicaid programs with coverage decisions regarding puberty blockers:

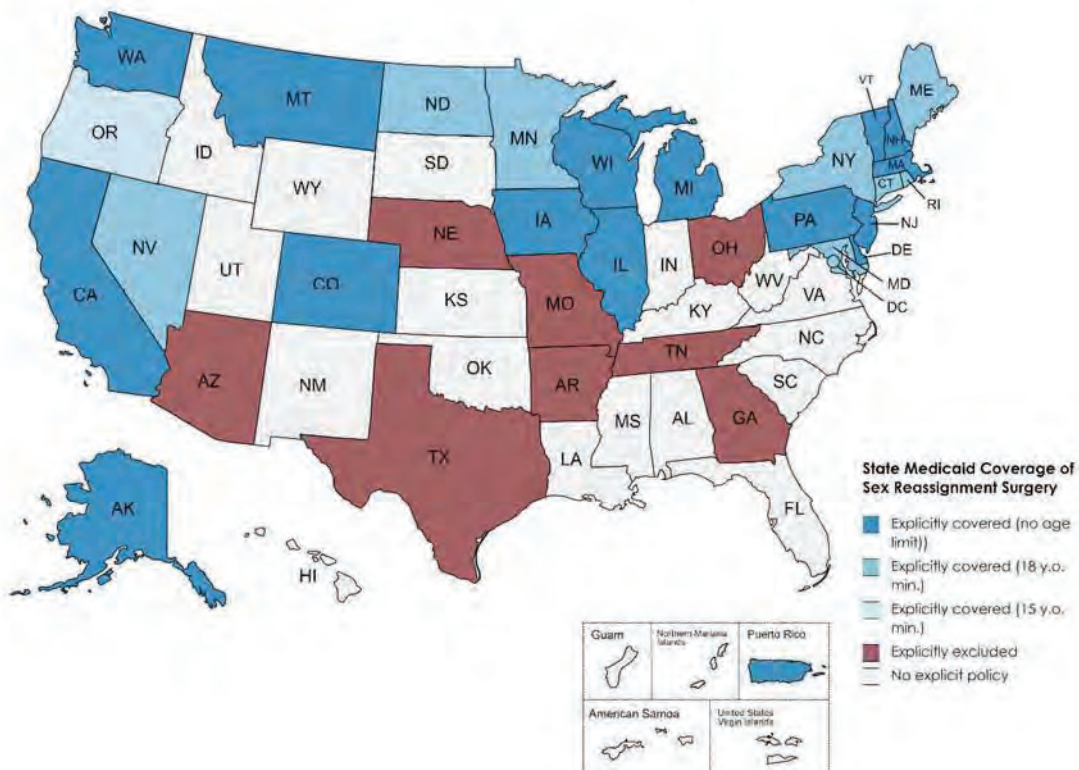




State Medicaid programs with coverage decisions regarding cross-sex hormones:



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).

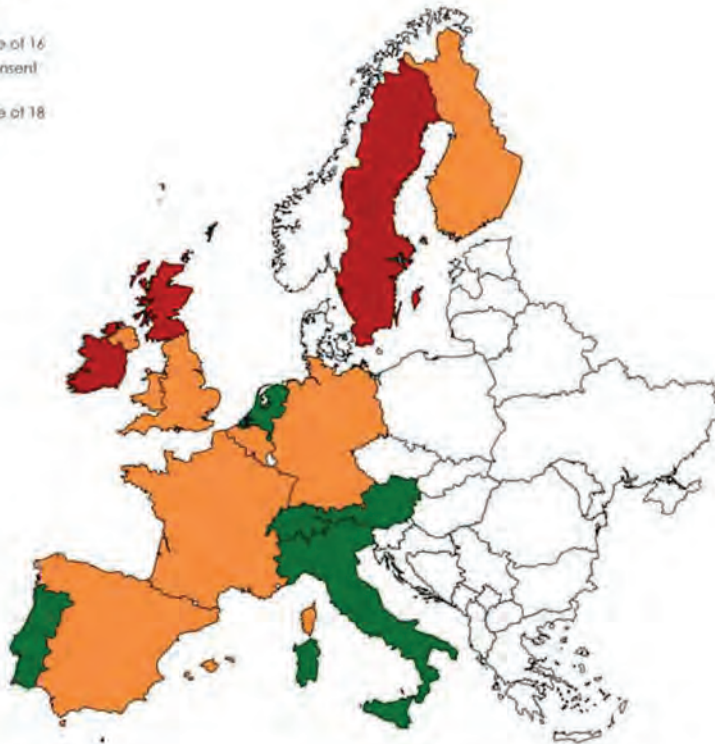
Like state Medicaid programs, health systems across Western Europe also vary in their coverage of sex reassignment treatment.



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



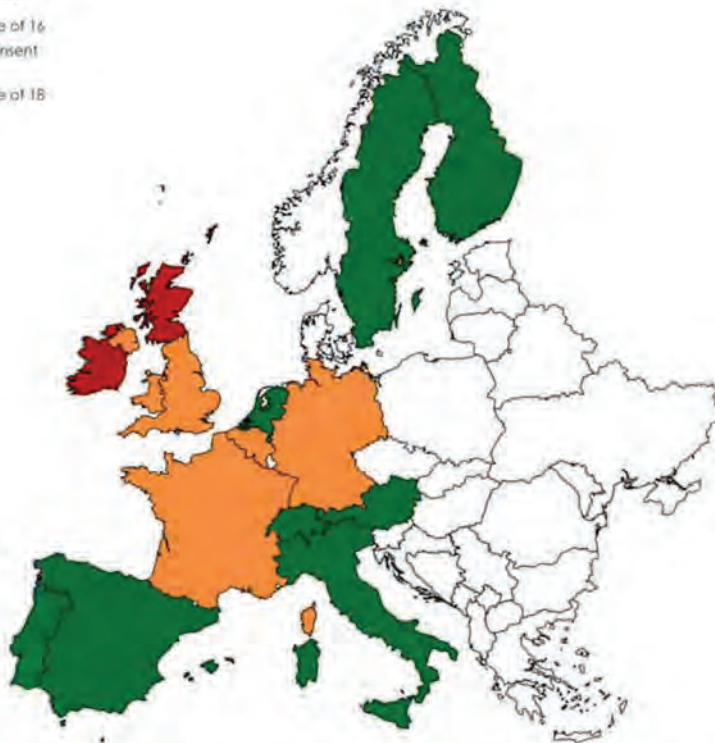
*In this context, the age requirement for access to any medical treatment without consent of parents or of a public authority. This age may range from 16 to 18 years depending on each country's laws.*



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:

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\_\_\_\_\_  
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.<sup>1</sup> 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 cursive.

Simone Marstiller  
Secretary

<sup>1</sup> 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. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Main report; May 16, 2022

**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



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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**



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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.



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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



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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.



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## 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:



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- **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)



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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.<sup>1</sup> 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.<sup>1</sup> 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



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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.



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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.<sup>2</sup> 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:

- $\bar{A}$  Outcomes: measurement method (including scales, if applicable) and follow-up
- $\bar{A}$  Estimates of effect: absolute and relative estimates of effect, and their corresponding 95% CIs.
- $\bar{A}$  Number of studies and participants providing evidence for the outcome
- $\bar{A}$  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
- $\bar{A}$  A narrative statement about what happens with the outcome, based on the estimate of effect and certainty of evidence.



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**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) tool<sup>3</sup> (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
<b>Confounding</b>	Adjusted for all relevant confounding factors	No adjustment
<b>Classification of intervention</b>	Intervention recorded prospectively or from medical records	Asked patients to recall whether they received the intervention
<b>Deviation from intended interventions</b>	No cointerventions or cointerventions balanced between the groups	Cointerventions unbalanced between the groups



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<b>Missing data</b>	More than 90% of patients who started the study provided outcome data	Less than 50% of patients who started the study provided outcome data
<b>Measurement of outcome</b>	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
<b>Representativeness of the sample</b>	Included all consecutive patients	Highly selected sample based on specific characteristics related with the prognosis after treatment
<b>Classification of the intervention</b>	Intervention recorded prospectively or from medical records	Asked patients to recall whether they received the intervention
<b>Deviation from intended interventions</b>	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
<b>Missing data</b>	More than 90% of patients who started the study provided outcome data	Less than 50% of patients who started the study provided outcome data
<b>Measurement of outcome</b>	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 medic\* 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	prostap.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	

*Gender-affirming Surgeries*

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



## Agency for Healthcare Research and Quality (AHRQ)

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

## Society for Evidence-based Gender Medicine (SEGM)

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

## National Institute for Health and Care Excellence (NICE)

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



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 ethinylestrad\* 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 cetorelix.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 cetorelix.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

#### *Surgery*

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



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

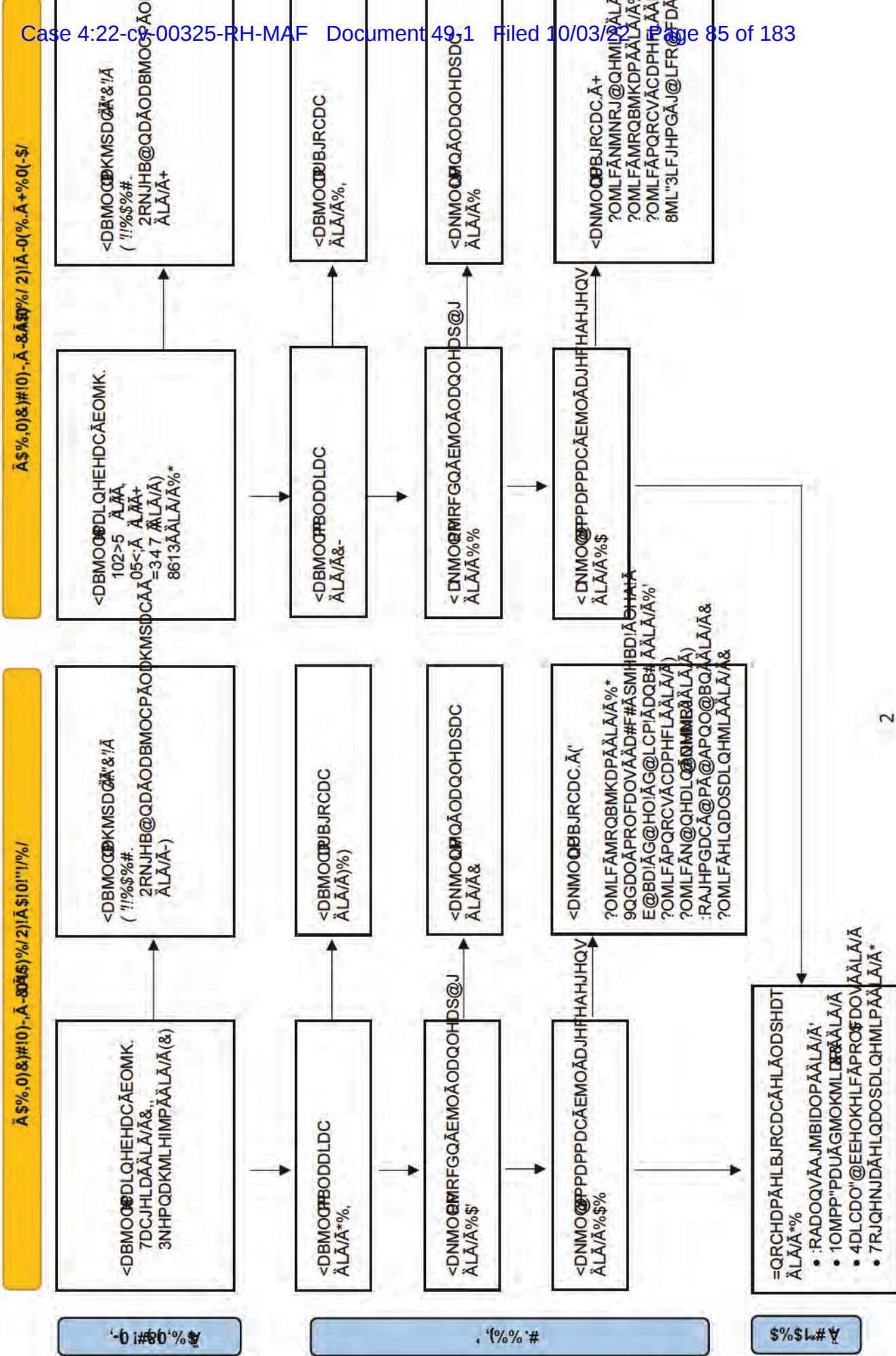
## Results

**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.



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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/>



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

## Outcomes:

**1. Puberty blockers:** We found 4 systematic reviews assessing the effects of puberty blockers published between 2020 and 2022.<sup>1-4</sup> 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.<sup>2,3</sup> 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

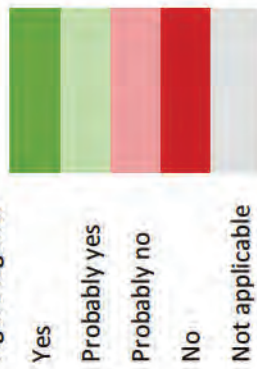


Effects of gender affirming therapies in people with gender dysphoria: evaluation of the best available evidence. Dr. Romina Brignardello-Petersen and Dr. Wojtek Wiercioch; Results; May 16, 2022

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	Probably yes	Probably yes	Probably yes	Probably yes	Probably no	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	No	No	No	No	No	No	No	No	No	CRITICALLY LOW
Rew 2020	Yes	No	No	Probably yes	Probably no	Probably yes	No	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 <sup>1</sup>	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



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

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

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
<b>Depression</b> 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 <sup>1</sup>	The mean depression score may decrease by 3.4 points after puberty blockers
<b>Anxiety</b> assessed with: difference (effect) in anxiety proportion or severity	Not reported	Not reported			The effects of puberty blockers on anxiety are unknown
<b>Anxiety</b> 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 <sup>1</sup>	The mean anxiety score may decrease by 1.5 points after puberty blockers



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

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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
<b>Quality of life</b> assessed with: any measure	Not reported				
<b>Suicidal ideation</b> difference (effect) in suicidal ideation (Rew, 2020) Follow-up: cross-sectional survey		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 <sup>2</sup>	We are very uncertain about the effect of puberty blockers on suicidal ideation
<b>Adverse effects</b> assessed with: proportion of patients reporting adverse effects (NICE, 2020a) Follow up: mean 2.3 years (range 0.0 to 11.3 years)		11% <sup>3</sup> (2% to 29%)	27 (1 study)	 LOW <sup>4</sup>	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.Å 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.Å 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.Å 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.Å 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).



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**2.  $\bar{A}$ Cross-sex hormones:** We found 9 systematic reviews assessing the effects of cross-sex hormones published between 2020 and 2022.<sup>4-12</sup> One of these, however, included both puberty blockers and cross-sex hormones combined in their evidence synthesis as was not prioritized.<sup>5</sup> 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 quality<sup>7</sup> 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.<sup>6,9,11,12</sup> 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.



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

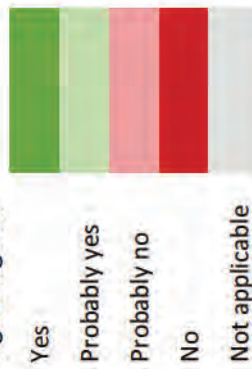


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Figure 3: AMSTAR assessment judgements for systematic reviews addressing cross-sex hormones

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	Red	Red	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	MODERATE
Baker 2021	Green	Green	Green	Green	Green	Green	Green	Green	Red	Red	Green	Green	Green	Red	Red	Red	MODERATE
Fledderus 2020	Green	Red	Red	Green	Green	Green	Red	Green	Green	Red	Red	Red	Red	Red	Red	Red	CRITICALLY LOW
Haupt 2020	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	HIGH
Karalexi 2020	Green	Green	Green	Green	Green	Green	Green	Green	Green	Red	Green	Red	Red	Green	Green	Green	LOW
Kotamarti 2021	Green	Green	Red	Green	Red	Red	Green	Green	Red	Red	Green	Red	Green	Green	Red	Red	CRITICALLY LOW
Mattawanon 2021	Green	Red	Red	Green	Green	Red	Red	Green	Red	Red	Green	Green	Red	Red	Red	Red	CRITICALLY LOW
NICE 2021b	Green	Red	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	Green	MODERATE
Totaro 2021	Green	Green	Red	Green	Green	Green	Green	Green	Green	Red	Green	Red	Red	Green	Green	Green	LOW

Figure legend:





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**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
<b>Gender dysphoria</b> assessed with: difference (effect) in gender dysphoria percentage or severity			Not reported			The effects of cross-sex hormones on gender dysphoria are unknown
<b>Gender dysphoria</b> 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 <sup>1</sup>	The mean gender dysphoria score may decrease by 42 points after cross-sex hormones
<b>Depression</b> 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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**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
<b>Depression</b> 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 <sup>2</sup>	NA	73 (2 studies)	⊕⊕○○ LOW <sup>1</sup>	The mean depression score may decrease after cross-sex hormones
<b>Depression</b> 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 <sup>1</sup>	The percentage of participants requiring treatment may be reduced by 39% after cross- sex hormones
<b>Anxiety</b> assessed with: difference (effect) in anxiety percentage or severity	Not reported		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)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
<b>Anxiety</b> assessed with: mean change score in anxiety scales (higher scores represent more severe anxiety) (NICE, 2020b) Follow-up: 1 year	Risk / mean with no cross-sex hormones NA	NA	23 (1 study)	⊕⊕○○ LOW <sup>1</sup>	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
<b>Anxiety</b> assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	Risk / mean with no cross-sex hormones NA	NA	52 (1 study)	⊕⊕○○ LOW <sup>1</sup>	The percentage of participants requiring treatment may decrease after cross-sex hormones
<b>Quality of life</b> assessed with: difference (effect) in quality of life improvement	Not reported				
The effects of cross-sex hormones on quality of life are unknown					



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

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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
<b>Quality of life</b> 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 <sup>3</sup>	We are very uncertain about the quality of life change after cross-sex hormones
<b>Suicide / suicidal ideation</b> assessed with: difference (effect) in suicide or suicidal ideation			Not reported			The effects of cross-sex hormones on suicide/ suicidal ideation are unknown
<b>Suicidality</b> 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 <sup>1</sup>	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
<b>Suicidal ideation</b> 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 <sup>3</sup>	We are very uncertain about the change in percentage of patients in suicidal ideation after cross-sex hormones
<b>Suicide attempts</b> assessed with: not reported (NICE, 2020b) Follow up: not reported	NA	NA	130 (1 study)	⊕○○○ VERY LOW <sup>3</sup>	We are very uncertain about the percentage of people with suicide attempts after cross-sex hormones
<b>Suicidality/ self-harm</b> assessed with: change in percentage of patients with need for treatment (NICE, 2020b) Follow-up: 1 year	NA	NA	52 (1 study)	⊕⊕○○ LOW <sup>1</sup>	The percentage of participants requiring treatment may be reduced by 31% after cross-sex hormones
<b>Venous thromboembolism</b> assessed with: Risk of VTE		Not reported			The effects of cross-sex hormones on the risk of VTE are unknown



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**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	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
<b>Venous thromboembolism</b> 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 <sup>4</sup>	The prevalence of VTE among assigned males at birth is probably 2% after cross-sex hormones
<b>Venous thromboembolism</b> assessed with: Prevalence among assigned females at birth (Kotamarti, 2021) Mean follow up: 5.7 years	NA	6 per 1,000 (CI not reported) <sup>5</sup>	NA	4,218 (8 studies)	⊕⊕⊕⊕ MODERATE <sup>6</sup>	The prevalence of VTE among assigned females at birth is probably 0.6% after cross-sex hormones
<b>Breast cancer</b> 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 <sup>7</sup>	The risk of breast cancer may not increase or decrease due to the use of cross-sex hormones



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**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	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
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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

**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.Ā** 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.



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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.



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**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).

**3.1.1 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.<sup>13 14</sup> 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:

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

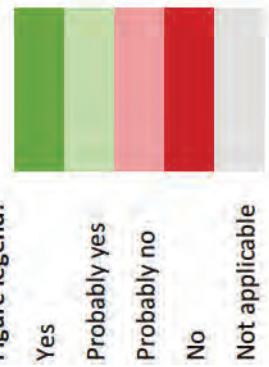


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Figure 4: AMSTAR assessment judgements for systematic reviews addressing gender-affirming surgery

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><b>Quality of life</b> 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)<sup>1</sup></p>	<p>NA</p>	<p>633 (5 studies)</p> <p> VERY LOW<sup>2</sup></p> <p>We are very uncertain about the quality of life after surgeries</p>
<p><b>Regret</b> 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><b>Regret</b> assessed with: percentage of people with regret (Bustos, 2021) Mean follow up: 4 years</p>	<p>NA</p>	<p>1% (0 to 2%)<sup>3</sup></p>	<p>NA</p>	<p>7928 (27 studies)</p> <p> LOW<sup>4</sup></p> <p>The percentage of people who experience regret is low</p>
<p>CI: Confidence interval NA: Not applicable</p>				
<p><b>GRADE Working Group grades of evidence</b> 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



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**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.<sup>13-17</sup> 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
<b>Chest surgery</b>					
<b>Satisfaction</b> assessed with: percentage of people who reported being satisfied (Bustos VP, 2020b) Range of follow up: 6 weeks to 46 months <sup>1</sup>	NA	NA	733 (14 studies)	⊕⊕○○ LOW <sup>3</sup>	The percentage of people who reports being satisfied may be 92%
<b>Surgical complications</b> 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 <sup>4</sup>	We are very uncertain about the rate of surgical complications
<b>Reoperation</b> 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 <sup>4</sup>	We are very uncertain about the rate of reoperation
<b>Bottom surgery</b>					



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**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><b>Satisfaction</b> 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%) <sup>§</sup>	NA	1458 (27 studies)	⊕○○○ VERY LOW <sup>4</sup>	We are very uncertain about the percentage of people who reports being satisfied
<p><b>Surgical complications- Major</b> 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) <sup>¶</sup>	⊕○○○ VERY LOW <sup>4</sup>	We are very uncertain about the percentage of people who experience major surgical complications
<p><b>Surgical complications- Minor</b> 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 <sup>7</sup>	NA	4466 (52 studies) <sup>§</sup>	⊕○○○ VERY LOW <sup>4</sup>	We are very uncertain about the percentage of people who experience minor surgical complications



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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
<b>Reoperation</b> assessed with: rate of reoperation across patients (Oles, 2022b) follow up: not reported	NA 27.6% Range (2.5% to 40%)	NA	1624 (15 studies)	 VERY LOW <sup>4</sup>	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. **⊖** Studies used different scales to assess satisfaction
2. **⊖** 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. **⊖** 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. **⊖** 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. **⊖** 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



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**3.3 Effects of surgeries on assigned males at birth:** Table 5 summarizes the evidence about the effects of all surgeries on surgical outcomes among assigned at birth males. We used information from 3 systematic reviews.<sup>16 18 19</sup> 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 vaginoplasty is high (91%)
- $\bar{A}$  There is very low certainty evidence about the percentage of people who are satisfied, the rate of complications, and the rate of reoperations after chest surgery (see Table 5 for details)
- $\bar{A}$  There is low certainty evidence suggesting that the percentage of people who have regret after vaginoplasty is low (2%)
- $\bar{A}$  There is very low certainty evidence about the rate of complications and the rate of reoperations after vaginoplasty (see Table 5 for details)



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**Table 5: All surgeries compared to no surgeries in assigned males at birth (<21 years old) with gender dysphoria**

Patient or population: assigned males at birth (<21 years old) with gender dysphoria  
 Intervention: surgeries  
 Comparison: no surgeries

Outcomes	Risk / mean with no surgery	Risk/ mean with surgery (95% CI)	Relative effect (95% CI)	No of participants (studies)	Certainty of the evidence (GRADE)	What happens
<b>Chest surgery</b>						
<b>Satisfaction</b> assessed with: percentage of people who reported being satisfied (Oles 2022) Range of follow up: 12 months to 17 years	NA	Range 75% (80/107) to 95% (33/35) <sup>1</sup>	NA	142 (2 studies)	⊕○○○ VERY LOW <sup>2</sup>	We are very uncertain about the percentage of people who report being satisfied
<b>Surgical complications</b> assessed with: rate of complications across patients (Oles 2022) Range of follow up: 2 weeks to 16 years	NA	The complication rates were: - 3.8% (range 0% to 5.5%) of capsular contracture - 2.2% of major hematoma - 2.2% of implant extrusion <sup>3</sup>	NA	432 (5 studies)	⊕○○○ VERY LOW <sup>2</sup>	We are very uncertain about the rate of surgical complications
<b>Reoperation</b> assessed with: rate of reoperation across patients (Oles 2022) Range of follow up: Not reported	NA	8.6% Range (4.4% to 10.4%)	NA	291 (2 studies)	⊕○○○ VERY LOW <sup>2</sup>	We are very uncertain about the rate of reoperation
<b>Bottom surgery</b>						



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Patient or population: assigned males at birth (<21 years old) with gender dysphoria  
 Intervention: surgeries  
 Comparison: no surgeries


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
<b>Satisfaction</b> assessed with: percentage of people who reported being satisfied for overall outcomes (Bustos SS, 2021) Range of follow up: 1 week to 11.3 years	NA	91% (81% to 98%) <sup>4</sup>	NA	1230 (12 studies)	⊕⊕○○ LOW <sup>5</sup>	The percentage of people who report being satisfied with overall outcomes may be 91%
<b>Regret</b> assessed with: percentage of people who reported regret (Bustos SS, 2021) Range of follow up: 2 months to 24.1 years	NA	2% (1% to 3%)	NA	1137 (15 studies)	⊕⊕○○ LOW <sup>6</sup>	The percentage of people who report regret may be 2%
<b>Surgical complications</b> assessed with: rate of complications across patients (Bustos SS, 2021) Range of follow up: 3 weeks to 24.1 years	NA	The complication rates were: - 1% (95% CI, <0.1% to 2%) of fistula - 11% (95% CI, 8% to 14%) of stenosis and/or strictures - 4% (95% CI, 1% to 9%) of tissue necrosis - 3% (95% CI, 1% to 4%) of prolapse <sup>7</sup>	NA	4196 (42 studies) <sup>3</sup>	⊕○○○ VERY LOW <sup>8</sup>	We are very uncertain about the rate of surgical complications



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 Intervention: surgeries  
 Comparison: no surgeries

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
<b>Reoperation</b> assessed with: rate of reoperation across patients (Tay, 2021) Range of follow up: 6 weeks to 14.8 months	NA	One study reported a surgical revision rate of 9% (1/11 patients), and a second study reported that 13% (19/145) patients required repeat surgery due to complications.	NA	156 (2 studies)	 VERY LOW <sup>s</sup>	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

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**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.A** Another systematic review, Sijben 2021, reported satisfaction from 3 additional studies: 82% (113/138) were satisfied or very satisfied, 93% (32/34) were happier and more satisfied with their chest, and 79% (28/36) were very satisfied with the overall cosmetic result (very low certainty of evidence due to risk of bias, imprecision, and indirectness).
2. **1.A** Rated down due to risk of bias, indirectness (the included studies were not restricted to youth or young adults), and imprecision (too few participants included, not meeting optimal information size).



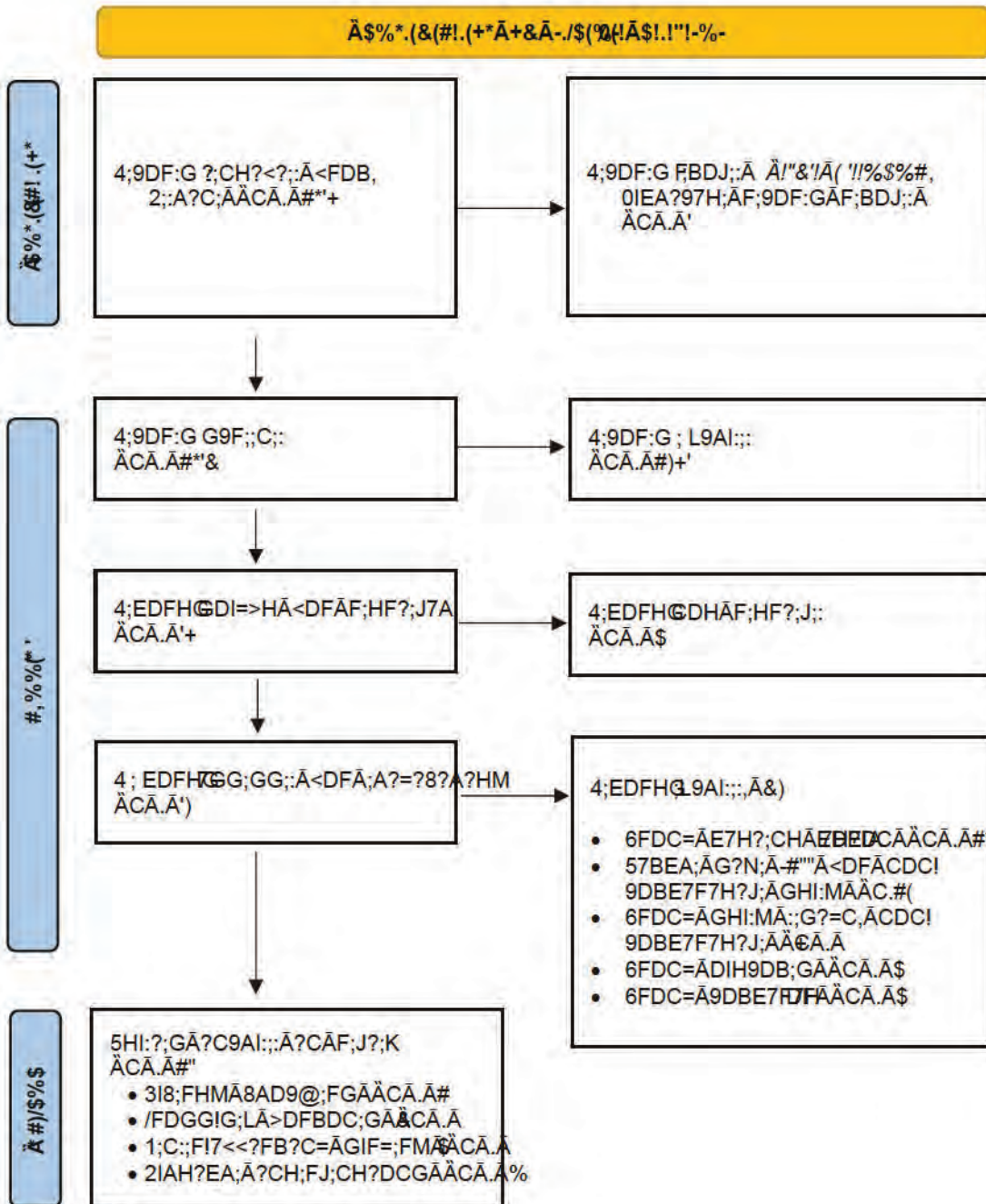
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3. Another systematic review, Sijben 2021, reported similar ranges for rates of complication requiring reoperation from 7 studies (835 patients): capsular contraction (range 0.0-5.6%), asymmetry (3.6%), hematoma (range 0.0-2.9%), infection (range 0.0-0.9%), striae distensae (0.7%), implant rupture (0.7%), abscess (0.4%), scarring (0.0%), hypersensitivity (0.0%), and numbness (0.0%) (very low certainty of evidence due to risk of bias, imprecision, and indirectness)
4. Bustos SS *et al.* 2021 additionally reported on satisfaction for functional (87%, 95% CI 77% to 94%) and aesthetic (90%, 95% CI 84% to 94%) outcomes. Another systematic review and meta-analysis, Oles 2022b, similarly reported that 92.3% (range 23.1% to 100%) of patients (2410/2601) were satisfied after vaginoplasty (very low certainty of evidence due to risk of bias, imprecision, and indirectness).
5. Rated down due to risk of bias (the systematic review authors reported the quality of the included studies to be low to moderate using the New Castle Ottawa scale), and indirectness as the included studies were not restricted to youth or young adults. We did not rate down for imprecision or inconsistency despite high  $I^2$  values as a satisfaction rate of 80% or above was deemed as a minimum threshold for clinical importance.
6. Rated down due to risk of bias (the systematic review authors reported the quality of the included studies to be low to moderate using the New Castle Ottawa scale), and indirectness as the included studies were not restricted to youth or young adults.
7. Another systematic review, Oles 2022b, similarly reported the percentage of patients experiencing complications from 51 studies, ranging from 2.4% to 12.0% (range 0% to 88%) for minor complications (intraoperative injury, wound dehiscence, superficial necrosis, infection, urinary issues, vaginal prolapse, stenosis, and bleeding) and 1.6% to 2.1% (range 0% to 31%) for major complications (flap/graft necrosis and infection) after genitoplasty (very low certainty of evidence due to risk of bias, imprecision, and indirectness).
8. Rated down due to risk of bias (the systematic review authors reported the quality of the included studies to be low to moderate using the New Castle Ottawa scale), imprecision and inconsistency, with wide confidence intervals and  $I^2$  values ranging from 65.8% to 94.3%, and indirectness as the included studies were not restricted to youth or young adults.
9. Rated down due to risk of bias, indirectness (the age range of patients in the included studies was 24 to 39 years; the studies included were restricted to those that investigated the use of peritoneum in neovagina construction), and imprecision (too few participants included, not meeting optimal information size).



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**Results from search for studies not included in the systematic reviews:** After screening 1854 records found through our searches, we found 10 eligible studies (figure 5). From these, 8 were comparative observational studies<sup>20-27</sup> and 2 were non-comparative<sup>28-29</sup>. We provide reasons for excluding studies in appendix 2.



**Figure 5:** PRISMA flow diagram for the selection of primary studies. *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/>



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None of the studies were judged as likely to importantly change the conclusions obtained from the systematic reviews (Tables 6 and 7). The main limitations of the comparative studies were risk of bias concerns (Figures 6 and 7) due to confounding, classification of intervention, and missing data; as well as small sample sizes. Although non-comparative studies were at lower risk of bias, because their results were consistent with those of the included evidence, they were also judged as unlikely to change the conclusions importantly.



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**Table 6: Characteristics of eligible comparative observational studies**

Study ID	Sample size*	Study design	Intervention	Comparator	Outcomes measured	Likely to change conclusions	Reasons
VanDerMiesen, 2020	450	Retrospective cohort study	Puberty blockers	Waiting for puberty blockers	Self-harm/suicidality, internalizing behaviors	No	Reports a small benefit on suicidality and moderate on internalizing behaviours, but high risk of bias
Becker-Hebly, 2021	75	Prospective cohort study	1. Puberty blockers 2. Cross-sex hormones 3. Surgery	No medical intervention yet; psychosocial intervention only	Health-related quality of life	No	Critical risk of bias (missing data due to low response rate, and confounding). Reports small benefit in mean change score for mental and physical dimension QoL as compared to no medical treatment. Imprecision; the 95% CIs for mean change scores are wide.
Green, 2021	3235	Cross-sectional study	Cross-sex hormones	Would like to take cross-sex hormones	Depression, suicidality	No	Critical risk of bias, no follow up of patients (measurement of current outcomes and not adjusting for baseline)
Tordoff, 2022	84	Prospective cohort study	1. Puberty blockers 2. Cross-sex hormones	No intervention	Depression, anxiety, suicidal thoughts	No	Moderate risk of bias, small sample size
Turban, 2022	9341	Cross-sectional study	Cross-sex hormones	Desired but never accessed gender affirming hormones	Suicidal ideation, suicidal attempt	No	Critical risk of bias, no follow up of patients (measurement of current outcomes and not adjusting for baseline)
Grannis, 2021	47	Cross-sectional study	Cross-sex hormones	No intervention yet	Anxiety, depression	No	Critical risk of bias, no follow up of patients, small sample size
Fontanari, 2020	350	Cross-sectional study	1. Cross-sex hormones 2. Cross-sex hormones or surgery	1. Waiting for cross-sex hormones 2. No intervention	Anxiety, depression, gender distress	No	Critical risk of bias (confounding, self-reported classification of interventions). Online cross-sectional survey reported small benefit in anxiety and depression mean scores, and little to no effect on gender distress with cross-sex hormones and/or surgery. Non-randomized comparative study provides very low certainty evidence due to



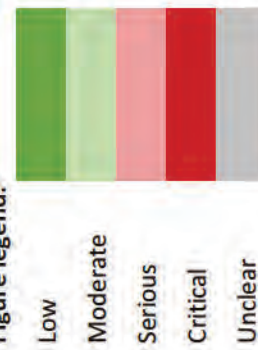


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Figure 6: Risk of bias judgements for comparative studies

Study ID	Intervention	Confounding	Classification of the intervention	Deviations from intended interventions	Missing data	Measurement of outcome	Overall
Becker-Hebly, 2021	Puberty blockers, cross-sex hormones, or surgery	Critical	Low	Low	Critical	Low	CRITICAL
Castelo-Branco, 2021	Cross-sex hormones	Critical	Low	Unclear	Low	Low	CRITICAL
Fontanari, 2020	Cross-sex hormones, cross-sex hormones or surgery	Critical	Moderate	Unclear	Low	Low	CRITICAL
Grannis, 2021	Cross-sex hormones	Critical	Low	Unclear	Low	Low	CRITICAL
Green, 2021	Cross-sex hormones	Critical	Critical	Unclear	Low	Low	CRITICAL
Tordoff, 2022	Puberty blockers, cross-sex hormones	Low	Low	Unclear	Low	Low	MODERATE
Turban, 2022	Cross-sex hormones	Critical	Critical	Unclear	Low	Low	CRITICAL
Van Der Miesen, 2020	Puberty blockers	Moderate	Low	Unclear	Low	Low	SERIOUS

Figure legend:



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Figure 7: Risk of bias judgements for non-comparative studies

Study ID	Intervention	Representativeness of sample	Classification of intervention	Deviation from intended interventions	Missing data	Measurement of outcome	Overall
Bordas, 2021	FtM bottom surgery	Low	Low	Low	Low	Low	LOW
Elias, 2022	FtM top surgery	Moderate	Moderate	Moderate	High	Moderate	MODERATE

Figure legend:





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ID	Study	Reason
#534	Abu-Ghname 2020	Wrong population: non transgender men
#434	Aires 2022	Wrong interventions: Other type of surgery: glottoplasty Wrong outcomes: It does not include any outcome of interest. Includes: serum total testosterone concentration, body fat redistribution, breast development, and facial/body hair reduction
#514	Angus 2021	Wrong intervention. Continuing vs stopping estrogen during perioperative period of vaginoplasty
#318	Baddredine 2022	Wrong outcomes: only clinical outcomes are sperm count, testicular histology, hormone levels, etc.
#40	Baram 2019	Wrong outcomes: sexual satisfaction, desire, and function outcomes only
#145	Barcelos 2022	No outcome data
#60	Boczar 2021	Wrong population: unclear that more than 80% are transgender
#386	Bouman 2014	Wrong intervention: nipple areola reconstruction
#208	Bustos 2021	Wrong outcomes: Blood pressure
#54	Connelly 2021	Wrong intervention: facial gender surgery
#43	Coon 2022	Wrong design: narrative review
#34	D'Angelo 2018	Wrong outcomes: bone density
#165	Delgado-Ruiz 2019	Other type of surgery: facial surgery
#355	Escandon 2022	Wrong outcomes: bone mass
#129	Fighera 2019	Practice guideline, does not report the methods/ results of the systematic review in details
#597	Hembree 2017	Wrong outcomes: histological findings
#120	Kakadekar 2021	Wrong intervention: self administered hormones
#451	Kennedy 2021	Wrong outcomes: sexual health and satisfaction outcomes only
#375	Kloer 2021	More than 20% participants did not have gender dysphoria
#439	Kovar 2019	Wrong outcomes: aggression and hostility
#297	Kristensen 2021	Wrong design: commentary of a systematic review
#637	Leclere 2015	Published in abstract format only
#293	Miranda 2021	Wrong intervention: facial feminization surgery
#624	Morrison 2016	Wrong design: narrative review
#270	Narayan 2021	Wrong intervention: phonosurgery
#119	Nolan 2019	Wrong intervention: facial hair transplantation
#167	Patel 2021	Wrong population: cisgender is the population of interest, transgender included as indirect evidence and not in a systematic manner
#287	Ray 2020	Published in abstract format only
#518	Rozga 2020	Wrong population: More than 20% participants did not have gender dysphoria
#265	Sariyaka 2017	Wrong intervention: facial masculinization surgery
#35	Sayegh 2019	Wrong intervention: laryngeal surgery
#124	Schwarz 2017	

#97	Siringo 2021	Wrong intervention: facial feminization surgery
#253	Song 2016	Wrong intervention: phonosurgery
#250	Song 2017	Wrong intervention: phonosurgery
#104	Spanos 2020	Wrong outcomes: lean mass, fat mass or insulin resistance
#257	Therattil 2017	Wrong intervention: thyroid cartilage reduction surgery
#328	Tirrell 2022	Wrong intervention: facial feminization surgery
#676	Traish 2010	Wrong design: narrative review
#279	VanDamme 2017	Wrong intervention: voice pitch raising surgery
#171	Vellho 2017	Wrong outcomes: BMI, blood pressure, hematocrit, hemoglobin, lipid profile, and liver enzymes
#112	Wilson 2020	Wrong outcomes: prolactine related outcomes (levels, hyperprolactinemia, prolactinoma)
#245	Worth 2018	Unable to access full text
#122	Ziegler 2018	Wrong outcomes: voice parameters and satisfaction with voice
#499	Zucker 2021	Unable to access full text



ID	Study	Reason
#1458	Al-Tamimi 2019	Wrong patient population
#287	Al-Tamimi 2020	Wrong study design: non comparative
#403	Alcon 2021	Wrong study design: non comparative
#214	Aldridge 2021	Wrong study design: non comparative
#54	Almazan 2021	Wrong patient population
#1387	Boas 2019	Wrong patient population
#1323	Branstrom 2020	Wrong patient population
#1447	Breidenstein 2019	Wrong study design: non comparative
#114	Briles 2022	Insufficient Sample Size <100
#1804	Butler 2019	Wrong patient population
#716	Carmichael 2021	Wrong study design: non comparative
#622	Cocchetti 2021	Wrong outcomes
#1067	Coon 2020	Wrong patient population
#1835	Cristofari 2019	Wrong patient population
#1486	Cuccolo 2019	Wrong patient population
#1276	deBlok 2020	Wrong patient population
#577	deRooij 2021	Wrong patient population
#1625	DeWolf 2019	Wrong patient population
#1759	Djordjevic 2019	Wrong patient population
#244	Falcone 2020	Insufficient Sample Size <100
#258	FosterSkewis 2021	Wrong comparator
#1583	Gallagher 2019	Wrong patient population
#139	Gumussoy 2022	Wrong study design: non comparative
#515	Hisle-Gorman 2021	Wrong study design: non comparative
#350	Hougen 2021	Insufficient Sample Size <100
#1007	Meyer 2020	Wrong study design: non comparative
#499	Miller 2021	Wrong patient population
#621	Mullins 2021	Wrong study design: non comparative
#1653	Naeimi 2019	Insufficient Sample Size <100
#1691	Namba 2019	Insufficient Sample Size <100
#1770	Neuville 2019	Insufficient Sample Size <100
#623	Neuville 2021	Insufficient Sample Size <100
#644	Nieder 2021	Insufficient Sample Size <100
#1624	Nikkels 2019	Wrong patient population
#353	Opsomer 2021	Wrong patient population
#1306	Papadopulos 2020	Wrong comparator
#640	Papadopulos 2021	Insufficient Sample Size <100
#1472	Pigot 2019	Wrong patient population
#899	Pigot 2020	Insufficient Sample Size <100
#1212	Segev-Becker 2020	Insufficient Sample Size <100
#1351	Staples 2020	Wrong outcomes
#645	Staud 2021	Insufficient Sample Size <100
#864	Terrier 2020	Insufficient Sample Size <100
#1083	vanderSluis 2020	Insufficient Sample Size <100

#1204	Veerman 2020	Insufficient Sample Size <100
#1409	Watanabe 2019	Wrong patient population
#512	Waterschoot 2021	Insufficient Sample Size <100



## Appendix Attachment

1d

# ATTACHMENT D



**THE SCIENCE OF GENDER DYSPHORIA  
AND TRANSSEXUALISM**

**REPORT SUBMITTED TO THE  
FLORIDA AGENCY FOR HEALTHCARE ADMINISTRATION**

**JAMES M. CANTOR, PHD**

**17 MAY 2022**

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## **I.Ā Background & Credentials**

1.Ā I am a research scientist and clinical psychologist and am currently the Director of the Toronto Sexuality Centre in Canada. For my education and training, I received my Bachelor of Science degree from Rensselaer Polytechnic Institute, where I studied mathematics, physics, and computer science. I received my Master of Arts degree in psychology from Boston University, where I studied neuropsychology. I earned my Doctoral degree in psychology from McGill University, which included successfully defending my doctoral dissertation studying the effects of psychiatric medication and neurochemical changes on sexual behavior, and included a clinical internship assessing and treating people with a wide range of sexual and gender identity issues.

2.Ā Over my academic career, my posts have included Senior Scientist and Psychologist at the Centre for Addiction and Mental Health (CAMH), Head of Research for CAMH's Sexual Behaviour Clinic, Associate Professor of Psychiatry on the University of Toronto Faculty of Medicine, and Editor-in-Chief of the peer reviewed journal, *Sexual Abuse*. That journal is one of the top-impact, peer-reviewed journals in sexual behavior science and is the official journal of the Association for the Treatment of Sexual Abusers. In that appointment, I was charged to be the final arbiter for impartially deciding which contributions from other scientists in my field merited publication. I believe that appointment indicates not only my extensive experience evaluating scientific claims and methods, but also the faith put in me by the other scientists in my field. I have also served on the Editorial Boards of the *Journal of Sex Research*, the *Archives of Sexual Behavior*, and *Journal of Sexual Aggression*. Thus, although I cannot speak for other scientists, I regularly interact with and am routinely exposed to the views and opinions of most of the scientists active in our field today, within the United States and throughout the world.

3.Ā My scientific expertise spans the biological and non-biological development



of human sexuality, the classification of sexual interest patterns, the assessment and treatment of atypical sexualities, and the application of statistics and research methodology in sex research. I am the author of over 50 peer-reviewed articles in my field, spanning the development of sexual orientation, gender identity, hypersexuality, and atypical sexualities collectively referred to as *paraphilias*. I am the author of the past three editions of the gender identity and atypical sexualities chapter of the *Oxford Textbook of Psychopathology*. These works are now routinely cited in the field and are included in numerous other textbooks of sex research.

4. I began providing clinical services to people with gender dysphoria in 1998. I trained under Dr. Ray Blanchard of CAMH and have participated in the assessment and treatment of over one hundred individuals at various stages of considering and enacting both transition and detransition, including its legal, social, and medical (both cross-hormonal and surgical) aspects. My clinical experience includes the assessment and treatment of several thousand individuals experiencing other atypical sexuality issues. I am regularly called upon to provide objective assessment of the science of human sexuality by the courts (prosecution and defense), professional media, and mental health care providers.

5. A substantial proportion of the existing research on gender dysphoria comes from two clinics, one in Canada and one in the Netherlands. The CAMH gender clinic (previously, Clarke Institute of Psychiatry) was in operation for several decades, and its research was directed by Dr. Kenneth Zucker. I was employed by CAMH between 1998 and 2018. Although I was a member of the hospital's adult forensic program, I remained in regular contact with members of the CAMH child psychiatry program (of which Dr. Zucker was a member), and we collaborated on multiple research projects.

## II. Summary of Conclusions



- The scientific research consistently demonstrates that there is more than one distinct phenomenon that can lead to gender dysphoria. These types are distinguished by differing epidemiological and demographic patterns, unique psychological and behavioral profiles, and differing responses to the treatment options.
- Studies show that otherwise mentally healthy adults—undergoing thorough assessment (1–2 year Real Life Experience) and supervised by clinics engaged in gate-keeping roles—adjust well to life as the opposite sex.
- Regarding pre-pubescent children with gender dysphoria, there have been 11 outcomes studies. All 11 reported the majority of children to cease to feel dysphoric by puberty. They typically report being gay or lesbian instead.
- Regarding pubescent and adolescent age minors, there have been (also) 11 follow-up studies of puberty blockers and cross-sex hormones. In four, mental health failed to improve at all. In five, mental health improved, but because psychotherapy and medical interventions were both provided, which one caused the improvement could not be identified. The two remaining studies employed methods that did permit psychotherapy effects to be distinguished from medical effects, and neither found medical intervention to be superior to psychotherapy-only.
- The research importantly distinguishes completed suicides—which occur primarily in biological males and involve the intent to die—from suicidal ideation, gestures, and attempts—which occur primarily in biological females and represent psychological distress and cries for help. The evidence is minimally consistent with transphobia being the predominant cause of suicidality. The evidence is very strongly consistent with the hypothesis that other mental health issues, such as Borderline Personality Disorder (BPD), cause suicidality and unstable identities, including gender identity confusion.
- The international consensus of public health care services is that there remains no evidence to support medicalized transition for youth. The responses in the U.S. stand in stark contrast with Sweden, Finland, France, and the United Kingdom, which are issuing increasingly restrictive statements and policies, including bans on all medical transition of minors.

### III. Science of Gender Dysphoria and Transsexualism

6. One of the most widespread public misunderstandings about transsexualism and people with gender dysphoria is that all cases of gender dysphoria represent the same phenomenon; however, the clinical science has long and consistently demonstrated that gender dysphoric children (cases of *early-onset* gender dysphoria) do not represent the same phenomenon as adult gender dysphoria



(cases of *late-onset* gender dysphoria),<sup>1</sup> merely attending clinics at younger ages. That is, gender dysphoric children are not simply younger versions of gender dysphoric adults. They differ in every known regard, from sexual interest patterns, to responses to treatments. A third presentation has recently become increasingly observed among people presenting to gender clinics: These cases appear to have an onset in adolescence in the absence of any childhood history of gender dysphoria. Such cases have been called adolescent-onset or “rapid-onset” gender dysphoria (ROGD). Very many public misunderstandings and expert misstatements come from misattributing evidence or personal experience from one of these types to another.

### **A. Adult-Onset Gender Dysphoria**

7. People with adult-onset gender dysphoria typically attend clinics requesting transition services in mid-adulthood, usually in their 30s or 40s. Such individuals are nearly exclusively biological males.<sup>2</sup> They typically report being sexually attracted to women and sometimes to both men and women. Some cases profess asexuality, but very few indicate any sexual interest in or behavior involving men.<sup>3</sup> Cases of adult-onset gender dysphoria are typically associated with a sexual interest pattern (medically, a *paraphilia*) involving themselves in female form.<sup>4</sup>

#### **1. Outcome Studies of Transition in Adult-Onset Gender Dysphoria**

8. Clinical research facilities studying gender dysphoria have repeatedly reported low rates of regret (less than 3%) among adult-onset patients who underwent complete transition (*i.e.*, social, plus hormonal, plus surgical transition). This has been widely reported by clinics in Canada,<sup>5</sup> Sweden,<sup>6</sup> and the Netherlands.<sup>7</sup>

9. Importantly, each of the Canadian, Swedish, and Dutch clinics for adults

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<sup>1</sup> Blanchard, 1985.

<sup>2</sup> Blanchard, 1990, 1991.

<sup>3</sup> Blanchard, 1988.

<sup>4</sup> Blanchard 1989a, 1989b, 1991.

<sup>5</sup> Blanchard, *et al.*, 1989.

<sup>6</sup> Dhejneberg, *et al.*, 2014.

<sup>7</sup> Wiepjes, *et al.*, 2018.



with gender dysphoria all performed “gate-keeping” procedures, disqualifying from medical services people with mental health or other contraindications. One would not expect the same results to emerge in the absence of such gate-keeping or when gate-keepers apply only minimal standards or cursory assessment.

10. An important caution applies to interpreting these results: The side-effect of removing these people from the samples of transitioners is that if a researcher compared the average mental health of individuals coming into the clinic with the average mental health of individuals going through medical transition, then the post-transition group would appear to show a substantial improvement, even though transition had *no effect at all*: The removal of people with poorer mental health created the statistical illusion of improvement among the remaining people.

## **2. Mental Health Issues in Adult-Onset Gender Dysphoria**

11. The research evidence on mental health issues in gender dysphoria indicates it to be different between adult-onset versus adolescent-onset versus prepubescent-onset types. The co-occurrence of mental illness with gender dysphoria in adults is widely recognized and widely documented.<sup>8</sup> A research team in 2016 published a comprehensive and systematic review of all studies examining rates of mental health issues in transgender adults.<sup>9</sup> There were 38 studies in total. The review indicated that many studies were methodologically weak, but nonetheless demonstrated (1) that rates of mental health issues among people are highly elevated both before *and after* transition, (2) but that rates were less elevated among those who completed transition. Analyses were not conducted in a way so as to compare the elevation in mental health issues observed among people newly attending clinics to improvement after transition. Also, several studies showed more than 40% of patients to become “lost to follow-up.” With attrition rates that high, it is unclear to what

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<sup>8</sup> See, e.g., Hepp, *et al.*, 2005.

<sup>9</sup> Dhejne, *et al.*, 2016.



extent the information from the remaining participants would accurately reflect the whole population. The very high rate of “lost to follow-up” leaves open the possibility of considerably more negative results overall.

12. The long-standing and consistent finding that gender dysphoric adults continue to show high rates of mental health issues after transition indicates a critical point: To the extent that gender dysphoric children resemble adults, we should not expect mental health to improve as a result of transition—that is, transition does not appear to be what causes mental health improvement. Rather, mental health issues should be resolved before any transition, as has been noted in multiple standards of care documents, as detailed in their own section of this report.

## **B. Childhood Onset (Pre-Puberty) Gender Dysphoria**

### **1. Follow-up Studies Show Most Children Desist by Puberty**

13. Prepubescent children (and their parents) have been approaching mental health professionals for help with their unhappiness with their sex and belief they would be happier living as the other for many decades. The large majority of childhood onset cases of gender dysphoria occur in biological males, with clinics reporting 2–6 biological male children to each female.<sup>10</sup>

14. In total, there have been 11 outcomes studies of these children, listed in Appendix 1. In sum, despite coming from a variety of countries, conducted by a variety of labs, using a variety of methods, all spanning four decades, every study without exception has come to the identical conclusion: Among prepubescent children who feel gender dysphoric, the majority cease to want to be the other gender over the course of puberty—ranging from 61–88% desistance across the large, prospective studies. Such cases are often referred to as “desisters,” whereas children who continue to feel gender dysphoric are often called “persisters.”

15. Notably, in most cases, these children were receiving professional

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<sup>10</sup> Cohen-Kettenis, *et al.*, 2003; Steensma, *et al.*, 2018; Wood, *et al.*, 2013.



psychosocial support across the study period aimed, not at affirming cross-gender identification, but at resolving stressors and issues potentially interfering with desistance. While beneficial to these children and their families, the inclusion of therapy in the study protocol represents a complication for the interpretation of the results: It is not possible to know to what extent the outcomes were influenced by the psychosocial support or would have emerged regardless. In science, this is referred to as a confound.

16.Ā While the absolute number of those who present as prepubescent children with gender dysphoria and “persist” through adolescence is very small in relation to the total population, persistence in some subjects was observed in each of these studies. Thus, a clinician cannot take either outcome for granted.

17.Ā It is because of this long-established and unanimous research finding of desistance being probable but not inevitable, that the “watchful waiting” method became the standard approach for assisting gender dysphoric children. The balance of potential risks to potential benefits is very different for groups likely to desist versus groups unlikely to desist: If a child is very likely to persist, then taking on the risks of medical transition might be more worthwhile than if that child is very likely to desist in transgender feelings.

18.Ā The consistent observation of high rates of desistance among pre-pubertal children who present with gender dysphoria demonstrates a pivotally important—yet often overlooked—feature: because gender dysphoria so often desists on its own, clinical researchers cannot assume that therapeutic intervention cannot facilitate or speed desistance for at least some patients. That is, gender identity is not the same as sexual orientation, and it cannot be assumed that gender identity is as unchangeable as is sexual orientation. Such is an empirical question, and there has not yet been any such study.

19.Ā It is also important to note that research has not yet identified any reliable



procedure for discerning which children who present with gender dysphoria will persist, as against the majority who will desist, absent transition and “affirmation.” Such a method would be valuable, as the more accurately that potential persisters can be distinguished from desisters, the better the risks and benefits of options can be weighted. Such “risk prediction” and “test construction” are standard components of applied statistics in the behavioral sciences. Multiple research teams have reported that, on average, groups of persisters are somewhat more gender non-conforming than desisters, but not so different as to usefully predict the course of a particular child.<sup>11</sup>

20. In contrast, one research team (the aforementioned Olson group) claimed the opposite, asserting that they developed a method of distinguishing persisters from desisters, using a single composite score representing a combination of children’s “peer preference, toy preference, clothing preference, gender similarity, and gender identity.”<sup>12</sup> They reported a statistical association (mathematically equivalent to a correlation) between that composite score and the probability of persistence. As they indicated, “Our model predicted that a child with a gender-nonconformity score of .50 would have roughly a .30 probability . . . of socially transitioning. By contrast, a child with gender-nonconformity score of .75 would have roughly a .48 probability.”<sup>13</sup> Although the Olson team declared that “social transitions may be predictable from gender identification and preferences,”<sup>14</sup> their actual results suggest the opposite: The gender-nonconforming group who went on to transition (socially) had a mean composite score of .73 (which is less than .75), and the gender-nonconforming group who did not transition had a mean composite score of .61, also less than .75.<sup>15</sup> Both of those are lower than the value of .75, so both of those would be more likely than not

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<sup>11</sup> Singh, *et al.* (2021); Steensma *et al.*, 2013.

<sup>12</sup> Rae, *et al.*, 2019, at 671.

<sup>13</sup> Rae, *et al.*, 2019, at 673.

<sup>14</sup> Rae, *et al.*, 2019, at 669.

<sup>15</sup> Rae, *et al.*, 2019, Supplemental Material at 6, Table S1, bottom line.



to desist, rather than to proceed to transition. That is, Olson’s model does not distinguish likely from unlikely to transition; rather, it distinguishes unlikely from even less likely to transition.

21. Although it remains possible for some future discovery to yield a method to identify with sufficient accuracy which gender dysphoric children will persist, there does not exist such a method at the present time. Moreover, in the absence of long-term follow-up, it cannot be known what proportions come to regret having transitioned and then *detransition*. Because only a minority of gender dysphoric children persist in feeling gender dysphoric in the first place, “transition-on-demand” increases the probability of unnecessary transition and unnecessary medical risks.

### **2. “Watchful Waiting” and “The Dutch Protocol”**

22. It was this state of the science—that the majority of prepubescent children will desist in their feelings of gender dysphoria and that we lack an accurate method of identifying which children will persist—that led to the development of a clinical approach, The Dutch Protocol,<sup>16</sup> including its “Watchful Waiting” period. Internationally, the Dutch Protocol remains the most empirically supported protocol for the treatment of children with gender dysphoria.

23. The purpose of the protocol was to compromise the conflicting needs among: clients’ initial wishes upon assessment, the long-established and repeated observation that those wishes will change in the majority of (but not in all) childhood cases, and that cosmetic aspects of medical transition are perceived to be better when they occur earlier rather than later.

24. The Dutch Protocol was developed over many years by the Netherlands’ child gender identity clinic, incorporating the accumulating findings from their own research as well as those reported by other clinics working with gender dysphoric

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<sup>16</sup> Delemarre-van de Waal & Cohen-Kettenis (2006).



children. They summarized and explicated the approach in their peer-reviewed report, *Clinical management of gender dysphoria in children and adolescents: The Dutch Approach*.<sup>17</sup> The components of the Dutch Approach are:

- Ã no social transition at all considered before age 12 (watchful waiting period),
- Ã no puberty blockers considered before age 12,
- Ã cross-sex hormones considered only after age 16, and
- Ã resolution of mental health issues before any transition.

25.Ã For youth under age 12, “the general recommendation is watchful waiting and carefully observing how gender dysphoria develops in the first stages of puberty.”<sup>18</sup>

26.Ã The age cut-offs of the Dutch Approach were not based on any research demonstrating their superiority over other potential age cut-off’s. Rather, they were chosen to correspond to the ages of consent to medical procedures under Dutch law. Nevertheless, whatever the original rationale, the data from this clinic simply contain no information about the safety or efficacy of employing these measures at younger ages.

27.Ã The authors of the Dutch Approach repeatedly and consistently emphasize the need for extensive mental health assessment, including clinical interviews, formal psychological testing with validated psychometric instruments, and multiple sessions with the child and the child’s parents.

28.Ã Within the Dutch approach, there is no social transition before age twelve. That is, social affirmation of the new gender may not begin until age 12—as desistance is less likely to occur past that age. “Watchful Waiting” refers to a child’s developmental period up to that age. Watchful waiting does not mean do nothing but passively observe the child. Rather, such children and families typically present with substantial distress involving both gender and non-gender issues, and it is during the watchful waiting period that a child (and other family members as appropriate) would

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<sup>17</sup> de Vries & Cohen-Kettenis, 2012

<sup>18</sup> de Vries & Cohen-Kettenis, 2012, at 301.



undergo therapy, resolving other issues which may be exacerbating psychological stress or dysphoria. As noted by the Dutch clinic, “[T]he adolescents in this study received extensive family or other social support . . . [and they] were all regularly seen by one of the clinic’s psychologists or psychiatrists.”<sup>19</sup> One is actively treating the person, while carefully “watching” the dysphoria.

### **3. Follow-Up Studies of Puberty Blockers and Cross-Sex Hormones**

29. Very many strong claims have appeared in the media and on social media asserting that transition results in improved mental health or, contradictorily, in decreased mental health. In the highly politicized context of gender and transgender research, many outlets have cited only the findings which appear to support one side, cherry-picking from the complete set of research reports. In total, there have been 11 prospective outcomes studies following up gender dysphoric children undergoing medically induced suppression of puberty or cross-sex hormone treatment. Four studies failed to find evidence of improvement in mental health functioning at all, and some groups deteriorated on some variables.<sup>20</sup> Five studies successfully identified evidence of improvement, but because patients received psychotherapy along with medical services, which of those treatments caused the improvement is unknowable.<sup>21</sup> In the remaining two studies, both psychotherapy and medical interventions were provided, but the studies were designed in such a way as to allow the effects of psychotherapy to be separated from the effects of the puberty-blocking medications.<sup>22</sup> As detailed in the following, neither identified benefits of medication over psychotherapy alone.

#### **a. Four studies found no mental health improvement**

30. Carmichael, *et al.* (2021) recently released its findings from the Tavistock

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<sup>19</sup> de Vries, *et al.*, 2011, at 2280-2281.

<sup>20</sup> Carmichael, *et al.*, 2021; Hisle-Gorman, *et al.*, 2021; Kaltiala, *et al.*, 2020; Kuper, *et al.*, 2020.

<sup>21</sup> de Vries, *et al.*, 2011; Tordoff, *et al.*, 2022; van der Miesen, *et al.*, 2020.

<sup>22</sup> Achille, *et al.*, 2020; Costa, *et al.*, 2015.



and Portman clinic in the U.K.<sup>23</sup> Study participants were ages 12–15 (Tanner stage 3 for natal males, Tanner stage 2 for natal females) and were repeatedly tested before beginning puberty-blocking medications and then every six months thereafter. Cases exhibiting serious mental illnesses (*e.g.*, psychosis, bipolar disorder, anorexia nervosa, severe body-dysmorphic disorder unrelated to gender dysphoria) were excluded. Relative to the time point before beginning puberty suppression, there were *no* significant changes in any psychological measure, from either the patients' or their parents' perspective.

31.Ā In Kuper, *et al.* (2020), a multidisciplinary team from Dallas published a prospective follow-up study which included 25 youths as they began puberty suppression.<sup>24</sup> (The other 123 study participants were undergoing cross-sex hormone treatment.) Interventions were administered according to practice guidelines from the Endocrine Society.<sup>25</sup> Their analyses found *no statistically significant changes* in the group undergoing puberty suppression on any of the nine measures of wellbeing measured, spanning tests of body satisfaction, depressive symptoms, or anxiety symptoms.<sup>26</sup> Notably, whereas the Dutch Protocol includes age 12 as a minimum for puberty suppression treatment, this team provided such treatment beginning at age 9.8 years (full range: 9.8–14.9 years).<sup>27</sup>

32.Ā Hisle-Gorman, *et al.* (2021) analyzed military families' healthcare data to compare 963 transgender and gender-diverse youth before versus after hormonal treatment, with their non-gender dysphoric siblings as controls. The study participants included youth undergoing puberty-blocking as well as those undergoing cross-sex hormone treatment, but these subgroups did not differ from each other. Study participants had a mean age of 18 years when beginning the study, but their

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<sup>23</sup> Carmichael, *et al.*, 2021.

<sup>24</sup> Kuper, *et al.*, 2020, at 5.

<sup>25</sup> Kuper, *et al.*, 2020, at 3, referring to Hembree, *et al.*, 2017.

<sup>26</sup> Kuper, *et al.*, 2020, at Table 2.

<sup>27</sup> Kuper, *et al.*, 2020, at 4.



initial clinical contacts and diagnoses occurred at a mean age of 10 years. According to the study, “mental health care visits overall did not significantly change following gender-affirming pharmaceutical care,”<sup>28</sup> yet, “psychotropic medication use *increased*,”<sup>29</sup> indicating *deteriorating* mental health.

33. Kaltiala et al. (2020) similarly reported that after cross-sex hormone treatment, “Those who had psychiatric treatment needs or problems in school, peer relationships and managing everyday matters outside of home continued to have problems during real-life.”<sup>30</sup> They concluded, “Medical gender reassignment is not enough to improve functioning and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development.”<sup>31</sup>

**b. Five studies confounded psychotherapy and medical treatment**

34. The initial enthusiasm for medical blocking of puberty followed largely from early reports from the Dutch clinical research team suggesting at least some mental health improvement.<sup>32</sup> It was when subsequent research studies failed to replicate those successes that it became apparent that the successes were due, not to the medical interventions, but to the psychotherapy that accompanied such interventions in most clinics, including the Dutch clinic.

35. The Dutch clinical research team followed up a cohort of youth at their clinic undergoing puberty suppression<sup>33</sup> and later cross-hormone treatment and surgical sex reassignment.<sup>34</sup> The youth improved on several variables upon follow-up as compared to pre-suppression measurement, including depressive symptoms and

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<sup>28</sup> Hisle-Gorman, et al., 2021, at 1448.

<sup>29</sup> Hisle-Gorman, et al., 2021, at 1448, emphasis added.

<sup>30</sup> Kaltiala et al., 2020, at 213.

<sup>31</sup> Kaltiala et al., 2020, at 213.

<sup>32</sup> de Vries, *et al.*, 2011; de Vries, *et al.*, 2014

<sup>33</sup> de Vries, *et al.*, 2011.

<sup>34</sup> de Vries, *et al.*, 2014.



general functioning. No changes were detected in feelings of anxiety or anger or in gender dysphoria as a result of puberty suppression; however, natal females using puberty suppression suffered *increased* body dissatisfaction both with their secondary sex characteristics and with nonsexual characteristics.<sup>35</sup>

36. As the report authors noted, while it is possible that the improvement on some variables was due to the puberty-blockers, it is also possible that the improvement was due to the mental health support, and it is possible that the improvement occurred only on its own with natural maturation. So any conclusion that puberty blockers improved the mental health of the treated children is not justified by the data. Because this study did not include a control group (another group of adolescents matching the first group, but *not* receiving medical or social support), these possibilities cannot be distinguished from each other. The authors of the study were explicit in noting this themselves: “All these factors may have contributed to the psychological well-being of these gender dysphoric adolescents.”<sup>36</sup>

37. In a 2020 update, the Dutch clinic reported continuing to find improvement in transgender adolescents’ psychological functioning, reaching age-typical levels, “after the start of specialized transgender care involving puberty suppression.”<sup>37</sup> Unfortunately, because the transgender care method of that clinic involves both psychosocial support and puberty suppression, it again cannot be known which of those (or their combination) is driving the improvement. Also, the authors indicate that the changing demographic and other features among gender dysphoric youth might have caused the treated group to differ from the control group in unknown ways. As the study authors noted again, “The present study can, therefore, not provide evidence about the direct benefits of puberty suppression over time and long-

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<sup>35</sup> Biggs, 2020.

<sup>36</sup> de Vries, *et al.* 2011, at 2281.

<sup>37</sup> van der Miesen, *et al.*, 2020, at 699.



term mental health outcomes.”<sup>38</sup>

38. Allen, *et al.* (2019) reported on a sample of 47 youth, ages 13–20, undergoing cross-sex hormone treatment. They reported observing increases in measures of well-being and decreases in measures of suicidality; however, as the authors also noted, “whether a patient is actively receiving psychotherapy” may have been a confounding variable.<sup>39</sup>

39. Tordoff, *et al.* (2022) reported on a sample of youth, ages 13–20 years, treated with either puberty blockers or cross-sex hormones. There were improvements in mental health functioning; however, 62.5% of the sample was again receiving mental health therapy.<sup>40</sup>

**c. Two studies showed no superiority of medical intervention above psychotherapy**

40. Costa, *et al.* (2015) reported on preliminary outcomes from the Tavistock and Portman NHS Foundation Trust clinic in the UK. They compared the psychological functioning of one group of youth receiving psychological support with a second group receiving both psychological support as well as puberty blocking medication. Both groups improved in psychological functioning over the course of the study, but no statistically significant differences between the groups was detected at any point.<sup>41</sup> As those authors concluded, “Psychological support and puberty suppression were both associated with an improved global psychosocial functioning in GD adolescence. Both these interventions may be considered effective in the clinical management of psychosocial functioning difficulties in GD adolescence.”<sup>42</sup> Because psychological support does not pose the physical health risks that hormonal interventions or surgery does (such as loss of reproductive function) however, one

<sup>38</sup> van der Miesen, *et al.*, 2020, at 703.

<sup>39</sup> Allen, *et al.*, 2019.

<sup>40</sup> Tordoff, *et al.*, 2022, Table 1.

<sup>41</sup> Costa, *et al.*, at 2212 Table 2.

<sup>42</sup> Costa, *et al.*, at 2206.



cannot justify taking on the greater risks of social transition, puberty blockers or surgery without evidence of such treatment producing superior results. Such evidence does not exist. Moreover, this clinical team subsequently released the final version of this preliminary report, finding that neither group actually experienced significant improvement,<sup>43</sup> making moot any discussion of the source any improvement.

41. Achille, *et al.* (2020) at Stony Brook Children’s Hospital in New York treated a sample of 95 youth with gender dysphoria, providing follow-up data on 50 of them. (The report did not indicate how these 50 were selected from the 95.) As well as receiving puberty blocking medications, “Most subjects were followed by mental health professionals. Those that were not were encouraged to see a mental health professional.”<sup>44</sup> The puberty blockers themselves “were introduced in accordance with the Endocrine Society and the WPATH guidelines.”<sup>45</sup> Upon follow-up, some incremental improvements were noted; however, after statistically adjusting for psychiatric medication and engagement in counselling, “*most predictors did not reach statistical significance.*”<sup>46</sup> That is, puberty blockers did not improve mental health any more than did mental health care on its own.

#### **d. Conclusions**

42. The authors of the original Dutch studies were careful not to overstate the implications of their results, “We *cautiously* conclude that puberty suppression *may be a valuable element* in clinical management of adolescent gender dysphoria.”<sup>47</sup> Nonetheless, many other clinics and clinicians intrepidly proceeded on the basis of only the perceived positives, broadened the range of people beyond those represented in the research findings, and removed the protections applied in the procedures that

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<sup>43</sup> Carmichael, *et al.*, 2021.

<sup>44</sup> Achille, *et al.*, 2020, at 2.

<sup>45</sup> Achille, *et al.*, 2020, at 2.

<sup>46</sup> Achille, *et al.*, 2020, at 3 (italics added).

<sup>47</sup> de Vries, *et al.* 2011, at 2282, italics added.



led to those outcomes. Many clinics and individual clinicians have reduced the minimum age for transition to 10 instead of 12. While the Dutch Protocol involves interdisciplinary teams of clinicians, many clinics now rely on a single assessor, in some cases one without adequate professional training in childhood and adolescent mental health. Comprehensive, longitudinal assessments (*e.g.*, 1 to 2 years<sup>48</sup>) became approvals after one or two assessment sessions. Validated, objective measures of youths' psychological functioning were replaced with clinicians' subjective (and first) opinions, often reflecting only the clients' own self-report. Systematic recordings of outcomes, so as to allow for detection and correction of clinical deficiencies, were eliminated.

43. Notably, Dr. Thomas Steensma, central researcher of the Dutch clinic, has decried other clinics for "blindly adopting our research" despite the indications that those results may not actually apply: "We don't know whether studies we have done in the past are still applicable to today. Many more children are registering, and also a different type."<sup>49</sup> Steensma opined that "every doctor or psychologist who is involved in transgender care should feel the obligation to do a good pre- and post-test." But few if any are doing so.

#### **4. Mental Health Issues in Childhood-Onset Gender Dysphoria**

44. As shown by the outcomes studies, there is little evidence that transition improves the mental well-being of children. As shown repeatedly by clinical guidelines from multiple professional associations, mental health issues are expected or required to be resolved *before* undergoing transition. The reasoning behind these conclusions is that children may be expressing gender dysphoria, not because they are experiencing what gender dysphoric adults report, but because they mistake what their experiences indicate or to what they might lead. For example, a child

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<sup>48</sup> de Vries, *et al.*, 2011.

<sup>49</sup> Tetelepta, 2021.



experiencing depression from social isolation might develop the hope—and the unrealistic expectation—that transition will help them fit in, this time as and with the other sex.

45.Ā If a child undergoes transition, discovering only then that their mental health or social situations will not in fact change, the medical risks and side-effects (such as sterilization) will have been borne for no reason. If, however, a child resolves the mental health issues first, with the gender dysphoria resolving with it (which the research literature shows to be the case in the large majority), then the child need not undergo transition at all, but retains the opportunity to do so later.

46.Ā Elevated rates of multiple mental health issues among gender dysphoric children are reported throughout the research literature. A formal analysis of children (ages 4–11) undergoing assessment at the Dutch child gender clinic showed 52% fulfilled criteria for a DSM axis-I disorder.<sup>50</sup> A comparison of the children attending the Canadian versus Dutch child gender dysphoria clinic showed only few differences between them, but a large proportion in both groups were diagnosable with clinically significant mental health issues. Results of standard assessment instruments (Child Behavior Check List, or CBCL) demonstrated that the average score was in the clinical rather than healthy range, among children in both clinics.<sup>51</sup> When expressed as percentages, among 6–11-year-olds, 61.7% of the Canadian and 62.1% of the Dutch sample were in the clinical range.

47.Ā A systematic, comprehensive review of all studies of Autism Spectrum Disorders (ASDs) and Attention-Deficit Hyperactivity Disorder (ADHD) among children diagnosed with gender dysphoria was recently conducted. It was able to identify a total of 22 studies examining the prevalence of ASD or ADHD in youth with gender dysphoria. Studies reviewing medical records of children and adolescents

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<sup>50</sup> Wallien, *et al.*, 2007.

<sup>51</sup> Cohen-Kettenis, *et al.*, 2003, at 46.



referred to gender clinics showed 5–26% to have been diagnosed with ASD.<sup>52</sup> Moreover, those authors gave specific caution on the “considerable overlap between symptoms of ASD and symptoms of gender variance, exemplified by the subthreshold group which may display symptoms which could be interpreted as either ASD or gender variance. Overlap between symptoms of ASD and symptoms of GD may well confound results.”<sup>53</sup> As noted elsewhere herein, when two or more issues are present at the same time, researchers cannot distinguish when a result is associated with or caused by the issue of interest or one of the side issues.<sup>54</sup> The rate of ADHD among children with GD was 8.3–11%. Conversely, in data from children (ages 6–18) with Autism Spectrum Disorders (ASDs) show they are more than seven times more likely to have parent-reported “gender variance.”<sup>55</sup>

### **C. Adolescent-Onset Gender Dysphoria**

#### **1. Features of Adolescent-Onset Gender Dysphoria**

48. In the social media age, a third profile has recently begun to present clinically or socially, characteristically distinct from the two previously identified profiles.<sup>56</sup> Unlike adult-onset or childhood-onset gender dysphoria, this group is predominately biologically female. This group typically presents in adolescence, but lacks the history of cross-gender behavior in childhood like the childhood-onset cases have. It is that feature which led to the term Rapid Onset Gender Dysphoria (ROGD).<sup>57</sup> The majority of cases appear to occur within clusters of peers and in association with increased social media use<sup>58</sup> and especially among people with autism or other neurodevelopmental or mental health issues.<sup>59</sup>

49. It cannot be easily determined whether the self-reported gender dysphoria

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<sup>52</sup> Thrower, *et al.*, 2020.

<sup>53</sup> Thrower, *et al.*, 2020, at 703.

<sup>54</sup> Cohen-Kettenis *et al.*, 2003, at 51; Skelly *et al.*, 2012.

<sup>55</sup> Janssen, *et al.*, 2016.

<sup>56</sup> Kaltiala-Heino, *et al.*, 2015; Littman, 2018.

<sup>57</sup> Littman, 2018.

<sup>58</sup> Littman, 2018.

<sup>59</sup> Kaltiala-Heino, *et al.*, 2015; Littman, 2018; Warrier, *et al.*, 2020.



is a result of other underlying issues or if those mental health issues are the result of the stresses of being a sexual minority, as some writers are quick to assume.<sup>60</sup> (The science of the *Minority Stress Hypothesis* appears in its own section.) Importantly, and unlike other presentations of gender dysphoria, people with rapid-onset gender dysphoria often (47.2%) experienced *declines* rather than improvements in mental health when they publicly acknowledged their gender status.<sup>61</sup> Although long-term outcomes have not yet been reported, these distinctions demonstrate that one cannot apply findings from the other types of gender dysphoria to this type. That is, in the absence of evidence, researchers cannot assume that the pattern found in childhood-onset or adult-onset gender dysphoria also applies to adolescent-onset gender dysphoria. The multiple differences already observed between these groups argue against predicting that features present in one type would generalize to be present in all types of gender dysphoria.

## **2. Social Transition and Puberty Blockers with Adolescent Onset**

50. There do not yet exist prospective outcomes studies either for social transition or for medical interventions for people whose gender dysphoria began in adolescence. That is, instead of taking a sample of individuals and following them forward over time (thus permitting researchers to account for people dropping out of the study, people misremembering the order of events, etc.), all studies have thus far been *retrospective*. It is not possible for such studies to identify what factors caused what outcomes. No study has yet been organized in such a way as to allow for an analysis of the adolescent-onset group, as distinct from childhood-onset or adult-onset cases. Many of the newer clinics (not the original clinics which systematically tracked and reported on their cases' results) fail to distinguish between people who had childhood-onset gender dysphoria and have aged into adolescence versus people

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<sup>60</sup> Boivin, *et al.*, 2020.

<sup>61</sup> Biggs, 2020; Littman, 2018.



whose onset was not until adolescence. (Analogously, there are reports failing to distinguish people who had adolescent-onset gender dysphoria and aged into adulthood from adult-onset gender dysphoria.) Studies selecting groups according to their current age instead of their ages of onset produces confounded results, representing unclear mixes according to how many of each type of case wound up in the final sample.

### 3. Mental Illness in Adolescent-Onset Gender Dysphoria

51. In 2019, a Special Section appeared in the *Archives of Sexual Behavior* titled, “Clinical Approaches to Adolescents with Gender Dysphoria.” It included this brief yet thorough summary of rates of mental health issues among adolescents expressing gender dysphoria, by Dr. Aron Janssen of the Department of Child and Adolescent Psychiatry of New York University.<sup>62</sup> The literature varies in the range of percentages of adolescents with co-occurring disorders. The range for depressive symptoms ranges was 6–42%,<sup>63</sup> with suicide attempts ranging 10 to 45%.<sup>64</sup> Self-injurious thoughts and behaviors range 14–39%.<sup>65</sup> Anxiety disorders and disruptive behavior difficulties including Attention Deficit/Hyperactivity Disorder are also prevalent.<sup>66</sup> Gender dysphoria also overlaps with Autism Spectrum Disorder.<sup>67</sup>

52. Of particular concern in the context of adolescent onset gender dysphoria is Borderline Personality Disorder (BPD; diagnostic criteria to follow). It is increasingly hypothesized that very many cases appearing to be adolescent-onset gender dysphoria actually represent cases of BPD.<sup>68</sup> That is, some people may be misinterpreting their experiencing of the broader “identity disturbance” of symptom Criterion 3 to represent a gender identity issue specifically. Like adolescent-onset

<sup>62</sup> Janssen, *et al.*, 2019.

<sup>63</sup> Holt, *et al.*, 2016; Skagerberg, *et al.*, 2013; Wallien, *et al.*, 2007.

<sup>64</sup> Reisner, *et al.*, 2015.

<sup>65</sup> Holt, *et al.*, 2016; Skagerberg, *et al.*, 2013.

<sup>66</sup> de Vries, *et al.*, 2011; Mustanski, *et al.*, 2010; Wallien, *et al.*, 2007.

<sup>67</sup> de Vries, *et al.*, 2010; Jacobs, *et al.*, 2014; Janssen, *et al.*, 2016; May, *et al.*, 2016; Strang, *et al.*, 2014, 2016.

<sup>68</sup> *E.g.*, Anzani, *et al.*, 2020; Zucker, 2019.



gender dysphoria, BPD begins to manifest in adolescence, is three times more common in biological females than males, and occurs in 2–3% of the population, rather than 1-in-5,000 people. (Thus, if even only a portion of people with BPD experienced an identity disturbance that focused on gender identity and were mistaken for transgender, they could easily overwhelm the number of genuine cases of gender dysphoria.)

53.Ä DSM-5-TR Diagnostic Criteria for Borderline Personality Disorder:

A pervasive pattern of instability of interpersonal relationships, self-image, and affects, and marked impulsivity beginning by early adulthood and present in a variety of contexts, as indicated by five (or more) of the following:

- 1.ÄFrantic efforts to avoid real or imagined abandonment. (Note: Do not include suicidal or self-mutilating behaviour covered in Criterion 5.)
- 2.ÄA pattern of unstable and intense interpersonal relationship characterized by alternating between extremes of idealization and devaluation.
- 3.Ä*Identity disturbance: markedly and persistently unstable self-image or sense of self.*
- 4.ÄImpulsivity in at least two areas that are potentially self-damaging (e.g., spending, sex, substance abuse, reckless driving, binge eating). (Note: Do not include suicidal or self-mutilating behavior covered in Criterion 5.)
- 5.Ä*Recurrent suicidal behaviour, gestures, or threats, or self-mutilating behavior.*
- 6.ÄAffective instability due to a marked reactivity of mood (e.g., intense episodic dysphoria, irritability, or anxiety usually lasting a few hours and only rarely more than a few days).
- 7.ÄChronic feelings of emptiness.
- 8.ÄInappropriate, intense anger or difficulty controlling anger (e.g., frequent displays of temper, constant anger, recurrent physical fights).
- 9.ÄTransient, stress-related paranoid ideation or severe dissociative symptoms.

(Italics added.)

54.Ä Mistaking cases of BPD for cases of Gender Dysphoria may prevent such youth from receiving the correct mental health services for their condition, and a primary cause for concern is symptom Criterion 5: Recurrent suicidality. (The research on suicide and suicidality are detailed in their own section herein.)



Regarding the provision of mental health care, the distinction between these conditions is crucial: A person with BPD going undiagnosed will not receive the appropriate treatments (the currently most effective of which is Dialectical Behavior Therapy). A person with a cross-gender identity would be expected to feel relief from medical transition, but someone with BPD would not: The problem was not about *gender* identity, but about having an *unstable* identity. Moreover, after a failure of medical transition to provide relief, one would predict for these people increased levels of hopelessness and increased risk of suicidality.

55. Regarding research, there have now been several attempts to document rates of suicidality among gender dysphoric adolescents. The scientific concern presented by BPD is that it poses a potential confound: Samples of gender dysphoric adolescents could appear to have elevated rates of suicidality, not because of the gender dysphoria (or transphobia in society), but because of the number of people with BPD in the sample.

#### **IV. Other Scientific Claims Assessed**

##### **A. Suicide and Suicidality**

56. Social media increasingly circulate demands for transition accompanied by hyperbolic warnings of suicide should there be delay or obstacle. Claims accompany admissions that “I’d rather have a trans daughter than a dead son,” and such threats are treated as the justification for referring to affirming gender transitions as ‘life-saving’ or ‘medically necessary’. Such claims convey only grossly misleading misrepresentations of the research literature, however, deploying terms for their shock value rather than accuracy, and exploiting common public misperceptions about suicide. Indeed, suicide prevention research and public health campaigns repeatedly warn against circulating such exaggerations, due to the risk of copy-cat



behavior they encourage.<sup>69</sup>

57. Despite that the media treat them as near synonyms, suicide and suicidality are distinct phenomena. They represent different behaviors with different motivations, with different mental health issues, and with different clinical needs. *Suicide* refers to completed suicides and the sincere intent to die. It is substantially associated with impulsivity, using more lethal means, and being a biological male.<sup>70</sup> *Suicidality* refers to parasuicidal behaviors, including suicidal ideation, threats, and gestures. These typically represent cries for help rather than an intent to die and are more common among biological females. Suicidal threats can indicate any of many problems or represent emotional blackmail, as typified by “If you leave me, I will kill myself.” Professing suicidality is also used for attention-seeking or for the support or sympathy it evokes from others, denoting distress much more frequently than an intent to die.

58. Notwithstanding public misconceptions about the frequency of suicide and related behaviors, the highest rates of suicide are among middle-aged and elderly men in high income countries.<sup>71</sup> Biological males are at three times greater risk of death by suicide than are biological females, whereas suicidal ideation, plans, and attempts are three times more common among biological females.<sup>72</sup> In contrast with completed suicides, the frequency of suicidal ideation, plans, and attempts is highest during adolescence and young adulthood, with reported ideation rates spanning 12.1–33%.<sup>73</sup> Relative to other countries, Americans report elevated rates of each of suicidal ideation (15.6%), plans (5.4%), and attempts (5.0%).<sup>74</sup> Suicide attempts occur up to 30

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<sup>69</sup> Gould & Lake, 2013.

<sup>70</sup> Freeman, *et al.*, 2017.

<sup>71</sup> Turecki & Brent, 2016

<sup>72</sup> Klonsky et al., 2016; Turecki & Brent, 2016

<sup>73</sup> Borges et a., 2010; Nock et al., 2008

<sup>74</sup> Klonsky, et al., 2016.



times more frequently than completed suicides.<sup>75</sup> The rate of completed suicides in the U.S. population is 14.5 per 100,000 people.<sup>76</sup> The widely discrepant numbers representing completed suicides versus transient suicidal ideation has left those statistics open to substantial abuse in the media and social media. Despite public media guidelines urging “Avoid dramatic headlines and strong terms such as ‘suicide epidemic,’”<sup>77</sup> that is exactly what mainstream outlets have done.<sup>78</sup>

59. There is substantial research associating sexual orientation with suicidality, but much less so with completed suicide.<sup>79</sup> More specifically, there is some evidence suggesting gay adult men are more likely to die by suicide than are heterosexual men, but there is less evidence of an analogous pattern among lesbian women. Regarding suicidality, surveys of self-identified LGB Americans repeatedly report rates of suicidal ideation and suicide attempts 2–7 times higher than their heterosexual counterparts. Because of this association of suicidality with sexual orientation, one must apply caution in interpreting findings allegedly about gender identity: Because of the overlap between people who self-identify as non-heterosexual and as non-cis-gendered, correlations detected between suicidality and gender dysphoria may instead reflect (be confounded by) homosexuality. Indeed, other authors have made explicit their surprise that so many studies, purportedly of gender identity, entirely omitted measurement or consideration of sexual orientation, creating the situation where features that seem to be associated with gender identity instead reflect the sexual orientation of the members of the sample.<sup>80</sup>

60. Among post-transition transsexuals, completed suicide rates are elevated,

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<sup>75</sup> Bachman, 2018.

<sup>76</sup> World Health Organization, 2022.

<sup>77</sup> Samaritans, 2020.

<sup>78</sup> E.g., MSNBC, 2015, *Trans youth and suicide: An epidemic*.

<sup>79</sup> Haas, *et al.*, 2011.

<sup>80</sup> McNeil, *et al.* (2017)



but are nonetheless rare.<sup>81</sup> Regarding suicidality, there have been three recent, systematic reviews of the research literature.<sup>82</sup> All three included specific methods to minimize any potential effects of cherry-picking findings from within the research literature. Compiling the results of 108 articles reported from 64 research projects, Adams and Vincent (2019) found an overall average rate of 46.55% for suicidal ideation (ranging 18.18%–95.5%) and an overall average rate of 27.19% for suicidal attempts (ranging 8.57%–52.4%). These findings confirmed those reported by McNeil, *et al.* (2017), whose review of 30 articles revealed a range of 37%–83% for suicidal ideation and 9.8%–43% for suicidal attempts. Thus, on the one hand, these ranges are greater than those reported for the mainstream population—They instead approximate the rates reported among sexual orientation minorities. On the other hand, with measures so lacking in reliability that they produce every result from ‘rare’ to ‘almost everyone’, it is unclear which, if any of them, represents a valid conclusion.

61. McNeil *et al.* (2017) observed also the research to reveal rates of suicidal ideation and suicidal attempts to be related—not to transition status—but to the social support received: The studies reviewed showed support to decrease suicidality, but transition not to. Indeed, in some situations, social support was associated with *increased* suicide attempts, suggesting the reported suicidality may represent attempts to evoke more support.<sup>83</sup>

62. Marshall *et al.* (2016) identified and examined 31 studies, again finding rates of suicidal ideation and suicide attempts to be elevated, particularly among biological females, indicating that suicidality patterns correspond to biological sex rather than self-identified gender.<sup>84</sup>

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<sup>81</sup> Wiepjes, *et al.*, 2020.

<sup>82</sup> Adams & Vincent, 2019; Marshall, *et al.*, 2016; McNeil, *et al.* (2017).

<sup>83</sup> Bauer, *et al.*, 2015; Canetto, *et al.*, 2021.

<sup>84</sup> Marshall, *et al.*, 2016.



63. Despite that mental health issues, including suicidality, are repeatedly required by clinical standards of care to be resolved before transition, threats of suicide are instead oftentimes used as the very justification for labelling transition a ‘medical necessity’. However plausible it might seem that failing to affirm transition causes suicidality, the epidemiological evidence indicates that hypothesis to be incorrect: Suicide rates remains elevated even after complete transition, as shown by a comprehensive review of 17 studies of suicidality in gender dysphoria.<sup>85</sup>

64. The scientific study of suicide is inextricably linked to that of mental illness, and Borderline Personality Disorder is repeatedly documented to be greatly elevated among sexual minorities<sup>86</sup>.

### **B. Conversion Therapy**

65. Activists and social media increasingly, but erroneously, apply the term “conversion therapy” moving farther and farther from what the research has reported. “Conversion therapy” (or “reparative therapy” and other names) was the attempt to change a person’s sexual orientation; however, with the public more frequently accustomed to “LGB” being expanded to “LGBTQ+”, the claims relevant only to sexual orientation are being misapplied to gender identity. The research has repeatedly demonstrated that once one explicitly acknowledges being gay or lesbian, this is only very rarely are mistaken. That is entirely unlike gender identity, wherein the great majority of children who declare cross-gender identity cease to do so by puberty, as already shown unanimously by all follow-up studies. As the field grows increasingly polarized, any therapy failing to provide affirmation-on-demand is mislabeled “conversion therapy.”<sup>87</sup> Indeed, even actions of non-therapists, unrelated

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<sup>85</sup> McNeil, *et al.*, 2017.

<sup>86</sup> Reuter, *et al.*, 2016; Rodriguez-Seiljas, *et al.*, 2021; Zanarni, *et al.*, 2021.

<sup>87</sup> D’Angelo, *et al.*, 2021.



to any therapy, have been labelled conversion therapy, including the prohibition of biological males competing on female teams.<sup>88</sup>

**C. Assessing Demands for Social Transition and Affirmation-Only or Affirmation-on-Demand Treatment in Pre-Pubertal Children.**

66.Ã Colloquially, affirmation refers broadly to any actions that treat the person as belonging to a new gender. In different contexts, that could apply to social actions (use of a new name and pronouns), legal actions (changes to birth certificates), or medical actions (hormonal and surgical interventions). That is, social transition, legal transition, and medical transition (and subparts thereof) need not, and rarely do, occur at the same time. In practice, there are cases in which a child has socially only partially transitioned, such as presenting as one gender at home and another at school or presenting as one gender with one custodial parent and another gender with the other parent.

67.Ã Referring to “affirmation” as a treatment approach is ambiguous: Although often used in public discourse to take advantage of the positive connotations of the term, it obfuscates what exactly is being affirmed. This often leads to confusion, such as quoting a study of the benefits and risks of social affirmation in a discussion of medical affirmation, where the appearance of the isolated word “affirmation” refers to entirely different actions.

68.Ã It is also an error to divide treatment approaches into affirmative versus non-affirmative. As noted already, the widely adopted Dutch Approach (and the guidelines of the multiple professional associations based on it) cannot be said to be either: It is a staged set of interventions, wherein social transition (and puberty blocking) may not begin until age 12 and cross-sex hormonal and other medical interventions, later.

69.Ã Formal clinical approaches to helping children expressing gender dysphoria

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<sup>88</sup> Turban, 2021, March 16.



employ a gate-keeper model, with decision trees to help clinicians decide when and if the potential benefits of affirmation of the new gender would outweigh the potential risks of doing so. Because the gate-keepers and decision-trees generally include the possibility of affirmation in at least some cases, it is misleading to refer to any one approach as “the affirmation approach.” The most extreme decision-tree would be accurately called *affirmation-on-demand*, involving little or no opportunity for children to explore at all whether the distress they feel is due to some other, less obvious, factor, whereas more moderate gate-keeping would endorse transition only in select situations, when the likelihood of regretting transition is minimized.

70. Many outcomes studies have been published examining the results of gate-keeper models, but no such studies have been published regarding *affirmation-on-demand* with children. Although there have been claims that *affirmation-on-demand* causes mental health or other improvement, these have been the result only of “retrospective” rather than “prospective” studies. That is, such studies did not take a sample of children and follow them up over time, to see how many dropped out altogether, how many transitioned successfully, and how many transitioned and regretted it or detransitioned. Rather, such studies took a sample of successfully transitioned adults and asked them retrospective questions about their past. In such studies, it is not possible to know how many other people dropped out or regretted transition, and it is not possible to infer causality from any of the correlations detected, despite authors implying and inferring causality.

#### **D. Assessing the “Minority Stress Hypothesis”**

71. The elevated levels of mental health problems among lesbian, gay, and bisexual populations is a well-documented phenomenon, and the idea that it is caused by living within a socially hostile environment is called the *Minority Stress Hypothesis*.<sup>89</sup> The association is not entirely straight-forward, however. For example,

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<sup>89</sup> Meyer, 2003.



although lesbian, gay, and bisexual populations are more vulnerable to suicide ideation overall, the evidence specifically on adult lesbian and bisexual women is unclear. Meyer did not include transgender populations in originating the hypothesis, and it remains a legitimate question to what extent and in what ways it might apply to gender identity.

72.Ã Minority stress is associated, in large part, with being a visible minority. There is little evidence that transgender populations show the patterns suggested by the hypothesis. For example, the minority stress hypothesis would predict differences according to how visibly a person is discernable as a member of the minority, which often changes greatly upon transition. Biological males who are very effeminate stand out throughout childhood, but in some cases can successfully blend in as adult females; whereas the adult-onset transitioners blend in very much as heterosexual cis-gendered males during their youth and begin visibly to stand out in adulthood, only for the first time.

73.Ã Also suggesting minority stress cannot be the full story is that the mental health symptoms associated with minority stress do not entirely correspond with those associated with gender dysphoria. The primary symptoms associated with minority stress are depressive symptoms, substance use, and suicidal ideation.<sup>90</sup> The symptoms associated with gender dysphoria indeed include depressive symptoms and suicidal ideation, but also include anxiety symptoms, Autism Spectrum Disorders, and personality disorders.

74.Ã A primary criterion for readiness for transition used by the clinics demonstrating successful transition is the absence or resolution of other mental health concerns, such as suicidality. In the popular media, however, indications of mental health concerns are instead often dismissed as an expectable result caused by Sexual Minority Stress (SMS). It is generally implied that such symptoms will resolve

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<sup>90</sup> Meyer, 2003.



upon transition and integration into an affirming environment.

## **V.Ā Assessing Statements from Professional Associations**

### **A. Understanding the Value of Statements from Professional Associations**

75.Ā The value of position statements from professional associations should be neither over- nor under-estimated. In the ideal, an organization of licensed health care professionals would convene a panel of experts who would systematically collect all the available evidence about an issue, synthesizing it into recommendations or enforceable standards for clinical care, according to the quality of the evidence for each alternative. For politically neutral issues, with relevant expertise contained among association members, this ideal can be readily achievable. For controversial issues with no clear consensus, the optimal statement would summarize each perspective and explicate the strengths and weaknesses of each, providing relatively reserved recommendations and suggestions for future research that might resolve the continuing questions. Several obstacles can hinder that goal, however. Committees within professional organizations are typically volunteer activities, subject to the same internal politics of all human social structures. That is, committee members are not necessarily committees of experts on a topic—they are often committees of generalists handling a wide variety of issues or members of an interest group who feel strongly about political implications of an issue, instead of scientists engaged in the objective study of the topic.

76.Ā Thus, documents from professional associations may represent required standards, the violation of which may merit sanctions, or may represent only recommendations or guidelines. A document may represent the views of an association's full membership or only of the committee's members (or majorities thereof). Documents may be based on systematic, comprehensive reviews of the available research or selected portions of the research. In sum, the weight best placed



on any association's statement is the amount by which that association employed evidence versus other considerations in its process.

**B. Misrepresentations of statements of professional associations.**

77. In the presently highly politicized context, official statements of professional associations have been widely misrepresented. In preparing the present report, I searched the professional research literature for documentation of statements from these bodies and from my own files, for which I have been collecting such information for many years. I was able to identify statements from six such organizations. Although not strictly a medical association, the World Professional Association for Transgender Health (WPATH) also distributed a set of guidelines in wide use and on which other organizations' guidelines are based.

78. Notably, despite that all these medical associations reiterate the need for mental health issues to be resolved before engaging in medical transition, only the AACAP members have medical training in mental health. The other medical specialties include clinical participation with this population, but their assistance in transition generally assumes the mental health aspects have already been assessed and treated beforehand.

79. With the broad exception of the AAP, their statements repeatedly noted instead that:

- Desistance of gender dysphoria occurs in the majority of prepubescent children.
- Mental health issues need to be assessed as potentially contributing factors and need to be addressed before transition.
- Puberty-blocking medication is an experimental, not a routine, treatment.
- Social transition is not generally recommended until after puberty.

Although some other associations have published broad statements of moral support for sexual minorities and against discrimination, they did not include any specific standards or guidelines regarding medical- or transition-related care.



### 1. World Professional Association for Transgender Health (WPATH)

80. The WPATH standards as they relate to prepubescent children begin with the acknowledgement of the known rates of desistance among gender dysphoric children:

[I]n follow-up studies of prepubertal children (mainly boys) who were referred to clinics for assessment of gender dysphoria, the dysphoria persisted into adulthood for only 6–23% of children (Cohen-Kettenis, 2001; Zucker & Bradley, 1995). Boys in these studies were more likely to identify as gay in adulthood than as transgender (Green, 1987; Money & Russo, 1979; Zucker & Bradley, 1995; Zuger, 1984). Newer studies, also including girls, showed a 12–27% persistence rate of gender dysphoria into adulthood (Drummond, Bradley, Peterson-Badali, & Zucker, 2008; Wallien & Cohen-Kettenis, 2008).<sup>91</sup>

81. That is, “In most children, gender dysphoria will disappear before, or early in, puberty.”<sup>92</sup>

82. Although WPATH does not refer to puberty blocking medications as “experimental,” the document indicates the non-routine, or at least inconsistent availability of the treatment:

Among adolescents who are referred to gender identity clinics, the number considered eligible for early medical treatment—starting with GnRH analogues to suppress puberty in the first Tanner stages—differs among countries and centers. Not all clinics offer puberty suppression. If such treatment is offered, the pubertal stage at which adolescents are allowed to start varies from Tanner stage 2 to stage 4 (Delemarre-van de Waal & Cohen-Kettenis, 2006; Zucker et al., [2012]).<sup>93</sup>

83. WPATH neither endorses nor proscribes social transitions before puberty, instead recognizing the diversity among families’ decisions:

Social transitions in early childhood do occur within some families with early success. This is a controversial issue, and divergent views are held by health professionals. The current evidence base is insufficient to predict the long-term outcomes of completing a gender role transition during early childhood.<sup>94</sup>

84. It does caution, however, “Relevant in this respect are the previously described relatively low persistence rates of childhood gender dysphoria.”<sup>95</sup>

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<sup>91</sup> Coleman, *et al.*, 2012, at 172.

<sup>92</sup> Coleman, *et al.*, 2012, at 173.

<sup>93</sup> Coleman, *et al.*, 2012, at 173.

<sup>94</sup> Coleman, *et al.*, 2012, at 176.

<sup>95</sup> Coleman, *et al.*, 2012, at 176 (quoting Drummond, *et al.*, 2008; Wallien & Cohen-Kettenis, 2008).



85. The WPATH standards have been subjected to standardized evaluation, the Appraisal of Guidelines for Research and Evaluation (“AGREE II”) method, as part of an appraisal of all published Clinical Practice Guidelines (CPGs) regarding sex and gender minority healthcare.<sup>96</sup> Utilizing community stakeholders to set domain priorities for the evaluation, the assessment concluded that the guidelines regarding HIV and its prevention were of high quality, but that “[t]ransition-related CPGs tended to lack methodological rigour and rely on patchier, lower-quality primary research.”<sup>97</sup> The WPATH guidelines were recommended for use. Indeed, the WPATH guidelines received unanimous ratings of “Do not recommend.”<sup>98</sup>

86. Finally, it should be noted that WPATH is in stark opposition to international standards: Public healthcare systems throughout the world have instead been ending the practice of medical transition of minors, responding to the increasingly recognized risks associated with hormonal interventions and the now clear lack of evidence that medical transition was benefitting most children, as opposed to the mental health counseling accompanying transition.

## **2. Endocrine Society (ES)**

87. The 150,000-member Endocrine Society appointed a nine-member task force, plus a methodologist and a medical writer, who commissioned two systematic reviews of the research literature and, in 2017, published an update of their 2009 recommendations, based on the best available evidence identified. The guideline was co-sponsored by the American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Paediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society (PES), and the World Professional Association for Transgender Health (WPATH).

88. The document acknowledged the frequency of desistance among gender

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<sup>96</sup> Dahlen, *et al.*, 2021.

<sup>97</sup> Dahlen, *et al.*, 2021, at 6.

<sup>98</sup> Dahlen, *et al.*, 2021, at 7.



dysphoric children:

Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called “desisters”). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence. . . . In adolescence, a significant number of these desisters identify as homosexual or bisexual.<sup>99</sup>

89.Ā The statement similarly acknowledges inability to predict desistance or persistence, “With current knowledge, we cannot predict the psychosexual outcome for any specific child.”<sup>100</sup>

90.Ā Although outside their area of professional expertise, mental health issues were also addressed by the Endocrine Society, repeating the need to handle such issues before engaging in transition, “In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues.”<sup>101</sup> This ordering—to address mental health issues before embarking on transition—avoids relying on the unproven belief that transition will solve such issues.

91.Ā The Endocrine Society did not endorse any affirmation-only approach. The guidelines were neutral with regard to social transitions before puberty, instead advising that such decisions be made only under clinical supervision: “We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional.”<sup>102</sup>

92.Ā The Endocrine Society guidelines make explicit that, after gathering information from adolescent clients seeking medical interventions and their parents, the clinician “provides correct information to prevent unrealistically high expectations [and] assesses whether medical interventions may result in unfavorable

<sup>99</sup> Hembree, *et al.*, 2017, at 3876.

<sup>100</sup> Hembree, *et al.*, 2017, at 3876.

<sup>101</sup> Hembree, *et al.*, 2017, at 3877.

<sup>102</sup> Hembree, *et al.*, 2017, at 3872.



psychological and social outcomes.”<sup>103</sup>

### **3. Pediatric Endocrine Society and Endocrine Society (ES/PES)**

93. In 2020, the 1500-member Pediatric Endocrine Society partnered with the Endocrine Society to create and endorse a brief, two-page position statement.<sup>104</sup> Although strongly worded, the document provided no specific guidelines, instead deferring to the Endocrine Society guidelines.<sup>105</sup>

94. It is not clear to what extent this endorsement is meaningful, however. According to the PES, the Endocrine Society “recommendations include evidence that treatment of gender dysphoria/gender incongruence is medically necessary and should be covered by insurance.”<sup>106</sup> However, the Endocrine Society makes neither statement. Although the two-page PES document mentioned insurance coverage four times, the only mention of health insurance by the Endocrine Society was: “If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action.”<sup>107</sup> Despite the PES asserting it as “medically necessary,” the Endocrine Society stopped short of that. Its only use of that phrase was instead limiting: “We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient’s overall health and/or well-being.”<sup>108</sup>

### **4. American Academy of Child & Adolescent Psychiatry (AACAP)**

95. The 2012 statement of the American Academy of Child & Adolescent Psychiatry (AACAP) is not an affirmation-only policy. It notes:

Just as family rejection is associated with problems such as depression,

<sup>103</sup> Hembree, *et al.*, 2017, at 3877.

<sup>104</sup> PES, online; Pediatric Endocrine Society & Endocrine Society, Dec. 2020.

<sup>105</sup> Pediatric Endocrine Society & Endocrine Society, Dec. 2020, at 1; Hembree, *et al.*, 2017.

<sup>106</sup> Pediatric Endocrine Society & Endocrine Society, Dec. 2020, at 1.

<sup>107</sup> Hembree, *et al.* 2017, at 3883.

<sup>108</sup> Hembree, *et al.*, 2017 at 3872, 3894.



suicidality, and substance abuse in gay youth, the proposed benefits of treatment to eliminate gender discordance in youth must be carefully weighed against such possible deleterious effects. . . . In general, it is desirable to help adolescents who may be experiencing gender distress and dysphoria to defer sex reassignment until adulthood, or at least until the wish to change sex is unequivocal, consistent, and made with appropriate consent.<sup>109</sup>

96.Ā The AACAP’s language repeats the description of the use of puberty blockers only as an exception: “For situations in which deferral of sex reassignment decisions until adulthood is *not clinically feasible*, one approach that has been described in case series is sex hormone suppression under endocrinological management with psychiatric consultation using gonadotropin-releasing hormone analogues.”<sup>110</sup>

97.Ā The AACAP statement acknowledges the long-term outcomes literature for gender dysphoric children: “In follow-up studies of prepubertal boys with gender discordance—including many without any mental health treatment—the cross gender wishes usually fade over time and do not persist into adulthood,”<sup>111</sup> adding that “[c]linicians should be aware of current evidence on the natural course of gender discordance and associated psychopathology in children and adolescents in choosing the treatment goals and modality.”<sup>112</sup>

98.Ā The policy similarly includes a provision for resolving mental health issues: “Gender reassignment services are available in conjunction with mental health services focusing on exploration of gender identity, cross-sex treatment wishes, counseling during such treatment if any, and *treatment of associated mental health problems*.”<sup>113</sup> The document also includes minority stress issues and the need to deal with mental health aspects of minority status (*e.g.*, bullying).<sup>114</sup>

99.Ā Rather than endorse social transition for prepubertal children, the AACAP

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<sup>109</sup> Adelson & AACAP, 2012, at 969.

<sup>110</sup> Adelson & AACAP, 2012, at 969 (*italics added*).

<sup>111</sup> Adelson & AACAP, 2012, at 963.

<sup>112</sup> Adelson & AACAP, 2012, at 968.

<sup>113</sup> Adelson & AACAP, 2012, at 970 (*italics added*).

<sup>114</sup> Adelson & AACAP, 2012, at 969.



indicates: “There is similarly no data at present from controlled studies to guide clinical decisions regarding the risks and benefits of sending gender discordant children to school in their desired gender. Such decisions must be made based on clinical judgment, bearing in mind the potential risks and benefits of doing so.”<sup>115</sup>

### 5. American College of Obstetricians & Gynecologists (ACOG)

100. The American College of Obstetricians & Gynecologists (ACOG) published a “Committee Opinion” expressing recommendations in 2017. The statement indicates it was developed by the ACOG’s Committee on Adolescent Health Care, but does not indicate participation based on professional expertise or a systematic method of objectively assessing the existing research. It includes the disclaimer: “This document reflects emerging clinical and scientific advances as of the date issued and is subject to change. The information should not be construed as dictating an exclusive course of treatment or procedure to be followed.”<sup>116</sup>

101. Prepubertal children do not typically have clinical contact with gynecologists, and the ACOG recommendations include that the client additionally have a primary health care provider.<sup>117</sup>

102. The ACOG statement cites the statements made by other medical associations—European Society for Pediatric Endocrinology (ESPE), PES, and the Endocrine Society—and by WPATH.<sup>118</sup> It does not cite any professional association of *mental* health care providers, however. The ACOG recommendations repeat the previously mentioned eligibility/readiness criteria of having no mental illness that would hamper diagnosis and no medical contraindications to treatment. It notes: “*Before* any treatment is undertaken, the patient must display eligibility and readiness (Table 1), meaning that the adolescent has been evaluated by a mental

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<sup>115</sup> Adelson & AACAP, 2012, at 969.

<sup>116</sup> ACOG, 2017, at 1.

<sup>117</sup> ACOG, 2017, at 1.

<sup>118</sup> ACOG, 2017, at 1, 3.



health professional, has no contraindications to therapy, and displays an understanding of the risks involved.”<sup>119</sup>

103. The “Eligibility and Readiness Criteria” also include, “Diagnosis established for gender dysphoria, transgender, transsexualism.”<sup>120</sup> This standard, requiring a formal diagnosis, forestalls affirmation-on-demand because self-declared self-identification is not sufficient for DSM diagnosis.

104. ACOG’s remaining recommendations pertain only to post-transition, medically oriented concerns. Pre-pubertal social transition is not mentioned in the document, and the outcomes studies of gender dysphoric (prepubescent) children are not cited.

#### **6. American College of Physicians (ACP)**

105. The American College of Physicians published a position paper broadly expressing support for the treatment of LGBT patients and their families, including nondiscrimination, antiharassment, and defining “family” by emotional rather than biological or legal relationships in visitation policies, and the inclusion of transgender health care services in public and private health benefit plans.<sup>121</sup>

106. ACP did not provide guidelines or standards for child or adult gender transitions. The policy paper opposed attempting “reparative therapy;” however, the paper confabulated sexual orientation with gender identity in doing so. That is, on the one hand, ACP explicitly recognized that “[s]exual orientation and gender identity are inherently different.”<sup>122</sup> It based this statement on the fact that “the American Psychological Association conducted a literature review of 83 studies on the efficacy of efforts to change *sexual orientation*.”<sup>123</sup> The APA’s document, entitled “Report of the American Psychological Task Force on appropriate therapeutic responses to

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<sup>119</sup> ACOG, 2017, at 1, 3 (citing the Endocrine Society guidelines) (italics added).

<sup>120</sup> ACOG, 2017, at 3 Table 1.

<sup>121</sup> Daniel & Butkus, 2015a, 2015b.

<sup>122</sup> Daniel & Butkus, 2015b, at 2.

<sup>123</sup> Daniel & Butkus, 2015b, at 8 (italics added).



*sexual orientation*” does not include or reference research on gender identity.<sup>124</sup> Despite citing no research about transgenderism, the ACP nonetheless included in its statement: “Available research does not support the use of reparative therapy as an effective method in the treatment of LGBT persons.”<sup>125</sup> That is, the inclusion of “T” with “LGB” is based on something other than the existing evidence.

107. There is another statement,<sup>126</sup> which was funded by ACP and published in the *Annals of Internal Medicine* under its “*In the Clinic*” feature, noting that “‘In the Clinic’ does not necessarily represent official ACP clinical policy.”<sup>127</sup> The document discusses medical transition procedures for adults rather than for children, except to note that “[n]o medical intervention is indicated for prepubescent youth,”<sup>128</sup> that a “mental health provider can assist the child and family with identifying an appropriate time for a social transition,”<sup>129</sup> and that the “child should be assessed and managed for coexisting mood disorders during this period because risk for suicide is higher than in their cisgender peers.”<sup>130</sup>

### **7. American Academy of Pediatrics (AAP)**

108. The policy of the American Academy of Pediatrics (AAP) is unique among the major medical associations in being the only one to endorse an affirmation-on-demand policy, including social transition before puberty without any watchful waiting period. Although changes in recommendations can obviously be appropriate in response to new research evidence, the AAP provided none. Rather, the research studies AAP cited in support of its policy simply did not say what AAP claimed they did. In fact, the references that AAP cited as the basis of their policy instead outright contradicted that policy, repeatedly endorsing watchful waiting.<sup>131</sup> Moreover, of all

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<sup>124</sup> APA, 2009 (italics added).

<sup>125</sup> Daniel & Butkus, 2015b, at 8 (italics added).

<sup>126</sup> Safer & Tangpricha, 2019.

<sup>127</sup> Safer & Tangpricha, 2019, at ITC1.

<sup>128</sup> Safer & Tangpricha, 2019, at ITC9.

<sup>129</sup> Safer & Tangpricha, 2019, at ITC9.

<sup>130</sup> Safer & Tangpricha, 2019, at ITC9.

<sup>131</sup> Cantor, 2020.



the outcomes research published, the AAP policy cited *one*, and that without mentioning the outcome data it contained.<sup>132</sup>

109. Immediately following the publication of the AAP policy, I conducted a point-by-point fact-check of the claims it asserted and the references it cited in support. I submitted that to the *Journal of Sex & Marital Therapy*, a well-known research journal of my field, where it underwent blind peer review and was published. I append that article as part of this report. See Appendix 2. A great deal of published attention ensued; however, the AAP has yet to respond to the errors I demonstrated its policy contained. Writing for *The Economist* about the use of puberty blockers, Helen Joyce asked AAP directly, “Has the AAP responded to Dr Cantor? If not, have you any response now?” The AAP Media Relations Manager, Lisa Black, responded: “We do not have anyone available for comment.”

#### **8. The ESPE-LWPES GnRH Analogs Consensus Conference Group**

110. Included in the interest of completeness, there was also a collaborative report in 2009, between the European Society for Pediatric Endocrinology (ESPE) and the Lawson Wilkins Pediatric Endocrine Society (LWPES).<sup>133</sup> Thirty experts were convened, evenly divided between North American and European labs and evenly divided male/female, who comprehensively rated the research literature on gonadotropin-release hormone analogs in children.

111. The effort concluded that “[u]se of gonadotropin-releasing hormone analogs for conditions other than central precocious puberty requires additional investigation and cannot be suggested routinely.”<sup>134</sup> However, gender dysphoria was not explicitly mentioned as one of those other conditions.

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<sup>132</sup> Cantor, 2020, at 1.

<sup>133</sup> Carel et al., 2009.

<sup>134</sup> Carel et al. 2009, at 752.



## VI.Ā International Health Care Consensus

### 1. United Kingdom

112.Ā The National Health Service (NHS) of the United Kingdom centralizes gender counselling and transitioning services in a single clinic, the Gender Identity Development Service (GIDS) of the Tavistock and Portman NHS Foundation Trust. Between 2008 and 2018, the number of referrals to the clinic had increased by a factor of 40, leading to a government inquiry into the causes<sup>135</sup>. The GIDS was repeatedly accused of over-diagnosing and permitting transition in cases despite indicators against patient transition, including by 35 members of the GIDS staff, who resigned by 2019<sup>136</sup>.

113.Ā The NHS appointed Dr. Hilary Cass, former President of the Royal College of Paediatrics and Child Health, to conduct an independent review<sup>137</sup>. That review included a systematic consolidation of all the research evidence, following established procedures for preventing the “cherry-picking” or selective citation favouring or down-playing any one conclusion<sup>138</sup>. The review’s results were unambiguous: “The critical outcomes for decision making are the impact on gender dysphoria, mental health and quality of life. The quality of evidence for these outcomes was assessed as very low”<sup>139</sup>, again using established procedures for assessing clinical research evidence (called GRADE). The review also assessed as “very low” the quality of evidence regarding “body image, psychosocial impact, engagement with health care services, impact on extent of an satisfaction with surgery and stopping treatment”<sup>140</sup>. The report concluded that of the existing research, “The studies included in this evidence review are all small, uncontrolled observational studies, which are subject to bias and confounding....They suggest little change with GnRH analogues [puberty

<sup>135</sup> Marsh, 2020; Rayner, 2018.

<sup>136</sup> BBC, 2021; Donnelly, 2019.

<sup>137</sup> National Health Service, 2020, Sept. 22.

<sup>138</sup> National Institute for Health and Care Excellence, 2020.

<sup>139</sup> National Institute for Health and Care Excellence, 2020, p. 4.

<sup>140</sup> National Institute for Health and Care Excellence, 2020, p. 5.



blockers] from baseline to follow-up”<sup>141</sup>.

## 2. Finland

114. In Finland, the assessments of mental health and preparedness of minors for transition services are centralized by law into two research clinics, Helsinki University Central Hospital and Tampere University Hospital. The eligibility of minors began in 2011. In 2019, Finnish researchers published an analysis of the outcomes of adolescents diagnosed with transsexualism and receiving cross-sex hormone treatment<sup>142</sup>. That study showed that despite the purpose of medical transition to improve mental health: “Medical gender reassignment is not enough to improve functioning and relieve psychiatric comorbidities among adolescents with gender dysphoria. Appropriate interventions are warranted for psychiatric comorbidities and problems in adolescent development”<sup>143</sup>. The patients who were functioning well after transition were those who were already functioning well before transition, and those who were functioning poorly, continued to function poorly after transition.

115. Consistent with the evidence, Finland’s health care service (Council for Choices in Health Care in Finland—COHERE) thus ended the surgical transition of minors, ruling in 2020 that “Surgical treatments are not part of the treatment methods for dysphoria caused by gender-related conflicts in minors” (COHERE, 2020). The review of the research concluded that “[N]o conclusions can be drawn on the stability of gender identity during the period of disorder caused by a psychiatric illness with symptoms that hamper development.” COHERE also greatly restricted access to puberty-blocking and other hormonal treatments, indicating they “may be considered if the need for it continues *after* the other psychiatric symptoms have

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<sup>141</sup> National Institute for Health and Care Excellence, 2020, p. 13.

<sup>142</sup> Kaltiala et al., 2020.

<sup>143</sup> Kaltiala et al., 2020, p. 213.



ceased and adolescent development is progressing normally”<sup>144</sup>. The council was explicit in noting the lack of research needed for decision-making, “There is also a need for more information on the *disadvantages* of procedures and on people who regret them”<sup>145</sup>.

### 3. Sweden

116. Sweden’s national health care policy regarding trans issues has developed quite similarly to that of the UK. (Already in place 20 years ago, Swedish health care policy permitted otherwise eligible minors to receive puberty-blockers beginning at age 14 and cross-sex hormones at age 16.) At that time, only small numbers of minors sought medical transition services. An explosion of referrals ensued in 2013–2014. Sweden’s Board of Health and Welfare reported that, in 2018, the number of diagnoses of gender dysphoria was 15 times higher than 2008 among girls ages 13–17.

117. Sweden has long been very accepting with regard to sexual and gender diversity. In 2018, a law was proposed to lower the age of eligibility for surgical care from age 18 to 15, remove the requirement for parental consent, and lower legal change of gender to age 12. A series of cases of regret and suicide were reported in the Swedish media, leading to questions of mental health professionals failing to consider. In 2019, the Swedish Agency for Health Technology Assessment and Assessment of Social Services (SBU) therefore conducted its own comprehensive review of the research<sup>146</sup>. Like the UK, the Swedish investigation employed methods to ensure the encapsulation of the all the relevant evidence<sup>147</sup>.

118. The SBU report came to the same conclusions as the UK commission. From 2022 forward, the Swedish National Board or Health and Welfare therefore

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<sup>144</sup> Council for Choices in Health Care in Finland, 2020; italics added.

<sup>145</sup> Council for Choices in Health Care in Finland, 2020; italics added.

<sup>146</sup> Orange, 2020, Feb 22.

<sup>147</sup> Swedish Agency for Health Technology Assessment and Assessment of Social Services, 2019.



“recommends restraint when it comes to hormone treatment...Based on the results that have emerged, the National Board of Health and Welfare’s overall conclusion is that the risks of anti-puberty and sex-confirming hormone treatment for those under 18 currently outweigh the possible benefits for the group as a whole”<sup>148</sup>. Neither puberty blockers nor cross-sex hormones would be provided under age 16, and patients ages 16–18 would receive such treatments only within research settings (clinical trials monitored by the appropriate Swedish research ethics board).

#### 4.ÅFrance

119.Å In 2022, the Académie Nationale de Médecine of France issued a strongly worded statement, citing the Swedish ban on hormone treatments. “[A] great medical caution must be taken in children and adolescents, given the vulnerability, particularly psychological, of this population and the many undesirable effects, and even serious complications, that some of the available therapies can cause...such as impact on growth, bone fragility, risk of sterility, emotional and intellectual consequences and, for girls, symptoms reminiscent of menopause”<sup>149</sup>. For hormones, the Académie concluded “the greatest reserve is required in their use,” and for surgical treatments, “[T]heir irreversible nature must be emphasized.” The Académie did not outright ban medical interventions, but warned “the risk of over-diagnosis is real, as shown by the increasing number of transgender young adults wishing to “detransition”. Rather than medical interventions, it advised health care providers “to extend as much as possible the psychological support phase.” The Académie reviewed and emphasized the evidence indicating the very large and very sudden increase in youth requesting medical transition. It attributed the change, not to society now being more accepting of sexual diversity, but to social media, “underlining the addictive character of excessive consultation of social networks which is both

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<sup>148</sup> Swedish National Board of Health and Welfare, 2022.

<sup>149</sup> Académie Nationale de Médecine, 2022, Feb. 25.



harmful to the psychological development of young people and responsible, for a very important part, of the growing sense of gender incongruence.”



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