**IN THE UNITED STATES DISTRICT COURT**
**FOR THE NORTHERN DISTRICT OF FLORIDA**
**Tallahassee Division**

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| AUGUST DEKKER, legally known as KORI DEKKER; BRIT ROTHSTEIN; SUSAN DOE, a minor, by and through her parents and next friends, JANE DOE and JOHN DOE; and K.F., a minor, by and through his parent and next friend, JADE LADUE, | ) |
| Plaintiffs, | ) Civil Action No. 4:22-cv-00325-RH-MAF |
| | ) COMPLAINT FOR DECLARATORY, INJUNCTIVE, AND OTHER RELIEF |
| JASON WEIDA, in his official capacity as Secretary of the Florida Agency for Health Care Administration; and FLORIDA AGENCY FOR HEALTH CARE ADMINISTRATION, | ) **Expert Report of Paul W. Hruz, M.D., Ph.D.** |
| Defendants. | |

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Pursuant to 28 U.S.C. 1746, I declare:

1. I have been retained by counsel for Defendants as an expert witness in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this report. My professional background, experience, and publications are detailed in my curriculum vitae. A true and accurate copy of my CV is attached as Exhibit A to this report.

2. I received my Doctor of Philosophy degree from the Medical College of Wisconsin in 1993. I received my Medical Degree from the Medical College of Wisconsin in 1994. I am an Associate Professor of Pediatrics in the Division of Pediatric Endocrinology and Diabetes at Washington University School of Medicine. I also have a secondary appointment as Associate Professor of Cellular Biology and Physiology in the Division of Biology and Biological Sciences at Washington University School of Medicine. I served as Chief of the Division of Pediatric Endocrinology and Diabetes at Washington University from 2012-2017. I served as the Director of the Pediatric Endocrinology Fellowship Program at Washington University from 2008-2016. I am currently serving as Associate Fellowship Program Director at Washington University in St. Louis.

3. I am board certified in Pediatrics and Pediatric Endocrinology. I have been licensed to practice medicine in Missouri since 2000. I also have a temporary license to practice telemedicine in Illinois during the COVID-19 pandemic. My professional memberships include the American Diabetes Association, the Pediatric Endocrine Society, and the Endocrine Society.

4. I have published 62 scholarly articles over my academic career spanning over two decades. This includes peer-reviewed publications in the leading

journals in the fields of metabolism, cardiology, HIV, and ethics including the Gastroenterology, Circulation, Diabetes, Science Signaling, the Journal of Biological Chemistry and FASEB Journal. See Exhibit A.

5. I have served as a Reviewer for a number of leading science journals in relevant fields including the Journal of Clinical Endocrinology and Metabolism, the Journal of Biological Chemistry, Diabetes, Scientific Reports and PlosOne, assessing the quality of evidence that is put forward for publication. I have also been involved in the evaluation of clinical trials with colleagues. I have received over $4.6 million in governmental and non-governmental funding for scientific research including grants from the National Institutes of Health, the American Diabetes Association, The American Heart Association, the March of Dimes, and the Harrington Discovery Institute. I am a member of the Alpha Omega Alpha Medical Honor Society and have received the Armond J. Quick Award for Excellence in Biochemistry, the Eli Lilly Award for Outstanding Contribution to Drug Discovery, and the Julio V. Santiago Distinguished Scholar in Pediatrics Award.

6. During the more than 22 years that I have been in clinical practice, I have participated in the care of hundreds of infants and children, including adolescents, with disorders of sexual development. I was a founding member of the multidisciplinary Disorders of Sexual Development (DSD) program at Washington

University. I continue to contribute to the discussion of complex cases and the advancement of research priorities in this field. In the care of these patients, I have acquired expertise in the understanding and management of associated difficulties in gender identification and gender transitioning treatment issues. I have trained and/or supervised hundreds of medical students, residents and clinical fellows in the practice of medicine.

7. My CV (Exhibit A) contains a complete list of the cases I have testified in as an expert witness either at trial or in deposition. Related to the litigation of issues of sex and gender, I have been designated as an expert witness in Joaquín Carcaño et al. v. Patrick McCrory (United States District Court, M.D. North Carolina), Jane Doe v. Board of Education of the Highland School District (United States District Court For the Southern District of Ohio Eastern Division, Case No. 2:16-CV-524), Adams v. St John's School Board (United States District Court For the Middle District of Florida, FL Civil Action No. 3:17-cv-00739-TJCJBT), Ashton Whitaker v. Kenosha Unified School District (United States District Court Eastern District of Wisconsin, Civ. Action No. 2:16-cv-00943), Terri Bruce v. State of South Dakota (The United States District Court District of South Dakota Western Division, Case No. 17-5080), Kadel vs. Falwell (The United States District Court For The Middle District Of North Carolina, Case No.: 1:19-cv-272-LCB-LPA), Brandt v Rutledge (The United States District Court Eastern District

of Arkansas Central Division, Case No. 4:21-CV-00450-JM), Eknes-Tucker vs Ivy (United States District Court Middle District of Alabama Northern Division, Case 2:22-cv-00184-LCB-SRW), D.H. et al. v. Snyder (United States District Court of Arizona, Case No. 4:20-cv-00335-SHR), Cause DF-15-09887-SD of the 255th Judicial Circuit of Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children, and Bo v. Marshall (United States District Court For The Middle District Of Alabama Northern Division). I have also served as a science consultant or subjected written testimony for court cases in Canada (B.C. Supreme Court File No. E190334) and Great Britain (Bell v. Tavistock).

8. I am being compensated at an hourly rate for actual time devoted, at the rate of $400 per hour including report drafting, travel, testimony, and consultation. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide.

9. In my role as a scientist and as the Director of the Division of Pediatric Endocrinology at Washington University, I extensively studied the existing scientific research literature related to the incidence, potential etiology, and treatment of gender dysphoria as efforts were made to develop a Transgender Medicine Clinic at Saint Louis Children's Hospital. I have participated in local, national, and international meetings where the endocrine care of children with gender dysphoria has been discussed in detail and debated in depth. I have met individually

and consulted with several pediatric endocrinologists (including Dr. Norman Spack) and other professionals specializing in sexual health (including Eli Coleman) who have developed and led transgender programs in the United States. I have also consulted with, met with, and had detailed discussions with dozens of parents of children with gender dysphoria to understand the unique difficulties experienced by this patient population. I continue to evaluate the ongoing experimental investigation of this condition. I am frequently consulted by other medical professionals to help them understand the complex medical and ethical issues related to this emerging field of medicine.

10. In my 25 years of clinical practice, I have cared for children from birth to the completion of college in their early twenties who have a variety of hormone related diseases. This includes disorders of growth, puberty (both precocious and delayed), glucose homeostasis (both hypoglycemia and diabetes mellitus), adrenal function (both adrenal insufficiency and steroid excess), thyroid function, skeletal abnormalities, gonadal dysfunction (including polycystic ovarian syndrome and ovarian failure), hypopituitarism, and disorders of sexual development. Pediatric patients referred to our practice for the evaluation and treatment of gender dysphoria are cared for by an interdisciplinary team of providers that includes a psychologist and pediatric endocrinologist who have been specifically chosen for

this role based upon a special interest and professional knowledge and training in this patient population.

11. My opinions as detailed in this report are based upon my:

a. knowledge, training, and clinical experience in caring for thousands of patients over many years;
b. detailed methodological reviews of hundreds of relevant peer-reviewed science publications;
c. consults, discussions, and team analyses with colleagues and other experts in the field, including attendance and participation in various professional conferences;
d. publications in peer reviewed scientific journals;
e. editorial work for peer reviewed scientific journals; and,
f. peer reviewed research grant receipt and review work.

The materials that I have relied upon are the same types of materials that other experts in my field of clinical practice rely upon when forming opinions on the subject, including hundreds of published, peer reviewed scientific research (and professional) articles.

12. My opinions and hypotheses in this matter are—as all expert reports—subject to the limitations of documentary and related evidence, the impossibility of absolute predictions, and the limitations of social, biological, and medical science. I have not met with, or personally interviewed, anyone in this case. As always, I have no expert opinions regarding the veracity of witnesses in this case. I have not yet reviewed all of the evidence in this case and my opinions are subject to change at any time as new information becomes available to me. Only the trier of fact can determine the credibility of witnesses and how scientific research may

or may not be related to the specific facts of any particular case. In my opinion, a key role of an expert witness is to help the court, lawyers, parties, and the public understand and apply reliable scientific, technical, and investigative principles, hypotheses, methods, and information.

## Background on Sex and Gender

13. Sex is an objective biological trait intrinsically oriented toward specific roles in the conception and development of new members of a species. Both males and females contribute genetic information in distinct yet complimentary ways. Males have the role of delivering sperm produced by testes and the unique paternal DNA contained therein to a female. Females have the role of receiving this male genetic information to join with the maternal genetic information contained in ova produced by ovaries. Sex is not "assigned at birth"; it is permanently determined by biology at conception. This remains the standard definition that has been accepted by the relevant scientific community and used worldwide by scientists, medical personnel, and society in general for decades.

14. The scientific and clinical measurement of sex is done with highly reliable and valid objective methodologies. Visual medical examination of the appearance of the external genitalia is the primary methodology used by clinicians to

recognize sex. In cases where genital ambiguity is present, additional testing modalities including chromosomal analysis, measurement of hormone levels, radiographic imaging of internal sexual anatomy and biological response to provocative testing are utilized. The measurement and assessment of biological sex has been documented by valid and reliable research published in credible journals, and is accepted by the relevant scientific community. Medical recognition of an individual as male or female is correctly made at birth in nearly 99.98% of cases according to external phenotypic expression of primary sexual traits (i.e., the presence of a penis for males and presence of labia and vagina for females).

15. For members of the human species (and virtually all mammals), sex is normatively aligned in a binary fashion (i.e., either male or female) in relation to biologic purpose. The presence of individuals with disorders of sexual development (along the range of the established Prader scale) does not alter this fundamental reality.

16. Due to genetic and hormonal variation in the developing fetus, normative development of the external genitalia in any individual differs with respect to size and appearance while maintaining an ability to function with respect to biologic purpose (i.e., reproduction). Internal structures (e.g., gonad, uterus, vas deferens) normatively align in more than 99.9%+ of mammals with external genitalia, including humans.

17. Due to the complexity of the biological processes that are involved in normal sexual development, it is not surprising that a very small number of individuals are born with defects in this process (1 in 5,000 births).[1] Defects can occur through either inherited or *de novo* mutations in genes that are involved in sexual determination or through environmental insults during critical states of sexual development. Persons who are born with such abnormalities are considered to have a disorder of sexual development (DSD). Most often, this is first detected as ambiguity in the appearance of the external genitalia. Such detection measurements are reliable and valid and accepted by the relevant scientific community.

18. The medical care of persons with DSDs is primarily directed toward identification of the etiology of the defect and treatment of any associated complications. Similar to other diseases, diagnostic tools such as the Prader scale are used to assess, measure, and assign a "stage" to the severity of the deviation from normal (e.g., assessments of objective, reliable evidence). In children with DSDs, characterization based upon phenotype alone does not reliably predict the sex chromosomes present nor does it necessarily correlate with potential for biological sexual function. Decisions on initial sex assignment in these very rare cases require detailed assessment of objective, reliable medical evidence by a team of expert

[1] See Sax, How common is Intersex? A response to Anne Fausto-Sterling, The Journal of Sex Research, 39:3, 174-178, DOI: 10.1080/00224490209552139 (2002).

medical providers. Previously, it was felt that a definitive sex assignment was necessary shortly after birth with the belief that this would allow patients with a disorder of sexual development to best conform to the assigned sex and so parents-caregivers could help socialize the child to the assigned sex. Current practice is to defer sex assignment until the etiology of the disorder is determined and, if possible, a reliable prediction can be made on likely biologic and psychologic outcomes. When this cannot be done with confidence, a presumptive sex assignment is made. Factors used in making such decisions include karyotype (46XX, 46XY, or other), phenotypic appearance of the external genitalia, and parental desires. The availability of new information can, in rare circumstances, lead to a change in sex determination. Decisions on whether to surgically alter the external genitalia to align with sex are generally deferred until the patient is able to provide consent.[2]

19. "Gender," a term that had traditionally been reserved for grammatical purposes, is currently used to describe the psychological and cultural characteristics of a person in relation to biological sex. Gender in such new definitions would therefore exist only in reference to subjective personal perceptions and feelings and societal expectations, not biology. The reliability and validity of various usages of the term "gender" is currently controversial and the relevant scientific community

[2] See Lee et al., Global Disorders of Sex Development Update since 2006: Perceptions, Approach and Care, Horm Res Paediatr 85, 158-180, doi:10.1159/000442975 (2016).

has accepted no use other than in relation to biological sex, which includes participate in activities related to reproduction. The dangers of incorrectly using the term "gender" in place of "sex" have been acknowledged by the Endocrine Society.[3]

20. "Gender identity" refers to a person's individual experience and perception and unverified verbal patient reports of how they experience being male or female or a combination of these or other categories. The term "gender identity" is controversial. There is no current worldwide definition of "gender identity" accepted by the relevant clinical communities. The measurement error rate for non-biological "gender identity" is unknown.

21. People who identify as "transgender" transiently or persistently experience a sex-discordant gender identity.[4]

**Puberty**

22. Puberty is "the morphological and physiological changes that occur in the growing boy or girl as the gonads change from the infantile to the adult state. These changes involve nearly all the organs and structures of the body but they do not begin at the same age nor take the same length of time to reach completion in

[3] See Bhargava et al., Considering Sex as a Biological Variable in Basic and Clinical Studies: An Endocrine Society Scientific Statement, 42 *Endocrine reviews*, No. 3, pp. 219-58, https://doi.org/10.1210/endrev/bnaa034 (2021).
[4] APA, DSM-5, 451.

all individuals. Puberty is not complete until the individual has the physical capacity to conceive and successfully rear children."[5]

23. The principal manifestations of puberty are:

- The adolescent growth spurt; i.e., an acceleration followed by a deceleration of growth in most skeletal dimensions and in many internal organs.
- The development of the gonads.
- The development of the secondary reproductive organs and the secondary sex characters.
- Changes in body composition, i.e., in the quantity and distribution of fat in association with growth of the skeleton and musculature.
- Development of the circulatory and respiratory systems leading, particularly in boys, to an increase in strength and endurance.[6]

24. The ability to physically conceive children is made possible by the maturation of the primary sex characteristics, the organs and structures that are involved directly in reproduction. In boys, these organs and structures include the scrotum, testes, and penis while in girls they include the ovaries, uterus, and

[5] William A. Marshall and James M. Tanner, "Puberty," in Human Growth: A Comprehensive Treatise, Second Edition, Volume 2, eds. Frank Falkner and James M. Tanner (New York: Springer, 1986), 171.
[6] *Id.* at 171–72.

vagina. In addition to these primary sex characteristics, secondary sex characteristics also develop during puberty — the distinctive physical features of the two sexes that are not directly involved in reproduction. Secondary sex characteristics that develop in girls include "the growth of breasts and the widening of the pelvis" and in boys "the appearance of facial hair and the broadening of shoulders," while other patterns of body hair and changes in voice and skin occur during puberty in both girls and boys.[7]

25. Physicians characterize the progress of puberty by marking the onset of different developmental milestones. The earliest visible event, the initial growth of pubic hair, is known as "pubarche"; it occurs between roughly ages 8 and 13 in girls, and between ages 9.5 and 13.5 in boys.[8] In girls, the onset of breast development, known as "thelarche," occurs around the same time as pubarche.[9] "Menarche" is another manifestation of sexual maturation in females, referring to the onset of menstruation, which typically occurs at around 13 years of age and is generally a sign of the ability to conceive.[10] Roughly corresponding to menarche in girls is "spermarche" in boys; this refers to the initial presence of viable sperm in semen,

[7] Robert V. Kail and John C. Cavanaugh, Human Development: A Life-Span View, Seventh Edition (Boston, Mass.: Cengage Learning, 2016), 276.
[8] Jamie Stang and Mary Story, "Adolescent Growth and Development," in Guidelines for Adolescent Nutrition Services, eds. Jamie Stang and Mary Story (Minneapolis, Minn.: University of Minnesota, 2005), 4.
[9] *Id.* at 3.
[10] Marshall and Tanner, "Puberty," 191–192.

which also typically occurs around 13.[11] (The "-arche" in the terms for these milestones comes from the Greek for beginning or origin.)

26. Scientists distinguish three main biological processes involved in puberty: adrenal maturation, gonadal maturation, and somatic growth acceleration. "Adrenarche"—the beginning of adrenal maturation—begins between ages 6 and 9 in girls, and ages 7 and 10 in boys. The hormones produced by the adrenal glands during adrenarche are relatively weak forms of androgens (masculinizing hormones) known as dehydroepiandrosterone and dehydroepiandrosterone sulfate. These hormones are responsible for signs of puberty shared by both sexes: oily skin, acne, body odor, and the growth of axillary (underarm) and pubic hair.[12]

27. "Gonadarche"—the beginning of the process of gonadal maturation—normally occurs in girls between ages 8 and 13 and in boys between ages 9 and 14.[13] The process begins in the brain, where specialized neurons in the hypothalamus secrete gonadotropin-releasing hormone (GnRH).[14] This hormone is secreted in a cyclical or "pulsatile" manner—the hypothalamus releases bursts of GnRH,

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[11] *Id.* at 185.
[12] Sharon E. Oberfield, Aviva B. Sopher, and Adrienne T. Gerken, "Approach to the Girl with Early Onset of Pubic Hair," Journal of Clinical Endocrinology and Metabolism 96, no. 6 (2011): 1610–1622, http://dx.doi.org/10.1210/jc.2011-0225.
[13] Selma Feldman Witchel and Tony M. Plant, "Puberty: Gonadarche and Adrenarche," in Yen and Jaffe's Reproductive Endocrinology, Sixth Edition, eds. Jerome F. Strauss III and Robert L. Barbieri (Philadelphia, Penn.: Elsevier, 2009), 395.
[14] Allan E. Herbison, "Control of puberty onset and fertility by gonadotropin-releasing hormone neurons," Nature Reviews Endocrinology 12 (2016): 452, http://dx.doi.org/10.1038/nrendo.2016.70.

and when the pituitary gland is exposed to these bursts, it responds by secreting two other hormones.[15] These are luteinizing hormone (LH) and follicle-stimulating hormone (FSH), which stimulate the growth of the gonads (ovaries in women and testes in men).[16] (The "follicles" that the latter hormone stimulates are not hair follicles but ovarian follicles, the structures in the ovaries that contain immature egg cells.) In addition to regulating the maturation of the gonads and the production of sex hormones, these two hormones also play an important role in regulating aspects of human fertility.[17]

28. As the gonadal cells mature under the influence of LH and FSH, they begin to secrete androgens (masculinizing sex hormones like testosterone) and estrogens (feminizing sex hormones).[18] These hormones contribute to the further development of the primary sex characteristics (the uterus in girls and the penis and scrotum in boys) and to the development of secondary sex characteristics (including breasts and wider hips in girls, and wider shoulders, breaking voices, and increased muscle mass in boys). The ovaries and testes both secrete androgens as

[15] *Id.* at 453.
[16] *Id.* at 454.
[17] *Id.* at 452.
[18] Michael A. Preece, "Prepubertal and Pubertal Endocrinology," in Human Growth: A Comprehensive Treatise, Volume 2, 212.

well as estrogens, however the testes secrete more androgens and the ovaries more estrogens.[19]

29. The gonads and the adrenal glands are involved in two separate but interrelated pathways (or "axes") of hormone signaling. These are the hypothalamic-pituitary-gonadal (HPG) axis and the hypothalamic-pituitary-adrenal (HPA) axis.[20] Though both play essential roles in puberty, it is, as just noted, the HPG axis that results in the development of the basic reproductive capacity and the external sex characteristics that distinguish the sexes.[21]

30. The third significant process that occurs with puberty, the somatic growth spurt, is mediated by increased production and secretion of human growth hormone, which is influenced by sex hormones secreted by the gonads (both testosterone and estrogen). Similar to the way that the secretion of GnRH by the hypothalamus induces the pituitary gland to secrete FSH and LH, in this case short

[19] Rex A. Hess, "Estrogen in the adult male reproductive tract: A review," Reproductive Biology and Endocrinology 1, (2003), https://dx.doi.org/10.1186/1477-7827-1-52; Henry G. Burger, "Androgen production in women," Fertility and Sterility 77 (2002): 3–5, http://dx.doi.org/10.1016/S0015-0282(02)02985-0.
[20] Russell D. Romeo, "Neuroendocrine and Behavioral Development during Puberty: A Tale of Two Axes," Vitamins and Hormones 71 (2005): 1–25, http://dx.doi.org/10.1016/S0083-6729(05)71001-3.
[21] Margaret E. Wierman and William F. Crowley, Jr., "Neuroendocrine Control of the Onset of Puberty," in Human Growth, Volume 2, 225.

pulses of a hormone released by the hypothalamus cause the pituitary gland to release human growth hormone.[22] This process is augmented by testosterone and estrogen. Growth hormone acts directly to stimulate growth in certain tissues, and also stimulates the liver to produce a substance called "insulin-like growth factor 1," which has growth-stimulating effects on muscle.[23]

31. The neurological and psychological changes occurring in puberty are less well understood than are the physiological changes. Men and women have distinct neurological features that may account for some of the psychological differences between the sexes, though the extent to which neurological differences account for psychological differences, and the extent to which neurological differences are caused by biological factors like hormones and genes (as opposed to environmental factors like social conditioning), are all matters of debate.

32. Scientists distinguish between two types of effects hormones can have on the brain: organizational effects and activational effects. Organizational effects are the ways in which hormones cause highly stable changes in the basic architecture of different brain regions. Activational effects are the more immediate and temporary effects of hormones on the brain's activity. During puberty, androgens

[22] Preece, *supra*, at 218–19.
[23] Udo J. Meinhardt and Ken K. Y. Ho, "Modulation of growth hormone action by sex steroids," Clinical Endocrinology65, no. 4 (2006): 414, http://dx.doi.org/10.1111/j.1365-2265.2006.02676.x.

and estrogens primarily have activating effects, but long before then they have organizational effects in the brains of developing infants and fetuses.[24]

33. In sum: Puberty involves a myriad of complex, related, and overlapping physical processes, occurring at various points and lasting for various durations. During this period of life, adrenarche and changes in the secretion of growth hormone contribute to the child's growth and development. With gonadarche, the maturation of sex organs begins and with normal maturation will lead to the emergence of reproductive capacity, as well as the development of the other biological characteristics that distinguish males and females.

**Pediatric Endocrine Disorders and Treatments**

34. The field of endocrinology is directed toward the care of hormone related diseases. Pediatric endocrine diseases include disorders of glucose regulation (hypoglycemia and diabetes mellitus), disorders of thyroid function (hyper and hypothyroidism), disorders of growth (e.g. short stature, acromegaly, obesity and poor weight gain), disorders of sexual development and function (e.g. genital am-

[24] Herting MM, Sowell ER. Puberty and structural brain development in humans. Front Neuroendocrinol. 2017 Jan;44:122-137. doi: 10.1016/j.yfrne.2016.12.003; Hornung J, Lewis CA, Derntl B. Sex hormones and human brain function. Handb Clin Neurol. 2020;175:195-207. doi: 10.1016/B978-0-444-64123-6.00014-X

biguity, precocious and delayed puberty, hypogonadism, polycystic ovarian syndrome), disorders of adrenal function (e.g. adrenal insufficiency and Cushing's syndrome), disorders of pituitary function, lipid disorders, and disorders of bone and mineral metabolism. For all of these conditions, there are objective physical and biochemical criteria for diagnosis and treatment with well-established normal reference ranges for hormones and metabolites.

35. Hormone interventions to suppress puberty were not developed for the purpose of treating children with gender dysphoria. Rather, they were first used as a way to normalize puberty for children who undergo puberty too early, a condition known as "precocious puberty."

36. For females, precocious puberty is defined by the onset of puberty before age 8, while for males it is defined as the onset of puberty before age 9.[25] Premature thelarche (the appearance of breast development) is usually the first clinical sign of precocious puberty in girls. For males, precocious puberty is

[25] Karen Oerter Klein, "Precocious Puberty: Who Has It? Who Should Be Treated?," Journal of Clinical Endocrinology and Metabolism 84, no. 2 (1999): 411, http://doi.org/10.1210/jcem.84.2.5533. See also: Frank M. Biro et al., "Onset of Breast Development in a Longitudinal Cohort," Pediatrics 132, no. 6 (2013): 1019–1027, http://dx.doi.org/10.1542/peds.2012-3773; Carl-Joachim Partsch and Wolfgang G. Sippell, "Pathogenesis and epidemiology of precocious puberty. Effects of exogenous oestrogens," Human Reproduction Update 7, no. 3 (2001): 293, http://dx.doi.org/10.1111/j.1600-0463.2001.tb05760.x.

marked by premature testicular enlargement.[26] In addition to the psychological and social consequences that a child might be expected to suffer, precocious puberty can also lead to reduced adult height, since the early onset of puberty interferes with later bone growth.[27]

37. Precocious puberty is divided into two types, central precocious puberty (sometimes labeled "true precocious puberty") and peripheral precocious puberty (sometimes labeled "precocious pseudopuberty").[28] Central precocious puberty is caused by the early activation of the gonadal hormone pathway by GnRH, and is amenable to treatment by physicians. Peripheral precocious puberty, which is caused by secretion of sex hormones by the gonads or adrenal glands independent of signals from the pituitary gland, is less amenable to treatment. Effects of androgen or estrogen hypersecretion can be reduced by administration of drugs that block the activity of the sex hormone receptors. If a tumor is causing the disorder, surgical removal may be necessary.

38. Precocious puberty is rare, especially in boys. A recent Spanish study of central precocious puberty estimated the overall prevalence to be 19 in 100,000

[26] Anne-Simone Parent et al., "The Timing of Normal Puberty and the Age Limits of Sexual Precocity: Variations around the World, Secular Trends, and Changes after Migration," Endocrine Reviews 24, no. 5 (2011): 675, http://dx.doi.org/10.1210/er.2002-0019.
[27] Jean-Claude Carel et al., "Precocious puberty and statural growth," Human Reproduction Update 10, no. 2 (2004): 135, http://dx.doi.org/10.1093/humupd/dmh012.
[28] Partsch and Sippell, *supra*, at 294–95.

(37 in 100,000 girls affected, and 0.46 in 100,000 boys).[29] A Danish study of precocious puberty (not limited to central precocious puberty) found the prevalence to be between 20 to 23 per 10,000 in girls and less than 5 in 10,000 in boys.[30]

39. To diagnose central precocious puberty, hormones from the pituitary gland, LH and FSH, are objectively measured. This can sometime be done by measurement of baseline levels but often requires assessment after transient stimulation with GnRH. As discussed, these are two hormones that are made in the pituitary gland that signal to the gonads. In males, they lead to production of testosterone. In females, they lead to the production of estrogen. LH and FSH signaling are essential for normal sperm production and ovarian maturation in males and females, respectively.

40. Also subject to objective measurement when diagnosing and treating central precocious puberty are sex steroid hormones, either testosterone or estrogen, and bone growth.

41. Treatment for precocious puberty is somewhat counterintuitive. Rather than stopping the production of GnRH, physicians actually provide patients

[29] Leandro Soriano-Guillén et al., "Central Precocious Puberty in Children Living in Spain: Incidence, Prevalence, and Influence of Adoption and Immigration," Journal of Clinical Endocrinology and Metabolism 95, no. 9 (2011): 4307, http://dx.doi.org/10.1210/jc.2010-1025. In some cases, peripheral precocious puberty is caused by an underlying condition, such as a tumor, that can be treated.

[30] Grete Teilmann et al., "Prevalence and Incidence of Precocious Pubertal Development in Denmark: An Epidemiologic Study Based on National Registries," Pedriatics 116, no. 6 (2005): 1323, http://dx.doi.org/10.1542/peds.2005-0012.

more constant levels of synthetic GnRH (called GnRH analogues or GnRH agonists).[31] As discussed above, when produced endogenously (that is, by the body naturally), GnRH stimulates the pituitary gland to release gonad-stimulating hormones (gonadotropins, LH and FSH). When added exogenously, the additional GnRH "desensitizes" the pituitary, leading to a decrease in the secretion of gonadotropins, which in turn leads to the decreased maturation of and secretion of sex hormones by the gonads (ovaries and testes). The intent and effect of giving puberty blockers is identical when it is given to a male as when it is given to a female in this context: suppressing the secretion of gonadotropin hormones. Even the dosing is the same for males and females, and depends on the person's weight.

42. The first publication describing the use of GnRH analogues in children for precocious puberty appeared in 1981.[32] In the time since GnRH analogues were first proposed, they have become fairly well accepted as a treatment of precocious puberty, with one prominent GnRH analogue, Lupron, approved for that use by the FDA in 1993.[33] However, there remain some questions concerning the ef-

[31] William F. Crowley, Jr. et al., "Therapeutic use of pituitary desensitization with a long-acting LHRH agonist: a potential new treatment for idiopathic precocious puberty," Journal of Clinical Endocrinology and Metabolism 52, no. 2 (1981): 370–372, http://dx.doi.org/10.1210/jcem-52-2-370. (LHRH refers to "lutenizing hormone releasing hormone," another term for GnRH.)
[32] Crowley et al., *supra*, at 370–72.
[33] "Full Prescribing Information" for Lupron Depot-Ped, FDA.gov (undated), https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/020263s036lbl.pdf.

fectiveness of treatment with GnRH analogues. A 2009 consensus statement of pediatric endocrinologists concluded that GnRH analogues are an effective way to improve the height of girls with onset of puberty at less than 6 years of age, and also recommended the treatment be considered for boys with onset of precocious puberty who have compromised height potential.[34] Regarding the negative psychological and social outcomes associated with precocious puberty, the authors found that the available data were unconvincing, and that additional studies are needed.[35] Puberty blockers have recently been recognized to carry a risk of increased brain pressure that can adversely affect vision and cause severe headaches.[36]

43. When used to treat precocious puberty, the process of desensitization of the pituitary gland by synthetic GnRH is not permanent. After a patient stops taking the GnRH analogues, the pituitary will resume its normal response to the pulsatile secretion of GnRH by the hypothalamus, as evidenced by the fact that

[34] Jean-Claude Carel et al., "Consensus Statement on the Use of Gonadotropin-Releasing Hormone Analogs in Children," Pediatrics 123, no. 4 (2009): e753, http://dx.doi.org/10.1542/peds.2008-1783.
[35] *Id.*
[36] *Risk of pseudotumor cerebri added to labeling*, AAP (July 1, 2022), https://publications.aap.org/aapnews/news/20636/Risk-of-pseudotumor-cerebri-added-to-labeling-for.

children treated for precocious puberty using GnRH analogues will resume normal pubertal development, usually about a year after they withdraw from treatment.[37]

44. The goal of this treatment is to allow the child to have pubertal development enter the normal quiescence that is present at that age. This treatment helps to preserve their final adult height, by slowing the rate of bone age advancement. The goal is *not* to delay puberty beyond other children, as delaying too long can be adverse effects, including reduced bone marrow density, as discussed below.

45. In addition to being prescribed for children with precocious puberty, GnRH analogues have also been used in adults for a variety of indications, including hormone-sensitive tumors.[38] GnRH analogues have also been given to post-pubertal adolescents undergoing chemotherapy with drugs that can have toxic effects on the gonads.[39]

[37] Marisa M. Fisher, Deborah Lemay, and Erica A. Eugster, "Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant," The Journal of Pediatrics 164, no. 4 (2014): 3, http://dx.doi.org/10.1016/j.jpeds.2013.12.009.
[38] See Kumar & Sharma, Gonadotropin-Releasing Hormone Analogs: Understanding Advantages and Limitations, Journal of Human Reproductive Sciences 7, no. 3 (2014).
[39] Meli M, et al. Triptorelin for Fertility Preservation in Adolescents Treated With Chemotherapy for Cancer. J Pediatr Hematol Oncol. 40(4):269-276 (2018).

46. Sex steroids such as testosterone and estrogen are frequently used in the treatment of disorders of normal gonadal function. This includes hypogonadotropic hypogonadism, primary gonadal failure and delayed puberty.[40] In each of these conditions, there are objective laboratory tests that are used to diagnose these conditions and monitor response to treatment. Deficiency of sex steroids has bodily effects that extend beyond sexual function.[41] This includes significant effect on bone density, lean body mass, metabolism, immunity, and neural function.

47. There are major and highly significant differences between male and female responses to sex hormones.[42] Giving estrogen to a biological male is not equivalent to giving the same hormone to a biological female. Likewise, giving testosterone to a biological female is not equivalent to giving the same hormone to a biological male.[43] Differences are not limited to pharmacokinetic effect (i.e. how

[40] Kumar P, Kumar N, Thakur DS, Patidar A. Male hypogonadism: Symptoms and treatment. J Adv Pharm Technol Res. 2010 Jul;1(3):297-301. doi: 10.4103/0110-5558.72420. PMID: 22247861; PMCID: PMC3255409; Voutsadaki K, Matalliotakis M, Ladomenou F. Hypogonadism in adolescent girls: treatment and long-term effects. Acta Biomed. 2022 Oct 26;93(5):e2022317. doi: 10.23750/abm.v93i5.13719. PMID: 36300209; PMCID: PMC9686158.
[41] Alemany M. The Roles of Androgens in Humans: Biology, Metabolic Regulation and Health. Int J Mol Sci. 2022 Oct 8;23(19):11952. doi: 10.3390/ijms231911952. PMID: 36233256; PMCID: PMC9569951; Patel S, Homaei A, Raju AB, Meher BR. Estrogen: The necessary evil for human health, and ways to tame it. Biomed Pharmacother. 2018 Jun;102:403-411. doi: 10.1016/j.biopha.2018.03.078. Epub 2018 Mar 22. PMID: 29573619.
[42] See Madla et al., Let's talk about sex: Differences in drug therapy in males and females, *Advanced drug delivery reviews*, 113804. Advance online publication. https://doi.org/10.1016/j.addr.2021.05.014 (2021).
[43] See Soldin et al., Sex differences in pharmacokinetics and pharmacodynamics, Clinical pharmacokinetics, 48(3), 143–157 (2009); Pogun et al., Sex Differences in Drug Effects. In: Stolerman I.P. (eds) Encyclopedia of Psychopharmacology, Springer, Berlin, Heidelberg (2010).

drugs are absorbed, distributed throughout the body and metabolized) but are present even at the cellular level.[44] Sex steroids act by altering the expression of the genetic information present in all nucleated cells of the body. Epigenetic differences (i.e. chemical changes to DNA structure) result in sex-differential expression of over 6,500 genes in the body.[45] Consequences of a failure to recognize these differences can result in drug overdose, lack of treatment response, or serious side effects.

48. Several conditions in minors may indicate endocrinologic treatment with testosterone. For instance, primary hypogonadism from gonadal failure is caused damage or impaired function of the male testes. Secondary hypogonadism is caused by abnormalities in pituitary structure or function. Hypogonadism can be objectively diagnosed by measurement of testosterone (or its derivatives) and gonadotropin (LH and FSH) levels. When used for the treatment of affected males with hypogonadism, testosterone is administered to achieve levels that are normal

[44] See, e.g., Walker et al., Matters of the heart: Cellular sex differences, *Journal of molecular and cellular cardiology*, S0022-2828(21)00087-0. Advance online publication. https://doi.org/10.1016/j.yjmcc.2021.04.010 (2021).
[45] Gershoni, M., Pietrokovski, S. The landscape of sex-differential transcriptome and its consequent selection in human adults. *BMC Biol* **15**, 7 (2017). https://doi.org/10.1186/s12915-017-0352-z

for the individual's age. This requires careful monitored of serum testosterone levels, as excess levels can have serious adverse effects, including elevations of red blood cell counts, changes in blood pressure, and brain changes.[46]

49. Testosterone may also be used in males to treat delayed puberty. To treat the condition of constitutional delay (where the person has means to progress through puberty, but onset was delayed), the male would normally be given low doses of testosterone for 3-4 months to "prime the pump" for normal puberty. Assessment of this condition includes measuring levels of LH, FSH, and testosterone, as well as observation of testicular size. Once puberty has been initiated and is progressing, there is no need to administer ongoing testosterone therapy. The normal signals present within the body with the pituitary gland signaling to the testicles continue with maturation of the gonad leading to reproductive capacity.

50. Continuing to give external testosterone to a male in normal puberty would suppress the normal function of the testes and can lead to infertility—a result contrary to the goal of endocrinology, which is to restore health. Thus, for instance, a male adolescent undergoing normal puberty who simply desired increased

[46] Ohlander SJ, Varghese B, Pastuszak AW. Erythrocytosis Following Testosterone Therapy. Sex Med Rev. 2018 Jan;6(1):77-85. doi: 10.1016/j.sxmr.2017.04.001; Kienitz T, Quinkler M. Testosterone and blood pressure regulation. Kidney Blood Press Res. 2008;31(2):71-9. doi: 10.1159/000119417; Scarth M, Bjørnebekk A. Androgen abuse and the brain. Curr Opin Endocrinol Diabetes Obes. 2021 Dec 1;28(6):604-614. doi: 10.1097/MED.0000000000000675.

lean body mass (i.e., higher muscle mass) should not normally be given testosterone for that purpose, both because it is considered medically unnecessary and because of the adverse effects of extra testosterone. Among other reasons, these effects explain why testosterone is a controlled substance.

51. Outside the context of gender dysphoria, testosterone is not an indicated treatment for a female child or adolescent. Testosterone, or any androgen, would lead to virilization, which can come with serious adverse effects. This includes impaired fertility, alopecia (hair loss), disfiguring acne, and metabolic changes that increase risk of heart disease and diabetes.[47]

52. Estrogen can be given to young females for the same types of indications in males of either constitutional delay or hypogonadism, which could be either primary or secondary. Primary hypogonadism is caused by a defect in the presence or function of the ovaries. Secondary hypogonadism is caused by a defect in the structure or function of the pituitary gland. A female can experience premature ovarian insufficiency where the ovaries become inactive over time, both genetically and through environmental incidents. To diagnose these conditions, hormone levels can be objectively measured. This includes LH, FSH, estradiol, and

[47] Yang R, Yang S, Li R, Liu P, Qiao J, Zhang Y. Effects of hyperandrogenism on metabolic abnormalities in patients with polycystic ovary syndrome: a meta-analysis. Reprod Biol Endocrinol. 2016 Oct 18;14(1):67. doi: 10.1186/s12958-016-0203-8. PMID: 27756332; PMCID: PMC5069996

other levels. (Estradiol is a form of estrogen, and generally the main hormone followed and measured in female endocrinologic practice.) The physical response to the intervention can also be measured.

53. Estrogen treatments carry risks, including stroke, elevated blood pressure, and changes to bone development. Males are not generally prescribed estrogen (again, outside the context of gender dysphoria), and there is concern that the risks of estrogen are even higher in males.

## Gender Dysphoria and Treatments

### I. Diagnosis

54. In contrast to the conditions discussed above, gender dysphoria is not an endocrine disorder. Instead, it is a diagnostic term for "the distress that may accompany the incongruence between one's experienced or expressed gender and one's" biological sex.[48] Gender dysphoria is associated with high rates of comorbidity, including suicidal ideation, depression, anxiety, poverty, homelessness, eating disorders, and HIV infection.[49] Gender dysphoria as a psychiatric disorder should be distinguished from identifying as transgender and transsexual. As noted,

[48] APA, DSM-5, 451.
[49] M. D. Connolly et al., "The Mental Health of Transgender Youth: Advances in Understanding," J Adolesc Health 59, no. 5 (2016); Pinna F, et al. Italian Working Group on LGBTQI Mental Health. Mental health in transgender individuals: a systematic review. Int Rev Psychiatry.34(3-4):292-359 (2022).

people who identify as transgender "transiently or persistently identify with a gender different from their natal gender." Transsexual has an even more specific meaning; it "denotes an individual who seeks, or has undergone, a social transition from male to female or female to male, which in many, but not all, cases also involved a somatic transition by cross-sex hormone treatment and genital surgery."[50]

55. The clinical assessment methodology in sex discordant gender medicine is currently limited to self-reported information from patients without objective scientific markers or medical tests. There are no reliable radiological, genetic, physical, hormonal, or biomarker tests that can establish gender identity or reliably predict treatment outcomes.

56. The diagnosis of "gender dysphoria" encompasses a diverse array of conditions. While the contributors to sex discordant gender identity remain to be fully identified and characterized, differences both in kind and degree within individuals and across varied populations creates challenges in establishing specific approaches to alleviate associated suffering. For example, data from adults cannot be assumed to apply equally to children. Nor can data from children who present with sex discordant gender pre-pubertally be presumed to apply to the growing number of post-pubertal adolescent females presenting with this condition.

[50] APA, DSM-5, 451.

57. Assessment of gender dysphoria currently depends almost entirely upon unverified, self-reported evidence provided by patients. A patient's spoken or written reports of alleged "memories" of symptoms and behaviors are the only source of evidence for the diagnosis in many cases. This is a source of potentially profound unreliability in patient care as the relevant science documents that physicians are poor "lie detectors"—often no more reliable in discerning false reports than flipping a coin—and sometimes much worse. The relevant research also documents that even though humans (including therapists) are poor "lie detectors," many health professionals personally—and falsely—believe they are "experts" at this complex and difficult task.[51]

58. Although gender perceptions, feelings, and "identity" usually align with biological sex, some individuals report experiencing discordance in these distinct traits. Specifically, for example, biological females may report experiencing that they identify as males and biological males may report experiencing that they identify as females. As gender by definition is distinct from biological sex, one's gender identity does not change a person's biological sex. There is currently no

[51] See, e.g., Vrij, Aldert, Granhag, P. and Porter, S. (2010) Pitfalls and opportunities in nonverbal and verbal lie detection. Psychological Science In The Public Interest, 11 (3). pp. 89-121. ISSN 1529-1006 10.1177/1529100610390861.

known reliable and valid methodology for assessing the accuracy or nature of unverified, verbal reports of discordant "identity." There is thus no known "error rate" for relying upon such reports to engage in hormonal and surgical treatments.

## II. Treatments

59. Moving from diagnosis to treatment, three approaches have been proposed for treating children with gender dysphoria.[52]

### A. Reparative Therapy

60. The first approach, sometimes called "reparative therapy," is directed toward actively supporting and encouraging children to identify with their biological sex. Reparative therapy views sex/gender identity discordance as a pathologic condition. Accordingly, understanding and addressing factors that lead to this condition form the primary focus of reparative therapy, with an explicit goal of realigning one's gender identity with one's biological sex. Components of this approach have included play therapy for children and adolescents, counseling for patients and their families to help them understand and address underlying psycho-

[52] See Zucker, On the "natural history" of gender identity disorder in children, J. Am. Acad. Child Adolesc. Psychiatry 47, 1361-1363, doi:10.1097/CHI.0b013e31818960cf (2008).

logical dysfunction, and instruction on setting specific boundaries for behavior according to stereotypical gender norms.[53] Some have used the term conversion therapy to label efforts to realign gender identity with biological sex, but this ideologically loaded label has been used extensively in reference to same-sex attraction.[54]

### B. Watchful Waiting

61. The second "neutral" or "watchful waiting" approach, motivated by understanding of the natural history of transgender identification in children, is to neither encourage nor discourage transgender identification, recognizing existing evidence (discussed next) showing that the vast majority of affected children if left alone are likely to eventually realign their reports of gender identification with their sex. This realignment of expressed gender identity to be concordant with sex is sometimes called "desistance."

62. The "watchful waiting" approach does not advocate doing nothing. Rather, it focuses on affirming the inherent dignity of affected people and supporting them in other aspects of their lives, including the diagnosis and treatment of any comorbidities, as individuals proceed through the various stages of physical and psychological development. For instance, the approach may include the use of

[53] Kenneth J. Zucker et al., "A Developmental, Biopsychosocial Model for the Treatment of Children with Gender Identity Disorder," Journal of Homosexuality 59, no. 3 (2012).
[54] D. C. Haldeman, "The Practice and Ethics of Sexual Orientation Conversion Therapy," J Consult Clin Psychol 62, no. 2 (1994)Kenneth J. Zucker, "Editorial: The Politics and Science of "Reparative Therapy"," Archives of Sexual Behavior 32, no. 5 (2003).

scientifically validated treatments (e.g., cognitive behavioral therapy) for the patient's anxiety, depression, social skills deficits, or other issues.[55]

63. Despite differences in country, culture, decade, follow-up length and method, multiple studies have come to a remarkably similar conclusion: Very few gender dysphoric children still want to transition by the time they reach adulthood. Many turn out to have been struggling with sexual orientation issues rather than gender discordant "transgender" identity. The exact number of children who experience realignment of gender identity with biological sex by early adult life varies by study. Estimates within the peer reviewed published literature range from 50-98%, with most reporting desistance in approximately 85% of children before the widespread adoption of the "affirming" model discussed below.[56] In 2018, for instance, studies found that 67% of children meeting the diagnostic criteria for gender dysphoria no longer had the diagnosis as adults, with an even higher rate (93%) of natural resolution of gender-related distress for the less significantly impacted

[55] See van Bentum et al., Cognitive therapy and interpersonal psychotherapy reduce suicidal ideation independent from their effect on depression, 38 Depression & Anxiety 940 (2021).
[56] T. D. Steensma et al., "Factors Associated with Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-up Study," J Am Acad Child Adolesc Psychiatry 52, no. 6 (2013); K. D. Drummond et al., "A Follow-up Study of Girls with Gender Identity Disorder," Dev Psychol 44, no. 1 (2008); M. S. Wallien and P. T. Cohen-Kettenis, "Psychosexual Outcome of Gender-Dysphoric Children," J Am Acad Child Adolesc Psychiatry 47, no. 12 (2008); K. J. Zucker and S. J. Bradley, Gender Identity Disorder and Psychosexual Problem in Children and Adolescents (New York: Guilford Press., 1995).

cases.[57] A March 2021 study, with one of the largest samples in the relevant literature, suggests that most young gender dysphoric children grow out of the condition without medical interventions.[58] Thus, desistance (i.e., the child accepting their natal, biological sex identity and declining "transitioning" treatments) is the outcome for the vast majority of affected children who are not actively encouraged to proceed with sex-discordant gender affirmation.

64. Decades of peer-reviewed, published scientific research, including the pioneering work of Dr. Kenneth Zucker, have supported the efficacy of the psychological approaches for the majority of patients experiencing gender dysphoria.[59] Cognitive therapy and interpersonal psychotherapy have been found to reduce suicidal ideation independent of their effect on depression.[60] Within the "watchful

[57] See, e.g., Zucker, K. J. (2018). The myth of persistence: Response to "A critical commentary on follow-up studies and 'desistance' theories about transgender and gender non-conforming children" by Temple Newhook et al. (2018). International Journal of Transgenderism, 19(2), 231–245.
[58] See Devita Singh1, Susan J. Bradley 2 and Kenneth J. Zucker, Frontiers in Psychiatry, March 2021, Volume 12, Article 632784, www.frontiersin.org.
[59] See Zucker, K. J. On the "natural history" of gender identity disorder in children. J Am Acad Child Adolesc Psychiatry 47, 1361-1363, doi:10.1097/CHI.0b013e31818960cf (2008); Bradley, S. J. & Zucker, K. J. Gender Identity Disorder: A Review of the Past 10 YearsG. Journal of the American Academy of Child & Adolescent Psychiatry 36, 872-880, doi:10.1097/00004583-199707000-00008.).
[60] van Bentum JS et al. Cognitive therapy and interpersonal psychotherapy reduce suicidal ideation independent from their effect on depression. Depress Anxiety. 9:940-949 (2021). doi: 10.1002/da.23151.; Gallagher, M. W., Phillips, C. A., D'Souza, J., Richardson, A., Long, L. J., Boswell, J. F., Farchione, T. J., & Barlow, D. H. (2020). Trajectories of change in well-being during cognitive behavioral therapies for anxiety disorders: Quantifying the impact and covariation with improvements in anxiety. *Psychotherapy (Chicago, Ill.)*, *57*(3), 379–390. https://doi.org/10.1037/pst0000283.

waiting" model, these data support the investigative use of modern psychotherapeutic approaches to address suicidal ideation in children with gender dysphoria.

### C. Gender Affirming

65. The third, so-called "gender affirming," approach is to affirm the child's present gender identity. This affirmation may have social, medical, legal, and behavioral dimensions. Typically, the "affirming" approach encourages children to embrace transgender identity with social transitioning followed by puberty blockage and hormonal therapy (cross-sex hormones), and potential surgical interventions.[61] This approach is considered below.

66. Before analyzing this course of treatment, it is important to understand that underlying biology is not changed by altering bodily features to appear as the opposite sex, and such alterations do not change disease vulnerabilities associated with genetically defined sex. Despite the increasing ability of hormones and various surgical procedures to reconfigure some male bodies to visually pass as female, or vice versa, the biology of the person remains as defined by genetic makeup, normatively by his (XY) or her (XX) chromosomes, including cellular, anatomic, and physiologic characteristics and the particular disease vulnerabilities

[61] See Walch et al., Proper Care of Transgender and Gender Diverse Persons in the Setting of Proposed Discrimination: A Policy Perspective, J. Clin. Endocrinol Metab. 106(2):305-308. doi:10.1210/clinem/dgaa816 (2021).

associated with that chromosomally-defined sex.[62] For instance, the XX (genetically female) individual who takes testosterone to stimulate certain male secondary sex characteristics will nevertheless remain unable to produce sperm and father children. It is possible for some adolescents and adults to pass unnoticed as the opposite gender that they aspire to be—but with limitations, costs, and risks.[63] And their underlying biology does not change.

**Puberty Blockers**

67. Only in the 1990s did GnRH analogues begin being used to suppress puberty in children who identify as the opposite sex. In 1998, Peggy Cohen-Kettenis and Stephanie van Goozen, psychologists at a Dutch gender clinic, described the case of a 13-year-old female gender-dysphoria patient, on whom a GnRH analogue was used to suppress puberty before the patient received a definitive diagnosis of gender identity disorder at age 16. At age 18, the patient underwent sex-reassignment surgery.[64]

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[62] See "Institute of Medicine (US) Committee on Understanding the Biology of Sex and Gender Differences. Exploring the Biological Contributions to Human Health: Does Sex Matter?" Wizemann TM, Pardue ML, editors. Washington (DC): National Academies Press (US); 2001. PMID: 25057540.

[63] See S. Levine (2018), Informed Consent for Transgendered Patients, J. of Sex & Marital Therapy, at 6, DOI: 10.1080/0092623X.2018.1518885 ("Informed Consent"); S. Levine (2016), Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, J. Am. Acad Psychiatry Law 44, 236 at 238 ("Reflections").

[64] Cohen-Kettenis and van Goozen, "Pubertal delay as an aid in diagnosis and treatment of a transsexual adolescent," 246. See also Peggy T. Cohen-Kettenis, Thomas D. Steensma, and Annelou L.C. de Vries, "Treatment of Adolescents With Gender Dysphoria in the Netherlands," Child Adolescent Psychiatric Clinics of North America 20, (2011): 689–700, http://dx.doi.org/10.1016/j.chc.2011.08.001.

68. The clinic's scientists developed an influential protocol, often referred to as the "Dutch protocol," which involved puberty suppression followed by cross-sex hormones and potential surgical interventions. In many clinics that adhere to the gender affirmation model, the ages for initiating sex-discordant gender affirming sex steroid hormones has deviated substantially from the original Dutch protocol. The typical protocol is to initiate puberty blockers (GnRH analogs) as soon as puberty begins (Tanner stage 2) which can occur as early as 8 years in females and 9 years in males. While in the Dutch protocol, cross-sex hormones are started at 16 years, many programs in the United States offer these hormones earlier to coincide with the start of normal pubertal development in males (13-14 years) and females (12-13 years). Gender-affirming surgery in the Dutch model was reserved to patients 18 years or older. Again, programs in the United States have advocated for individualization of decisions on ages for surgery in minors. GnRH analogs are discontinued after gonadectomy is performed as this medication is no longer needed to suppress gonads that are no longer present. Due to the suppressive effect of exogenous sex-steroids on gonadal function, GnRH analogs are often stopped after gender affirming hormone administration has been titrated to maximal doses required to achieve the desired change in secondary sex characteristics.

69. This gender "affirming" model would make gender dysphoria unique: it would be "the only psychiatric condition to be treated by surgery, even though

no endocrine or surgical intervention package corrects any identified biological abnormality."[65]

70. These scientists, along with others, have claimed that puberty suppression is "fully reversible."[66] On this view, puberty suppression "give[s] adolescents, together with the attending health professional, more time to explore their gender identity, without the distress of the developing secondary sex characteristics. The precision of the diagnosis may thus be improved."[67]

71. This claim appears to presume that natural sex characteristics interfere with the "exploration" of gender identity, when one would expect that the development of natural sex characteristics might contribute to the natural consolidation of one's gender identity. It is based upon an untested scientific premise that interfering with the development of natural sex characteristics can allow for a more accurate diagnosis of the gender identity of the child. It seems equally plausible that the interference with normal pubertal development will influence the gender identity

[65] S. Levine (2016), Reflections on the Legal Battles Over Prisoners with Gender Dysphoria, J. American Academy of Psychiatry and Law, 44, 236 at 238 ("Reflections"), at 240.
[66] Henriette A. Delemarre-van de Waal and Peggy T. Cohen-Kettenis, "Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects," European Journal of Endocrinology 155 (2006): S133, http://dx.doi.org/10.1530/eje.1.02231.
[67] Peggy T. Cohen-Kettenis, Henriette A. Delemarre-van de Waal, and Louis J.G. Gooren, "The Treatment of Adolescent Transsexuals: Changing Insights," Journal of Sexual Medicine 5, no. 8 (2008): 1894, http://dx.doi.org/10.1111/j.1743-6109.2008.00870.x.

of the child by reducing the prospects for developing a gender identity corresponding to his or her biological sex.

72. Given their potential importance in the lives of the affected children, claims about reversibility are worth careful examination. In developmental biology, it makes little sense to describe anything as "reversible." If a child does not develop certain characteristics at age 12 because of a medical intervention, then his or her developing those characteristics at age 18 is not a "reversal," since the sequence of development has already been disrupted. This is especially important since there is a complex relationship between physiological and psychosocial development during adolescence. Gender identity is shaped during puberty and adolescence as young people's bodies become more sexually differentiated and mature. Given how little we understand about gender identity and how it is formed and consolidated, we should be cautious about interfering with the normal process of sexual maturation.

73. A more relevant question is whether the physiological and psychosocial development that occurs during puberty can resume in something resembling a normal way after puberty-suppressing treatments are withdrawn. In children with precocious puberty, this does appear to be the case. Puberty-suppressing hormones are typically withdrawn around the average age for the normal onset of gonadarche, at about age 12, and normal hormone levels and pubertal development

gradually resume. For one common method of treating precocious puberty, girls reached menarche approximately a year after their hormone treatments ended, at an average age of approximately 13, essentially the same average age as the general population.[68] The evidence for the safety and efficacy of puberty suppression in boys is less robust, chiefly since precocious puberty is much rarer in boys. Although the risks are speculative and based on limited evidence, boys who undergo puberty suppression may be at greater risk for the development of testicular microcalcifications, which may be associated with an increased risk of testicular cancer, and puberty suppression in boys may also be associated with obesity.[69]

74. Unlike children affected by precocious puberty, adolescents with gender dysphoria do not have any physiological disorders of puberty that are being corrected by the puberty-suppressing drugs. The fact that children with suppressed precocious puberty between ages 8 and 12 resume puberty at age 13 does not mean that adolescents suffering from gender dysphoria whose puberty is suppressed beginning at age 12 will simply resume normal pubertal development down the road if they choose to withdraw from the puberty-suppressing treatment and choose not

[68] Marisa M. Fisher, Deborah Lemay, and Erica A. Eugster, "Resumption of Puberty in Girls and Boys Following Removal of the Histrelin Implant," The Journal of Pediatrics 164, no. 4 (2014): 3, http://dx.doi.org/10.1016/j.jpeds.2013.12.009.
[69] Silvano Bertelloni and Dick Mul, "Treatment of central precocious puberty by GnRH analogs: long-term outcome in men," Asian Journal of Andrology 10, no. 4 (2008): 531, http://dx.doi.org/10.1111/j.1745-7262.2008.00409.x.

to undergo other sex-reassignment procedures. Interrupting puberty in this manner may have significant effects on final stature and bone density.[70]

75. After an extended period of pubertal suppression one cannot "turn back the clock" and reverse changes in the normal coordinated pattern of adolescent psychological development and puberty.[71] Once puberty is blocked, even if eventually unblocked (and assuming signaling from the pituitary gland resumes), the person cannot "buy back" the time when the physical process of puberty has been disrupted at the time when it would normally occur with complementary psychological processes in that stage in the person's life.

76. A possible effect of blocking normally timed puberty is alteration of normal adolescent brain maturation.[72]

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[70] Joseph T, Ting J, Butler G. The effect of GnRH analogue treatment on bone mineral density in young adolescents with gender dysphoria: findings from a large national cohort. J Pediatr Endocrinol Metab. 32(10):1077-1081 (2019); Klink, D., Caris, M., Heijboer, A., van Trotsenburg, M. & Rotteveel, J. Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. The Journal of Clinical Endocrinology & Metabolism 100, E270-E275, doi:10.1210/jc.2014-2439 (2015).

[71] See Hruz, Mayer, and McHugh, "Growing Pains, The New Atlantis: A Journal of Technology and Society, Spring 2017, pg 3-36; see also Vijayakumar N, Op de Macks Z, Shirtcliff EA, Pfeifer JH. Puberty and the human brain: Insights into adolescent development. Neurosci Biobehav Rev. 2018 Sep;92:417-436. doi: 10.1016/j.neubiorev.2018.06.004. Epub 2018 Jul 1. PMID: 29972766; PMCID: PMC6234123; see also Choudhury S, Culturing the adolescent brain: what can neuroscience learn from anthropology?, *Social Cognitive and Affective Neuroscience*, Volume 5, Issue 2-3, June/September 2010, Pages 159–167, https://doi.org/10.1093/scan/nsp030.

[72] See Arain, M., Haque, M., Johal, L., Mathur, P., Nel, W., Rais, A., Sandhu, R., & Sharma, S. (2013). Maturation of the adolescent brain. *Neuropsychiatric disease and treatment*, *9*, 449–461. https://doi.org/10.2147/NDT.S39776.

77. Another troubling question that has been largely uninvestigated is what psychological consequences there might be for children with gender dysphoria whose puberty has been suppressed and who later come to identify as their biological sex.

78. In addition to the reasons to suspect that puberty suppression may have side effects on physiological, psychological, and brain development, the evidence that something like normal puberty will resume for these patients after puberty-suppressing drugs are removed is very weak.

**Cross-Sex Hormones**

79. Rather than resuming biologically normal puberty, adolescents treated on the "affirming" model overwhelmingly go from suppressed puberty to medically conditioned cross-sex puberty, when they are administered cross-sex hormones. Specifically, exogenous estrogen is administered to biological men to induce gynecomastia (i.e., the enlargement of breast tissues), and testosterone is administered to biological women to induce virilization (i.e., the development of facial hair and other desired male features) and to interfere with normal ovarian function. Nearly all of the children that have been studied that have received puberty blockers go on to cross-sex hormones.[73]

[73] https://www.thelancet.com/journals/lanchi/article/PIIS2352-4642(22)00254-1/fulltext

80. Along with (and often before) estrogen is administered to biological males in this treatment, spironolactone may be used as an androgen blocker. Spironolactone is primarily used for the treatment of blood pressure and heart failure. It is a mineralocorticoid antagonist. But it also has effects in blocking the action of androgens. As discussed, androgens are masculinizing hormones that lead to virilization. Testosterone is a prime androgen, but other androgens are also made in the gonads and adrenal gland. Spironolactone is sometimes used in the treatment of polycystic ovarian syndrome, in which females will undergo virilization due to excess androgen production in the ovaries. This syndrome can have adverse effects on fertility, metabolic health, and cardiovascular health.[74] The diagnosis of polycystic ovarian syndrome is a clinical diagnosis based upon the physical evidence of virilization or androgen effects, insulin resistance, and irregular periods. There are objective biological measures to assess those androgen levels, most notably elevated free testosterone levels. And there are objective measures of dysregulation of relevant signals from the pituitary gland, the LH and the FSH, to complement the clinical diagnosis by looking at the degree of virilization that is present in the patient.

[74] Hunter MH, Sterrett JJ. Polycystic ovary syndrome: it's not just infertility. Am Fam Physician. 2000 Sep 1;62(5):1079-88, 1090

81. Spironolactone would not be prescribed to male patients for an endocrinologic purpose related to androgen production. Once again, this reflects a fundamental biological difference between males and females. Though spironolactone can be used to regulate the levels of potassium and sodium in the body, such treatment would be based on objective markers of those levels.

82. Likewise, the administration of the sex steroid hormones differ by the sex of the individual. It is not identical to give testosterone to a male as it is to give it to a female, nor is it the same treatment to give estrogen to a male versus female. This difference has an established scientific basis. The differences between males and females occurs in every nucleated cell of the body, for males and females have different genetic programming. This is a process known as epigenetics, meaning that there are modifications of the DNA itself that alter the expression of genes when exposed to the same stimulus. There are over 6,000 sex-differentially expressed genes. So, if one gives testosterone to a male, the physiologic effects of that treatment, even in the measurement at which genes are turned on and turned off, will be different than if one gives testosterone to a female.[75]

83. When a patient with gender dysphoria is placed on cross-sex hormones, per the Dutch protocol, puberty-suppressing GnRH analogues continue to

[75] Gershoni M, Pietrokovski S. The landscape of sex-differential transcriptome and its consequent selection in human adults. BMC Biol. 2017 Feb 7;15(1):7

be administered until exogenous administration of cross-sex hormones (i.e. sex hormones normally produced the gonads of the opposite sex) leads to sufficient suppression of endogenous sex hormone production or the gonads are surgically removed. Sex hormones that are normally secreted by the maturing gonads are not produced. This means that adolescents undergoing cross-sex hormone treatment circumvent the most fundamental form of sexual maturation—the maturation of their reproductive organs.

84. Patients undergoing gender affirming surgery discontinue GnRH treatment after having their gonads removed, since the secretion of sex hormones that the treatment is ultimately intended to prevent will no longer be possible. These patients are then sterile, as loss or alteration of primary sexual organs leads directly to impairment of reproductive potential.

85. Although the long-term effect of exposing immature gonads to cross-sex hormones is currently unknown, it is generally accepted, even by advocates of transgender hormone therapy, that hormonal treatment impairs fertility, which may be irreversible.[76] Specifically, estrogen administration to males who identify as women results in impaired spermatogenesis and an absence of Leydig cells in the

[76] See Nahata, L., Tishelman, A. C., Caltabellotta, N. M. & Quinn, G. P. Low Fertility Preservation Utilization Among Transgender Youth. Journal of Adolescent Health 61, 40-44, doi:https://doi.org/10.1016/j.jadohealth.2016.12.012 (2017).

testis.[77] Exogenous testosterone administration to females who identify as men causes ovarian stromal hyperplasia and follicular atresia.[78] Recognition of these consequences is the basis for the development of new arenas of medical practice where there is an attempt to restore fertility that has been intentionally destroyed.[79]

86. Gametes (sperm and ova) require natural puberty to mature to the point that they are viable for reproduction.[80] While it is expected that the exposure of immature gonads to cross-sex hormones will lead to infertility, whether affected individuals have permanent sterility has not been established. Much of the uncertainty arises from the novelty of this intervention and the lack of long term follow up. There are limited reports of successful pregnancies after cross-sex hormones, but all of the subjects started gender affirming hormones as adults after completing

[77] Schulze C. Response of the human testis to long-term estrogen treatment: Morphology of Sertoli cells, Leydig cells and spermatogonial stem cells. Cell Tissue Res 251:31e43 (1988)..
[78] [2] Pache TD, Chadha S, Gooren LJ, et al. Ovarian morphology in long-term androgen-treated female to male transsexuals. A human model for the study of polycystic ovarian syndrome? Histopathology 19: 445e52 (1991); Ikeda K, Baba T, Noguchi H, et al. Excessive androgen exposure in female-to-male transsexual persons of reproductive age induces hyperplasia of the ovarian cortex and stroma but not polycystic ovary morphology. Hum Reprod 28:453e61 (2013).
[79] See, e.g., Ainsworth AJ, Allyse M, Khan Z. Fertility Preservation for Transgender Individuals: A Review. Mayo Clin Proc. 2020 Apr; 95(4):784-792. doi: 10.1016/j.mayocp.2019.10.040. Epub 2020 Feb 27. PMID: 32115195.
[80] Howard E. Kulin, et al., "The Onset of Sperm Production in Pubertal Boys. Relationship to Gonadotropin Excretion," American Journal of Diseases in Children 143(2), 190-193 (1989).

puberty.[81] I am not aware of any reports that show this for children who were exposed to puberty blockers before completing puberty followed by cross-sex hormones.

87. There are many other known risks to puberty suppression followed by cross-sex hormones beyond fertility concerns. As noted, emerging data show that treated patients have lower bone density, which may lead to increased fracture risk later in life.[82] Other potential adverse effects include disfiguring acne, high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease.[83] In addition, non-physiological levels of

[81] de Nie I, van Mello NM, Vlahakis E, Cooper C, Peri A, den Heijer M, Meißner A, Huirne J, Pang KC. Successful restoration of spermatogenesis following gender-affirming hormone therapy in transgender women. Cell Rep Med. 2023 Jan 17;4(1):100858. doi: 10.1016/j.xcrm.2022.100858.

[82] See Klink, D., Caris, M., Heijboer, A., van Trotsenburg, M. & Rotteveel, J. Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria. The Journal of Clinical Endocrinology & Metabolism 100, E270-E275, doi:10.1210/jc.2014-2439 (2015).

[83] See Seal, L. J. A review of the physical and metabolic effects of cross-sex hormonal therapy in the treatment of gender dysphoria. Annals of Clinical Biochemistry 53, 10-20, doi:10.1177/0004563215587763 (2016); Banks, K., Kyinn, M., Leemaqz, S. Y., Sarkodie, E., Goldstein, D., & Irwig, M. S. (2021). See also, Blood Pressure Effects of Gender-Affirming Hormone Therapy in Transgender and Gender-Diverse Adults. *Hypertension (Dallas, Tex.: 1979)*, HYPERTENSIONAHA12016839. Advance online publication. https://doi.org/10.1161/HYPERTENSIONAHA.120.16839; Getahun, D., Nash, R., Flanders, W. D., Baird, T. C., Becerra-Culqui, T. A., Cromwell, L., Hunkeler, E., Lash, T. L., Millman, A., Quinn, V. P., Robinson, B., Roblin, D., Silverberg, M. J., Safer, J., Slovis, J., Tangpricha, V., & Goodman, M. (2018). Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. *Annals of internal medicine*, *169*(4), 205–213. https://doi.org/10.7326/M17-2785; Spyridoula Maraka, Naykky Singh Ospina, Rene Rodriguez-Gutierrez, Caroline J Davidge-Pitts, Todd B Nippoldt, Larry J Prokop, M Hassan Murad, Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis, *The Journal of Clinical Endocrinology & Metabolism*, Volume 102, Issue 11, 1 November 2017, Pages 3914–3923, https://doi.org/10.1210/jc.2017-01643.

estrogen in males has been shown to increase the risk of thromboembolic stroke above the incidence observed in females.[84]

**Endocrine Society and WPATH Guidelines**

88. A reasonable understanding of relative risk versus benefit for medical products or procedures is a fundamental obligation in providing appropriate clinical care. This is the bedrock standard of "evidence based medical practice." When considering clinical practice guidelines, it is essential that physicians recognize the relative risks and benefits of such documents. If done properly, they can distill large data sets into actionable clinical recommendations. However, there is a long history of clinical practice guidelines that have later been found to be deficient, resulting in wasted medical resources, have failed to achieve desired benefits, or have caused substantial harm to patients.[85]

89. As detailed throughout this report, this foundational standard of "evidence based medical practice" has never been met as to so-called gender affirming care. The field of "affirming care" is characterized by a poor quality of evidence

[84] E.g. Getahun, D., Nash, R., Flanders, W. D., Baird, T. C., Becerra-Culqui, T. A., Cromwell, L., Hunkeler, E., Lash, T. L., Millman, A., Quinn, V. P., Robinson, B., Roblin, D., Silverberg, M. J., Safer, J., Slovis, J., Tangpricha, V., & Goodman, M. (2018). Cross-sex Hormones and Acute Cardiovascular Events in Transgender Persons: A Cohort Study. Annals of internal medicine, 169(4), 205–213. https://doi.org/10.7326/M17-2785.

[85] See Woolf et al., Clinical guidelines: potential benefits, limitations, and harms of clinical guidelines. *BMJ (Clinical research ed.)*, 318(7182), 527–530, https://doi.org/10.1136/bmj.318.7182.527 (1999).

regarding safety and efficacy, as well as attempts to silence standard scientific discussion and consideration of alternative hypotheses, failures to acknowledge existing data showing persistence of suicidality after intervening, the intentional impairment and destruction of normally formed and functioning male and female sexual organs to address psychological-psychiatric distress, the manipulation of language from standard medical definitions, and widespread failures to properly report research data related to gender transitioning.

90. Because of ideological and political pressure, health providers in many fields are now not permitted to openly asks questions, properly investigate alternative diagnoses, or explore alternative hypotheses for the symptoms of gender dysphoric patients.[86] Providers are instead compelled (sometimes under fear of employment termination or legal attacks) to adopt a patient's self-diagnosis and only support "affirming" medical interventions. These providers are thus being pressured and/or compelled to commit the scientific and medical malpractice of confirmation bias—one of the most serious of all methodological diagnostic failures. As one paper explained, "physicians' desire to confirm a preliminary diagno-

[86] See https://store.samhsa.gov/sites/default/files/d7/priv/sma15-4928.pdf and https://williamsinstitute.law.ucla.edu/publications/conversion-therapy-and-lgbt-youth/

sis while failing to seek contradictory evidence" appears to be "an important reason for wrong diagnoses."[87] Such "[d]iagnostic errors can have tremendous consequences because they can result in a fatal chain of wrong decisions."[88]

91. Despite the dangers of confirmation basis, existing guidelines base recommendations for "affirming" medical interventions on uncorroborated patient self-reports, assessed by mental health professionals with no methodology for discerning true from false patient reports, with no ability to decipher accurate from contaminated "memories," with no alternative treatments offered, and no alternative explanations (e.g., social contagion) explored. Clinicians tasked with providing GnRH analogs to suppress normally timed puberty and gender affirming cross-sex hormones to induce secondary sexual characteristics coinciding with a sex-discordant gender identity rely upon subjective criteria to establish a diagnosis of sex-gender incongruence. There is no biological test to verify the diagnosis.

[87] Mendel et. al., Confirmation bias: why psychiatrists stick to wrong preliminary diagnoses, Psychological Medicine, Oxford University Press (2011).
[88] *Id.*; see also Doherty et al., Believing in Overcoming Cognitive Biases, American Medical Association Journal of Ethics 22(9):E773-778 (2020) ("Confirmation bias is the selective gathering and interpretation of evidence consistent with current beliefs and the neglect of evidence that contradicts them."); Hershberger et al., Teaching awareness of cognitive bias in medical decision making. *Acad Med*. 70(8):661 (1995).

## I. Endocrine Society

92. In 2009, the Endocrine Society published clinical guidelines for the treatment of patients with persistent gender dysphoria.[89] The recommendations include temporary suppression of pubertal development of children with GnRH agonists followed by hormonal treatments to induce the development of secondary sexual traits consistent with one's gender identity. In developing these guidelines, the authors assessed the quality of evidence supporting the recommendations made with use of the GRADE (Grading of Recommendations, Assessment, Development, and Evaluation) system for rating clinical guidelines. As stated in the Endocrine Society publication, "the strength of recommendations and the quality of evidence was low or very low." According to the GRADE system, low recommendations indicate that "[f]urther research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate." Very low recommendations mean that **"**any estimate of effect is very uncertain."[90]

[89] See Hembree et al., Endocrine treatment of transsexual persons: an Endocrine Society clinical practice guideline, *The Journal of clinical endocrinology and metabolism*, *94*(9), 3132–3154, https://doi.org/10.1210/jc.2009-0345 (2009).
[90] Guyatt et al., GRADE: an emerging consensus on rating quality of evidence and strength of recommendations, BMJ; 336:924 doi:10.1136/bmj.39489.470347 (2008).

93. The Endocrine Society published an updated set of guidelines in September 2017.[91] Those guidelines show that all recommendations as to "affirming" treatment of adolescents are supported by low or very low quality evidence.

94. It is highly misleading to imply that the current Endocrine Society guidelines represent the opinions of the Society's 18,000 members. The committee that drafted these guidelines was composed of *less than a dozen* members. The guidelines were never submitted to the entire Endocrine Society membership for comment and approval prior to publication. They also did not undergo external review. Such methodologies are common in association "statements" and "endorsement"; they are not scientific or generally reliable.

95. The panel that drafted the Endocrine Society guidelines was heavily composed of individuals who have significant associations with WPATH. Specifically, all but one of the committee members were leaders in WPATH. Two of the authors served as WPATH's president (Walter J. Meyer and Vin Tangpricha); at least four have served, or are serving, on WPATH's Board of Directors (Peggy Cohen-Kettenis, Louis Gorren, Stephen Rosenthal, Guy T'Sjoen); and at least four (Stephen Rosenthal, Joshua Safer, Vin Tangpricha, and Guy T'Sjoen) were authors

[91] See Hembree et al., Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline, *The Journal of clinical endocrinology and metabolism*, *102*(11), 3869–3903, https://doi.org/10.1210/jc.2017-01658 (2017).

of WPATH SOC 8. Three (Peggy Cohen-Kettenis, Walter Meyer, and Vin Tangpricha) were authors of WPATH SOC 7.

## II. WPATH

96. The World Professional Association for Transgender Health (WPATH) has also issued several iterations of guidelines. The first set of clinical practice guidelines was published in 1979. WPATH published its latest version of their "Standards of Care for the Health of Transgender and Gender Diverse People" (SOC 8) in September of 2022. [92] While this document has been presented as "authoritative" and "evidenced based", numerous concerns have been raised about the updated recommendations. This includes removal of age limits for initiation of cross sex hormones and gender affirming surgery, recommendations for excluding parents in the decision making process if they question or challenge medical interventions, elimination of safeguards for addressing underlying mental health illness before the start of gender affirming medical interventions, and the addition of a section on "eunuch-identified" people. [93] Many of the recommendations made reflect WPATH's acknowledged agenda as an advocacy group. In SOC8 they specifically state "Health is promoted through public policies and legal reforms that ad-

[92] ibid
[93] Coleman et al, Standards of Care for the Health of Transgender and Gender Diverse People, Version 8. Int J Transgend Health. 2022 Sep 6;23(Suppl 1):S1-S259. doi: 10.1080/26895269.2022.2100644..

vance tolerance and equity for gender diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these policy." Despite the claim that the SOC8 guidelines are based upon solid scientific evidence, such recommendations represent ideological positions devoid of rigorous scientific evidence. Scientific data on long-term outcomes in adolescents who are exposed to the U.S. affirmation model simply do not exist.

97. In sum, clinical guidelines or standards of care should provide practitioners with evidence-based standards by which they may reliably inform the patient of projected outcomes, and do so with a known error rate. Such data is the starting point for obtaining informed consent. This information is not provided by either WPATH or Endocrine Society's guidelines.

**Informed Consent**

98. The fundamental purpose of the practice of medicine is to treat disease and alleviate suffering. An essential tenet of medical practice is to avoid doing harm in the process. As discussed above, relying on clear, valid, reliable, and definitive evidence on how to best accomplish treatment goals is the essential ethical, professional, scientific, and clinical goals of physicians. Using "affirming"

treatments on minors violates this essential principle by using experimental treatments on vulnerable populations without properly informing them of the actual risks and limitations of the treatments.[94]

99. It is now universally agreed that medical and psychotherapy patients have a right to proper informed consent. Professional ethics codes, licensing rules and regulations, hospital rules and regulations, state and federal laws, and biomedical conventions and declarations all protect patients' right to informed consent discussions of the risks and benefits of proposed treatments and alternative treatments including no treatment.[95]

100. Essential requirements for informed consent include the ability of the patient or study subject to understand the proposed procedure, full disclosure of known and potential risks and benefits, discussion of alternative treatments, and freedom to act voluntarily. This information is presented verbally and in written form with allowance of sufficient time for the patient to ask questions and for the provider to assess adequate comprehension by the patient. It is well recognized that

[94] See Jonson et al., Clinical Ethics, New York: McGraw Hill (1998).
[95] See Jonson AR, Siegler M, Winslade, WJ: Clinical Ethics, New York: McGraw Hill, 1998, ("Informed consent is defined as the willing acceptance of a medical intervention by a patient after adequate disclosure by the physician of the nature of the intervention, its risks, and benefits, as well as of alternatives with their risks and benefits.") See also Katz, A., Webb, S., and Committee on Bioethics, Informed Consent in Decision-Making in Pediatric Practice, Pediatrics, August 2016, 138 (2) e20161485; DOI: https://doi.org/10.1542/peds.2016-1485 at https://pediatrics.aappublications.org/content/138/2/e20161485.

the signing of a formal consent form does not guarantee that informed consent has been obtained.

101. Several aspects of the care of individuals with gender dysphoria may substantially interfere with proper application of these foundational principles.[96] For adolescent children seeking medical gender affirmation medical, well established limitations in decision making ability raise serious concerns about their ability to consent to hormonals and surgical interventions. Adolescents have a known tendency to engage in risky behaviors, exercise poor impulse control, and show frequent failure to appreciate long-term consequences of current choices.[97]

102. For example, the ability of a child to understand implications for future fertility while still developmentally immature can pose a significant barrier to meeting the criterion of appreciating decision consequence. Children are often unlikely to be capable of giving truly informed consent, particularly when it comes to hormonal or surgical treatments that will result in lifelong sterility.[98] Adolescents' inability to adequately weigh potential short-term benefits against long-term risks

[96] Paul S. Appelbaum and Thomas Grisso, "Assessing Patients' Capacities to Consent to Treatment," New England Journal of Medicine 319, no. 25 (1988).
[97] Sarah-Jayne Blakemore and Trevor W. Robbins, "Decision-Making in the Adolescent Brain," *Nature Neuroscience* 15 (2012); Neuroscientists have found that the adolescent brain is too immature to make reliably rational decisions. B.J. Casey, Rebecca M. Jones, and Todd A. Hare, "The Adolescent Brain," Annals of the New York Academy of Sciences 1124 (2008): 111, http://dx.doi.org/10.1196/annals.1440.010.
[98] See Geier, Adolescent cognitive control and reward processing: Implications for risk taking and substance use, Hormones and Behavior 64, 333-342, doi:https://doi.org/10.1016/j.yhbeh.2013.02.008 (2013).

seems supported by the observation that few adolescents express concern over loss of fertility even when directly told of the potential sterilizing effect of medical intervention.[99]

103. Similarly, individuals with transgender identity who also have clinical depression or other serious psychiatric comorbidity may have limited capacity to objectively weight proposed clinical interventions with potentially irreversible consequences and would therefore fail to meet psychological abilities criteria.[100]

104. In addition, a study subject's underlying belief that he or she was born in the wrong body is the primary reason for seeking medical intervention. Thus any challenge to this underlying premise is seen as a threat to the affected individual. Under such conditions, an individual will find it difficult, if not impossible, to give truly informed consent.

105. A model relying on parental consent with child assenting to affirmative medical interventions does not remove concerns about the difficulty in obtaining truly informed consent. Since many of the long-term outcomes of gender affirming interventions are unknown, prospective patients are being asked to consent

[99] Leena Nahata et al., "Low Fertility Preservation Utilization among Transgender Youth," Journal of Adolescent Health 61, no. 1 (2017).
[100] H. Helmchen, "Ethics of Clinical Research with Mentally Ill Persons," Eur Arch Psychiatry Clin Neurosci 262, no. 5 (2012).

without sufficient knowledge of inherent risk versus benefit. Without understanding that nearly all adolescents who are put on puberty blockers will proceed to gender affirming hormones, with many subsequently opting for gender affirming surgeries, focus on gaining consent for this first stage of the affirmative model is difficult if not impossible.

106. Parents are often told by gender affirmation activists or providers that the failure to allow a gender dysphoric child to medically transition will result in suicide. These "threats" ignore data that challenge this biased assumption.[101]

107. While any cases of suicide are of utmost concern, suicide rates in children with sex-discordant gender identity must be put in context of overall suicidality in the pediatric population independent of gender dysphoria. When considered in this context, the rates of suicidal ideation and attempt in transgender adolescents are similar to those found in adolescents without gender dysphoria who present for psychological care (ref). Furthermore, it is necessary to critically assess, with rigorous scientific data, whether gender affirming medical interventions succeed in preventing suicides. While long-term data are not available for pediatric patients,

[101] See D'Angelo et al., One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria, *Arch Sex Behav* 50**,** 7–16, https://doi.org/10.1007/s10508-020-01844-2 (2021).

the adult literature consistently reports continued elevated suicidality after undergoing gender affirming medical interventions.[102]

108. Researchers have noted that in the "affirming" context, "the informed consent process rarely adequately discloses" either "the uncertain permanence of a child's or an adolescent's gender identity" or "the uncertain long-term physical and psychological health outcomes of gender transition."[103] Levine et al. recently noted the following major deficiencies in the informed consent process under existing "affirming" guidelines and approaches:

- "High rate of desistance/natural resolution of gender dysphoria in children is not disclosed";
- "Implications of very low-quality evidence that underlies the practice of pediatric gender transition are not explained"; and,
- "The question of suicide is inappropriately handled".[104]

As discussed above, the informed consent process for "affirming" treatments is further "limited by" "erroneous professional assumptions" and "poor quality of the initial evaluations."[105]

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[102] Adams N, Hitomi M, Moody C. Varied Reports of Adult Transgender Suicidality: Synthesizing and Describing the Peer-Reviewed and Gray Literature. Transgend Health. 2017 Apr 1;2(1):60-75. doi: 10.1089/trgh.2016.0036; Dhejne, C. et al. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 6, e16885, doi:10.1371/journal.pone.0016885 (2011).
[103] Levine et al., Reconsidering Informed Consent for Trans-Identified Children, Adolescents, and Young Adults, *Journal of sex & marital therapy*, 1–22, https://doi.org/10.1080/0092623X.2022.2046221 (2022).
[104] *Id.*
[105] *Id.*

109. Using experimental procedures on uninformed, vulnerable patients is unethical and improper. Some of the most tragic chapters in the history of medicine include violations of informed consent and improper experimentation on patients using methods and procedures that have not been tested and validated by methodologically sound science—such is the case with the gender transition industry. The infamous Tuskegee studies, Nazi and Imperial Japanese wartime experiments, lobotomies (e.g., Dr. Egas Moniz received the 1949 Nobel Prize in Medicine for inventing lobotomies as a "treatment" for schizophrenia[106]), recovered memory therapy-multiple personality disorders, rebirthing therapy,[107] coercive holding therapy,[108] and other tragic examples should serve as a stark warning to medical providers to properly protect the rights of patients and their families to a proper informed consent process and to not be subjected to experimental, unproven interventions.

**Existing Literature and Its Limitations**

110. Before turning to the existing literature on gender dysphoria and its treatments, it is important to understand the varying types of studies conducted in this and other medical fields, as well as the general approach to scientific testing.

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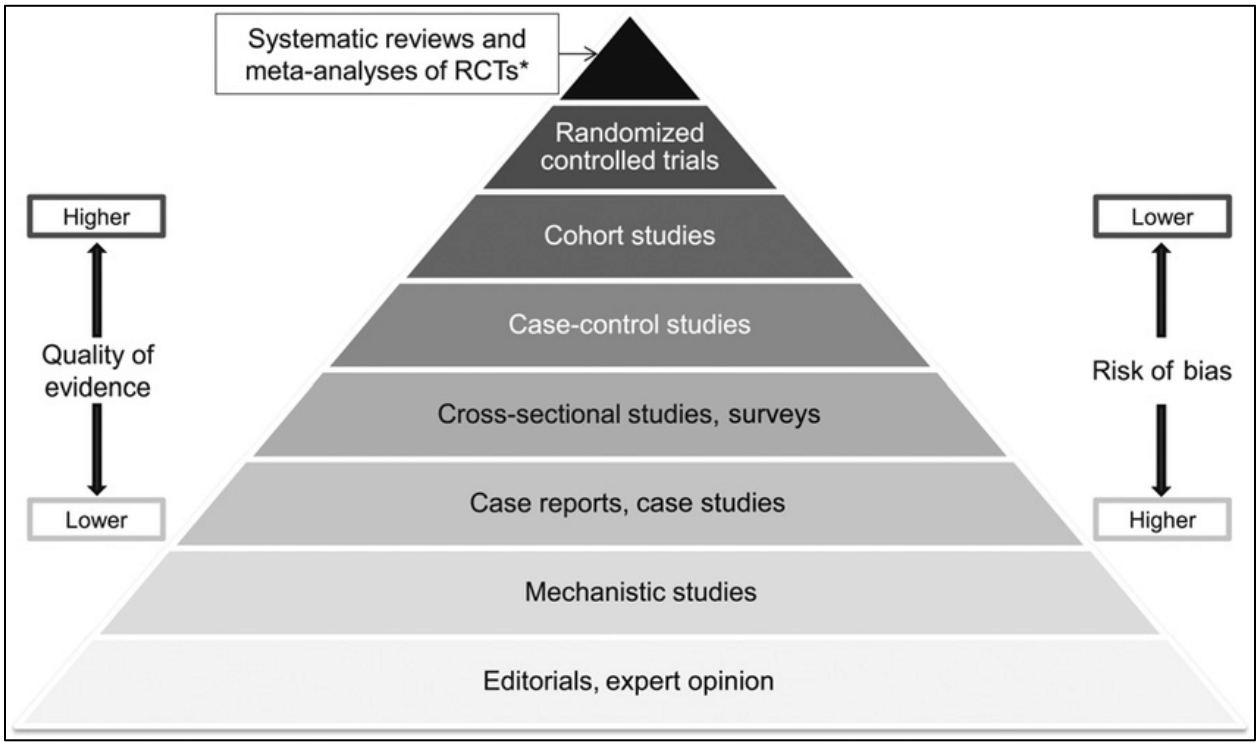
[106] See https://www.nobelprize.org/prizes/medicine/1949/moniz/article.
[107] See, e.g., Janofsky, M. Girl's Death Brings Ban on Kind of 'Therapy'. New York Times. April 18, 2001; see also Peggy Lowe, Rebirthing team convicted: Two therapists face mandatory terms of 16 to 48 years in jail, Rocky Mountain News, April 21, 2001.
[108] See, Hyde, J. "Holding therapy appears finished, State orders the last practitioner of holding therapy to end controversial method" Deseret News, Feb 13, 2005.

Appropriate testing of medical and other scientific hypothesis requires proper study design. First, the research formulates a hypothesis as to whether there is a difference—a cause and effect relationship—from the studied intervention. The study starts by assuming the "null hypothesis"—there is no difference—and then one looks for evidence sufficient to disprove the null hypothesis. When conducting the study, statistical significance is of central importance, for it states the likelihood that the observation would exist if the null hypothesis were true. Only if there is a very small likelihood that the null hypothesis is true is it generally appropriate to treat a study as providing evidence that the null hypothesis is, in fact, false. Accordingly, if a study finding does not reach statistical significance, it would be improper to use the finding as a rejection of the null hypothesis.

111. Case reports or experts' opinions are recognized as the lowest level of evidence. Those are based upon general experiences, not scientific testing. They can be useful for generating a novel hypotheses, which can then be tested through experimental testing to establish if there are cause/effect relationships. Next up on the pyramid of quality of evidence would be, for example, cross-sectional studies that are done where one looks at a condition at one point in time. One can merely infer associations from these types of studies. Randomized longitudinal studies can permit, to some extent, the elimination of unrecognized variables that may distort the results. The highest part of the evidence-based pyramid (for individual studies)

is randomized controlled trials, in which the investigator attempts to control all aspects of the study with the exception of the independent variable that is being tested. When done properly, this type of study can provide strong evidence of causation. The following illustrates this pyramid:[109]




112. Since the "affirming" model of treating transgender children, as summarized by the World Professional Association for Transgender Health (WPATH) and Endocrine Society guidelines discussed below, are relatively new, long-term outcomes are unknown. Evidence presented as support for short-term reductions

[109] https://www.researchgate.net/figure/Hierarchy-of-evidence-pyramid-The-pyramidal-shape-qualitatively-integrates-the-amount-of_fig1_311504831

in psychological distress following social transition in a "gender affirming" environment remains inconclusive. Multiple potential confounders are evident. The most notable deficiencies of existing research are the absence of proper control subjects and lack of randomization in study design.[110] No randomized control trials have been performed, and the existing longitudinal studies have serious limitations—most significantly, that they follow cohorts of patients in a non-controlled, unrandomized manner. This design severely limits any conclusions that can be drawn.

113. Moreover, many studies find no improvement—or negative effects—from "affirming" care. For instance, a 2020 British study (Carmichael et al.[111]) found "no evidence of change (no improvement) in psychological function with GnRHa treatment as indicated by parent report (CBCL) or self-report (YSR) of overall problems, internalizing or externalizing problems or self-harm." Puberty blockers used to treat children aged 12 to 15 who had severe and persistent gender dysphoria had no significant effect on their psychological function, thoughts of self-harm, or body image. However, as expected, the children experienced reduced growth in height and bone strength by the time they finished their treatment at age

[110] See Hruz, P. W. Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria. *Linacre Q* 87, 34-42, doi:10.1177/0024363919873762 (2020).
[111] Carmichael P, Butler G, Masic U, et al. Short-term outcomes of pubertal suppression in a selected cohort of 12 to 15 year old young people with persistent gender dysphoria in the UK. medRxiv 2020.12.01.20241653; doi:https://doi.org/10.1101/2020.12.01.20241653.

16. As Oxford's Professor Michael Biggs summarized the study's findings, "After a year on GnRHa [puberty blockers] children reported greater self-harm, and girls experienced more behavioral and emotional problems and expressed greater dissatisfaction with their body—so puberty blockers actually exacerbated gender dysphoria."[112]

114. The widely respected Cochrane Review examined hormonal treatment outcomes for male-to-female transitioners over 16 years.[113] They found "insufficient evidence to determine the efficacy or safety of hormonal treatment approaches for transgender women in transition." Thus, decades after the first transitioned male-to-female patient, quality evidence for the benefit of transitioning remains lacking.

115. Although appropriate caution is warranted in extrapolating the outcomes observed from prior studies with current treatments, adults who have undergone social transition with or without surgical modification of external genitalia

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[112] https://www.transgendertrend.com/tavistock-experiment-puberty-blockers/; Dyer, C. Puberty blockers: children under 16 should not be referred without court order, says NHS England. BMJ2020;371:m4717.doi:10.1136/bmj.m4717 pmid:33268453. See, Dyer, C., Puberty blockers do not alleviate negative thoughts in children with gender dysphoria, finds study, BMJ 2021;372:n356 doi: https://doi.org/10.1136/bmj.n356 (Published 08 February 2021); see also Dyer, C. Puberty blockers do not alleviate [suicidal] negative thoughts in children with gender dysphoria, finds study. BMJ 372, n356, doi:10.1136/bmj.n356 (2021). https://www.medrxiv.org/content/10.1101/2020.12.01.20241653v1; BBC summary: https://www.bbc.com/news/uk-55282113

[113] See Haupt, C., Henke, M. et. al., Cochrane Database of Systematic Reviews Review - Intervention, Antiandrogen or estradiol treatment or both during hormone therapy in transitioning transgender women, 28 November 2020 and https://www.cochranelibrary.com/cdsr/doi/10.1002/14651858.CD013138.pub2/full.

continue to have rates of depression, anxiety, substance abuse and suicide far above the background population.[114]

### A. Change in Patient Population

116. One important (and contentious) issue requiring more study is the recent trend of adolescent female to male gender discordant patients. In the United Kingdom, where centralized medical care provides data to track health care phenomenon, the number of adolescent girls seeking sex transitioning exploded over 4,000% in the last decade. Similarly, in the United States, where we lack the same kinds of centralized health care data, it has been reported that in 2018, 2% of high school students identified on surveys as "transgender"—this is 200 times greater response, a 20,000% increase—over reports during past decades which showed a rate of only .01 percent.[115]

117. Along with this increase in transgender patients and identifiers has come a radical and recent transformation of the patient population from early onset males to rapid onset adolescent girls. Currently the majority of new patients with

[114] See Adams, N., Hitomi, M. & Moody, C. Varied Reports of Adult Transgender Suicidality: Synthesizing and Describing the Peer-Reviewed and Gray Literature. Transgend Health 2, 60-75, doi:10.1089/trgh.2016.0036 (2017); see also Dhejne, C. et al. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 6, e16885, doi:10.1371/journal.pone.0016885 (2011).

[115] See Johns MM, Lowry R, Andrzejewski J, et al. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students—19 States and Large Urban School Districts, 2017. MMWR Morb Mortal Wkly Rep 2019; 68:67–71.

sex-gender discordance are not males with a long, stable history of gender dysphoria since early childhood—as they were for decades, and under the Dutch protocols—but instead adolescent females with no documented long-term history of gender dysphoria. One might say, as Dr. Lisa Littman has theorized, [116] that these females experienced "rapid onset" transgender identification.

118. This recent change in the typical patient raises questions about our understanding of the origins of transgender identity. For instance, a genetics or "immutable" theory of transgender identity cannot explain the rapid expansion of new GD cases (a 4,000% to 20,000% increase), given that our genome is simply not changing that fast. Nor can that theory explain the explosion of adolescent females presented with GD. A "brain structures" theory has only weak medical evidence, and it also cannot explain the rapid expansion of new gender dysphoria cases. As for the theory that increased social acceptance of the transgender lifestyle is leading many people who were transgender all along to come out. Yet this theory fails to explain why males and older women are not also coming out in the same large numbers and not coming out in "social peer group clusters," as adolescent females are reportedly doing.

[116] See Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One. 2018 Aug 16;13(8):e0202330. doi: 10.1371/journal.pone.0202330. Erratum in: PLoS One. 2019 Mar 19;14(3):e0214157. PMID: 30114286; PMCID: PMC6095578.

### B. Methodological Problems with "Affirming" Literature

119. The published literature relied on to advocate for the use of puberty blockers, cross-sex hormones and gender affirming surgeries in minors consists almost entirely of studies with major methodological limitations.[117] As detailed next, these include:

- Significant recruitment biases, including internet-based convenience sampling;
- Relatively small sample sizes for addressing a condition that is likely to be multifactorial;
- Short term follow-up;
- Lack of randomization to different treatment arms;
- Failure to consider alternate hypotheses;
- Failure to include proper control groups;
- Reliance on cross sectional sampling that may identify associations, but cannot establish causal relationships between intervention and outcome;
- A high rate of patients lost to follow up in longitudinal analyses, which is relevant to questions of regret, desistance and completed suicide;
- Biased interpretation of study findings with a goal of validating *a priori* conclusions rather than seeking evidence to disprove the null hypothesis; and
- Ignoring starkly contradictory research documenting the lack of effectiveness of "transitioning" procedures, the low quality of research in this area, and the ongoing contentions and disagreements over this highly controversial, experimental medical field.

[117] See generally Hruz, Deficiencies in Scientific Evidence for Medical Management of Gender Dysphoria, Linacre Q 87(1), 34-42, doi:10.1177/0024363919873762 (2020).

120. Some or all of these methodological and statistical flaws are present in the following studies, which are commonly relied on by advocates of "affirming" treatments.

**The Branstrom Long-Term Treatment Outcome Study**: The historic Branstrom study is a long-term treatment (10+ years) outcome research investigation testing the effects of hormonal and surgical "transitioning" treatments on patients. This historic research found no reliable benefits from these treatments, as well as evidence suggesting *increased* suicide attempts and anxiety disorders following the "gender transitioning" treatments. In addition, detailed methodological critiques discovered significant research errors by the authors that appear to support the investigative theory that the authors had initially attempted to manipulate and misreport the findings of the study. The authors ultimately recanted their initial misreporting and agreed that their study produced *no reliable evidence* of benefits for gender reassignment hormone and surgical treatments. This historic investigation has helped to generate a profound collapse of support for these experimental procedures across Europe.[118]

[118] See SEGM, *Correction of a Key Study: No Evidence of "Gender-Affirming" Surgeries Improving Mental Health*, https://segm.org/ajp_correction_2020 (Aug. 30, 2020); Van Mol et al., *Gender-Affirmation Surgery Conclusion Lacks Evidence.* Am. J. Of Psych., 177(8), 765-766 (2020).

**A 2011 Dutch study by de Vries et al.**[119] is often cited to support longitudinal evidence of benefit from pubertal blockade. Although the study found slight improvements in mood improved and the risk of behavioral disorders with pubertal blockade over baseline, the study included no control group, and all 70 participants received ongoing psychological support. Thus, the authors were unable to determine the basis of the limited observed improvement. The authors acknowledge that psychological support or other reasons may have contributed to (or wholly caused) this observation. By the very nature of the trial, at best the study can provide a rationale for doing further studies that could show whether "affirming" interventions provide a benefit. The study does not (and cannot) answer the central question: whether the administration of puberty blockers is the solution to the problem and whether alternative approaches that do not carry the same risks relative to purported benefits (i.e., psychological interventions) may have the same or superior benefits.

Moreover, there remain questions about the extent to which the protocol used in these early Dutch studies may be relevant to the patient population presenting today. For decades transgender patients were mostly older adults or very young boys. As noted, over the last few years, a tsunami of teenaged girls has

[119] de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 8(8):2276-2283 (2011).

flipped the demographics of transgender patients—now up to 7 to 1 teen girls. The newly presenting cases are vastly overrepresented by adolescent females, the majority of whom also have significant mental health problems and neurocognitive comorbidities such as autism-spectrum disorder or ADHD.[120] Furthermore, estimates of gender dysphoria-transgenderism are rocketing upwards from 1 in 10,000 to "the number of U.S. transgender-identified youth may be as high as 9%."[121] This unexplained, radical transformation of patient demographics raises questions about the applicability even of the limited existing literature on this issue, particularly as to the Dutch protocol. Dr. Thomas Steensma, a prominent investigator of the Dutch protocol—the original model for transitioning treatments—has recently noted that "[w]e don't know whether studies we have done in the past can still be applied to this time," specifically because of the unexplained surge in female adolescents reporting gender dysphoria. "Many more children are registering, but also of a different type… Suddenly there are many more girls applying who feel like a boy." He concluded with the warning that "[w]e conduct structural

[120] See de Graaf, Nastasja M., and Polly Carmichael. "Reflections on Emerging Trends in Clinical Work with Gender Diverse Children and Adolescents." Clinical Child Psychology and Psychiatry, vol. 24, no. 2, Apr. 2019, pp. 353–64.
[121] See Kidd, Kacie M., et al. "Prevalence of Gender-Diverse Youth in an Urban School District." Pediatrics, vol. 147, no. 6, June 2021, p. e2020049823.

research in the Netherlands. But the rest of the world is blindly adopting our research."[122]

**A 2014 follow-up study by de Vries et al.**[123] encompassed 55 of the original 70 patients; 15 were lost to follow-up or not included. It has the same limitations that was present in assessing the original 2011 study, including a carefully selected patient population that is not representative of the broader population, especially now. Having a longer study does not obviate the limitations of the study design in making a conclusion that can be applied to the gender clinics that are operating in the United States.

In addition to the concerns of the Dutch studies already exposed, "[t]he linchpin result of the Dutch studies is the reported resolution of gender dysphoria, as measured by the Utrecht Gender Dysphoria Scale (UGDS)." Yet, as several researchers recently explained, the observed "drop was an artifact of switching the scale from 'female' to 'male' versions (and vice versa) before and after treatment, prompting a problematic reversal in the scoring."[124] "The same gender dysphoric

[122] See https://www.voorzij.nl/more-research-is-urgently-needed-into-transgender-care-for-young-people-where-does-the-large-increase-of-children-come-from/.
[123] de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics. 2014 Oct;134(4):696-704. doi: 10.1542/peds.2013-2958
[124] Abbruzzese E, Levine SB, Mason JW. The Myth of "Reliable Research" in Pediatric Gender Medicine: A critical evaluation of the Dutch Studies-and research that has followed. J Sex Marital Ther. 2023 Jan 2:1-27. doi: 10.1080/0092623X.2022.2150346.

individual, effectively answering the same question (albeit linguistically inverted)"—e.g., "Every time someone treats me like a girl [or boy] I feel hurt"—"results in either the maximum or the minimum 'gender dysphoria' score—depending on which sexed version of the scale was used." Thus, because researches used different scales of the UGDS before and after treatment, "it is impossible to determine if [the result shows] a real difference in gender dysphoria between groups or if this is an artifact of measurement error." Indeed, if anything, "[t]he fact that after gender reassignment, the UGDS scores were low on the opposite-sex scale indicates that the subjects would have scored high on the natal sex scale, which corresponds to a *persistence in transgender identity*." This, of course, is the opposite result purportedly reached by the study.

**The 2018 paper by Wiepjies, et al.**[125] is a retrospective review of records from all patients of the Center of Expertise on Gender Dysphoria gender clinic in Amsterdam from 1972-2015. While the study appears to report on the regret rates among a large cohort of adolescents (812) and children (548), regret is only reported for children and adolescents who had undergone gonadectomy once over 18 years of age. Of the adolescents, 41% started puberty suppression. Of those who started GnRH agonists, only 2% stopped this intervention (meaning that 98% of

[125] Wiepjes et al., The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets, *The Journal of Sexual Medicine*, *15*(4), 582–590 (2018).

those who started puberty suppression progressed to cross-sex hormone therapy). An additional 32%, having already completed puberty, started cross-sex hormone therapy without use of a GnRH agonist. Classification of regret was very stringent, requiring physician documentation of patient verbalized regret after gonadectomy and start of sex-concordant hormones to treat the iatrogenic hypogonadism. This means there are significant limitations to the conclusions that can be drawn from this paper. There is no discussion in the paper regarding adolescent regret of use of puberty blockers, cross-sex hormones or mastectomies. Importantly, 36% of patients were lost to follow up. This is notable given that gonadectomy iatrogenically induces the pathologic state of primary hypogonadism. Affected patients have a lifelong dependency for exogenously administered sex-steroid hormones, and thus an acute need for ongoing follow-up. Their failure to return to the physicians who provided gender affirming interventions raises serious questions about their outcome. It is reasonable to hypothesize that some may have experienced regret or completed suicide. Yet due to missing data, their fate remains unknown. It is also significant that the average time to regret was 130 months. The authors themselves acknowledge that it may be too early to predict regret in patients who started hormone therapy in the past 10 years.

**The 2018 Olson-Kennedy et al. paper**[126] presents the results of a survey of biologically female patients with male gender identity at the lead author's institution using a novel rating system for "chest dysphoria" created by the study authors. There were an equal number (68) of nonsurgical and post-surgical subjects surveyed. Those who had undergone bilateral mastectomies were reported to have less chest dysphoria than those who did not receive this intervention. Limitations of this study include convenience sampling of nonsurgical study subjects with high potential for selection bias, cross-sectional design, lack of validation of the primary outcome measure, and short follow-up time (about 2 years). Test validation is particularly relevant in assessing adolescent questionnaires due to a variety of cognitive and situational factors in this population.[127] Rigorous validation methods have been previously used in several other established questionnaires addressing adolescent self-perception.[128] As previously noted, this study cannot provide information about a causal relationship between the intervention and outcomes observed.

[126] Olson-Kennedy et al., Chest Reconstruction and Chest Dysphoria in Transmasculine Minors and Young Adults: Comparisons of Nonsurgical and Postsurgical Cohorts, *JAMA Pediatr.* 172(5):431–436 (2018).
[127] See Brener et al., Assessment of Factors Affecting the Validity of Self-Reported Health-Risk Behavior among Adolescents: Evidence from the Scientific Literature, *Journal of Adolescent Health* 33 (6): 436–57 (2003).
[128] See Palenzuela-Luis et al., Questionnaires Assessing Adolescents' Self-Concept, Self-Perception, Physical Activity and Lifestyle: A Systematic Review, *Children (Basel, Switzerland)*, *9*(1), 91 (2022).

**A 2019 study by Allen et al.**[129] considered suicidality after cross-sex hormones. It was limited by a very small patient population (47), had no control group, had a short follow-up period (mean < 1 year), and again ignored that patients receiving the interventions also received psychological support.

**A 2020 study by Turban et al.**[130] is often cited as proof that pubertal blockade prevents suicide in transgender youth. However, this study used an unreliable, biased sampling methodology. As stated in the paper, the authors considered "a cross-sectional online survey of 20,619 transgender adults aged 18 to 36 years" from the 2015 U.S. Transgender Survey. This was an online survey of transgender and "genderqueer" adults recruited from trans-friendly websites. Among the many problems with this sampling methodology, there is no evidence of study subject identities, no way to assess for potential false subjects, and no medical diagnosis for entry. No causation can be determined from this retrospective, cross-sectional design. Furthermore, the study failed to even assess individuals who may have desisted or regretted transitions. Turban claimed that desisters and regretters would "not be likely" in this study group, which also only included

[129] Allen, L. R., Watson, L. B., Egan, A. M., & Moser, C. N. (2019). Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology, 7(3), 302–311. https://doi.org/10.1037/cpp0000288

[130] Turban et al., Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*, *145*(2), e20191725 (2020).

adults. Thus, the study "does not include outcomes for people who may have initiated pubertal suppression and subsequently no longer identify as transgender."

Turban's misleading claim of lower suicidal ideation for treated patients is based upon "lifetime suicidality". It fails to recognize or acknowledge that the decision to grant the wish to provide puberty blockers was likely influenced by the mental health of the subjects at the time of presentation. Specifically, the most seriously mentally ill patients would have been denied affirmation treatment. Those who received treatment with pubertal suppression, when compared with those who wanted pubertal suppression but did not receive it, had lower odds of lifetime suicidal ideation (adjusted odds ratio = 0.3; 95% confidence interval = 0.2– 0.6). In Table 3 of the paper, under "Suicidality (past 12 months)" reductions for suppressed group versus non-suppressed were seen for ideation (50.6% v 64.8%) and "ideation with plan" (55.6% v 58.2%). However, it is important to note that differences in suicidal "ideation with plan and suicide attempt" and "attempt resulting for inpatient care" did not reach statistical significance. This was ignored by the authors. It would be reasonable to be concerned from an observation of over 40% attempted suicide in the treated group that the intervention was unsuccessful in improving health.[131]

[131] See generally Biggs, Puberty Blockers and Suicidality in Adolescents Suffering from Gender Dysphoria. Archives of Sexual Behavior, DOI: 10.1007/s10508-020-01743-6 (2020) and the multiple Letters to the Editor that criticized the multiple methodological errors in this study,

**A 2020 study by van der Miesen, et al.**[132] was a cross-sectional Dutch study that measured some patients who received puberty blockers and some who did not. The study had three populations of subjects: One was patients presenting to the gender clinic who had not received any intervention. The second was patients who had received puberty blockers. The third was adolescents from the general population. Because of this study's cross-sectional nature, it cannot establish a causal relationship between intervention and effect. It also represents a non-probability sample with potential for significant biases in subject recruitment. In addition, the subjects assessed before and after treatment are difference populations. Among the differences between these groups is patient age (mean of 14.5 and 16.8 years before and after treatment, respectively). This two year age difference is important as developmental progress during adolescence is known to influence psychological well-being.[133] There was also the same limitation noted in the 2011 de Vries study, that the treated population also received psychological support.

https://pediatrics.aappublications.org/content/145/2/e20191725/tab-e-letters#re-pubertal-suppression-for-transgender-youth-and-risk-of-suicidal-ideation.

[132] van der Miesen AIR, Steensma TD, de Vries ALC, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared With Cisgender General Population Peers. J Adolesc Health. 2020 Jun;66(6):699-704. doi: 10.1016/j.jadohealth.2019.12.018

[133] He J, Sun S, Zickgraf HF, Lin Z, Fan X. Meta-analysis of gender differences in body appreciation. Body Image. 2020 Jun;33:90-100. doi: 10.1016/j.bodyim.2020.02.011.

**A 2021 study by Bustos, et al.**[134] attempts to provide a systematic review of 27 observational or interventional studies that report on regret or detransition following gender-transition surgeries. A total of 7,928 subjects were included in their meta analysis. The authors concluded that only 1% or less of those who had gender-transition surgeries expressed regret. It is important to understand the serious methodological limitations and high risk of bias contained within this study's analysis.[135] This includes failure to include major relevant studies addressing this question,[136] inaccurate analysis within one of the studies considered,[137] and the general lack of controlled studies, incomplete and generally short-term follow-up, large numbers of lost subjects, and lack of valid assessment measures in the published literature addressing this question. As noted by Expósito-Campos and D'Angelo (2021), moderate to high risk of bias was present in 23 of the 27 studies included in the analysis. Furthermore, 97% of subjects analyzed were found

[134] Bustos et al., Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence. *Plastic and reconstructive surgery. Global open*, *9*(3), e3477 (2021).
[135] See Expósito-Campos, P., & D'Angelo, R. (2021). Letter to the Editor: Regret after Gender-affirmation Surgery: A Systematic Review and Meta-analysis of Prevalence. *Plastic and reconstructive surgery. Global open*, *9*(11), e3951.
[136] E.g. Dhejne, C., Öberg, K., Arver, S., & Landén, M. (2014). An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Archives of sexual behavior*, *43*(8), 1535–1545.
[137] Wiepjes CM, Nota NM, de Blok CJM, et al. The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med 2018; 15: 582–590.

within studies deemed to be of fair to poor scientific quality. Thus, this study cannot be used as strong support for the contention that regret is rare.

**The 2021 study by Narayan et al.**[138] examines anonymous survey results from 154 surgeons affiliated with WPATH. The response rate for this survey was 30%. Of the respondents, 57% had encountered patients with surgical regret. It is important to recognize that this study was specifically directed toward patients who had undergone surgical transition. Acknowledged biases of this study include selection bias, recall bias, and response bias. This type of study cannot accurately identify the prevalence in the transgender population as a whole, and is particularly limited in the ability to assess potential for regret in the pediatric population.

**The 2021 Almazan study**[139] attempts to address mental health outcomes in relation to gender-transition surgery. This study relies upon data from the 2015 US Transgender Survey. Limitations and weaknesses of this survey tool includes convenience sampling, recruitment of patients through transgender advocacy organizations, demand bias (i.e., the good subject effect[140]), a high number of respondents

[138] Narayan et al., Guiding the conversation-types of regret after gender-affirming surgery and their associated etiologies, *Annals of translational medicine*, *9*(7), 605 (2021).
[139] Almazan et al., Association Between Gender-Affirming Surgeries and Mental Health Outcomes. *JAMA Surgery, 156*(7): 611–618 (2021).
[140] Nichols AL, Maner JK. The good-subject effect: investigating participant demand characteristics. J Gen Psychol. 2008 Apr;135(2):151-65. doi: 10.3200/GENP.135.2.151-166. PMID: 18507315.

who reported having not transitioned medically or surgically (and reported no desire to do so in the future), and several data irregularities. One notable data irregularity was that a high number of respondents reported that their age was exactly 18 years. As noted by D'Angelo and colleagues, these irregularities raise serious questions about the reliability of the USTS data and therefore the reliability of conclusions based on that data.[141]

The **2022 van der Loos** study[142] is a Dutch cohort study that investigates the continuation rate of gender affirming interventions in people who began puberty blockers and gender affirming hormones during adolescence. The authors claim that the study provides evidence against desistance after receiving gender affirming hormones. While the paper gives the impression that subjects represent a period of study extending from 1972 to 2018, the majority of subjects recently started hormone interventions. The length of time for follow-up (mean of 3.5 years for males and 2.3 years for females) and the average age at follow-up (20.2 years for males and 19.3 years for females) are inadequate to support the authors' claim. Notably,

[141] D'Angelo et al., One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria, *Archives of sexual behavior*, *50*(1): 7–16. https://doi.org/10.1007/s10508-020-01844-2 (2021).

[142] van der Loos MATC, Hannema SE, Klink DT, den Heijer M, Wiepjes CM. Continuation of gender-affirming hormones in transgender people starting puberty suppression in adolescence: a cohort study in the Netherlands. Lancet Child Adolesc Health. 2022 Dec;6(12):869-875. doi: 10.1016/S2352-4642(22)00254-1.

research from these same investigators has suggested that the average time to de-transition is over 10 years.[143] Thus, it would be necessary for the study to assess patients at least a decade after starting gender affirming hormones to make any meaningful conclusions on desistance. Furthermore, as a retrospective cohort study without a control group, the study design cannot determine the effect of gender affirming therapy on whether or not the intervention influences the rate of desistance that would have occurred without the provision of gender affirming hormones.

The **2022 Nos** study[144] is a retrospective cohort study that reports on the likelihood of starting on gender affirming hormones (GAH) based upon whether or not subjects were treated with puberty blockers. While the title and abstract give the impression that puberty blocker use is not linked to subsequent GAH, the data fail to support this conclusion. Since nearly all of the patients in this study who did not receive GnRHa were given GAH, it is not possible to determine whether GnRHa could increase this outcome. The comparison groups differed by age at time of initial presentation (age 10-13 years versus 14-17 years). GnRHa use was higher among the younger patients owing to the fact that they had not completed

[143] Wiepjes CM, Nota NM, de Blok CJM, Klaver M, de Vries ALC, Wensing-Kruger SA, de Jongh RT, Bouman MB, Steensma TD, Cohen-Kettenis P, Gooren LJG, Kreukels BPC, den Heijer M. The Amsterdam Cohort of Gender Dysphoria Study (1972-2015): Trends in Prevalence, Treatment, and Regrets. J Sex Med. 2018 Apr;15(4):582-590. doi: 10.1016/j.jsxm.2018.01.016.
[144] Nos AL, Klein DA, Adirim TA, Schvey NA, Hisle-Gorman E, Susi A, Roberts CM. Association of Gonadotropin-Releasing Hormone Analogue Use With Subsequent Use of Gender-Affirming Hormones Among Transgender Adolescents. JAMA Netw Open. 2022 Nov 1;5(11):e2239758. doi: 10.1001/jamanetworkopen.2022.39758.

puberty at the time of first visit. A lag in progression to GAH use in this group is heavily influenced by the difference in age at time of initial presentation. The older group was eligible to start GAH at the time of study entry while those in the younger group were not. When adjusted for age, the rates of progression to GAH use is nearly identical. Importantly, among the patients who received GnRHa, **94% (64 out of 70)** went on to take gender affirming hormones. Thus, the study further confirms that rather than serving as a "pause button" for gender dysphoric adolescents, it is an intervention that will lead to progression to gender affirming hormones.

**The 2022 Green at al. study**[145] purported to measure suicide attempts and access to cross-sex hormones. Though this study had a large cohort of patients, it suffered many biases in patient recruitment—which was done over the Internet and provided a cross-sectional analysis which can, at best, demonstrate correlation but not causation. Similar to other studies, it not assess the effect of psychiatric medications or psychotherapy on outcomes. It also failed to include variables to assess at what age youth began puberty blockers or the duration which they had received gender affirming hormones.

[145] Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy With Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. J Adolesc Health. 2022 Apr;70(4):643-649.

**The 2022 Turban et al. study**[146] is retrospective cross-sectional investigation to assess whether there is an association between adolescent access to gender affirming hormones and mental health. The authors claim that there is an association between getting gender affirming hormones and favorable mental health outcomes compared to those who desired but did not receive this intervention. The methodology used is similar to the author's 2020 study on the effects of access to puberty blockers on lifetime suicidality already discussed above. Specifically, it used the same 2015 U.S. Transgender Survey (USTS), with all of the associated limitations and biases.[147] Participants in the USTS were recruited through transgender advocacy organizations and subjects were asked to 'pledge' to promote the survey among friends and family. Thus, there are serious concerns of selection bias.[148] It also suffers from recall bias[149] and an inability to verify the veracity of the claims of treatments given to the study respondents. Even if one dis-

[146] Tordoff DM, Wanta JW, Collin A, Stepney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. JAMA Netw Open. 2022 Feb 1;5(2):e220978. doi: 10.1001/jamanetworkopen.2022.0978. Erratum in: JAMA Netw Open. 2022 Jul 1;5(7):e2229031.

[147] D'Angelo, R., Syrulnik, E., Ayad, S. *et al.* One Size Does Not Fit All: In Support of Psychotherapy for Gender Dysphoria. *Arch Sex Behav* **50**, 7–16 (2021). https://doi.org/10.1007/s10508-020-01844-2

[148] Tyrer S, Heyman B. Sampling in epidemiological research: issues, hazards and pitfalls. BJPsych Bull. 2016 Apr;40(2):57-60. doi: 10.1192/pb.bp.114.050203. PMID: 27087985; PMCID: PMC4817645.

[149] Coughlin SS. Recall bias in epidemiologic studies. J Clin Epidemiol. 1990;43(1):87-91. doi: 10.1016/0895-4356(90)90060-3. PMID: 2319285.

misses these concerns, by design, the study is not able to make any conclusions regarding a causal relationship between GAH access and mental health. Review of the data contained within the paper leads to conclusions that are far different than those stated by the study authors regarding mental health of the study participants. While the odds ratio for past year suicidal ideation was statistically different between those who did and those who did not get GAH, there was no difference in those who had a suicide plan, actually attempted suicide, or were hospitalized for a suicide attempt. This is important since the rationale for accepting the attendant risks of gender affirming hormones is to prevent suicide. Those with a suicide plan or attempt are far more likely to succumb to suicide than those who merely contemplated suicide. As pointed out by Michael Biggs in a commentary of this article,[150] the data presented in this study negate the purported significance of effects of puberty blocker access on mental health as reported in Turban's 2020 Pediatric article.

**The 2022 Tordoff study** is a prospective observational cohort study that assessed the mental health of patients presenting to the Seattle Children's gender clinic over a one year period of follow up. The authors claimed that access to gender affirming care had significantly improved mental health with lower odds ratios

[150] https://journals.plos.org/plosone/article/comment?id=10.1371/annotation/dcc6a58e-592a-49d4-9b65-ff65df2aa8f6

of depression and suicidality. This purported finding was widely publicized by the University of Washington and was featured on several news media sites. A detailed critique of the paper's data and flawed conclusions have been posted online.[151] Contrary to the claims, data contained in the paper did not show improvement in mental health over the one year study period. At entry into the study, 59% of the subjects had moderate to severe depression. At the end of the study, 56% had moderate to severe depression. Self-harm or suicidal thoughts were 45% and 37% at baseline and 12 months, respectively. These are alarmingly high numbers for an intervention that is touted to be lifesaving. The reported statistical difference in odds ratios were comparisons between those who started on puberty blockers and cross-sex hormones and those who did not receive hormones. Importantly, there was a marked difference in the number of dropout subjects in the treated and non-treated groups (17.5% versus 80%, respectively). It is reasonable to speculate that the small number of subjects who remained in the study but did not receive hormones had significant co-morbidities that prevented them from accessing this intervention. In any event, the actual data from this study demonstrates that access to puberty blockers and gender affirming hormones did not improve mental health over the first year of treatment. This is drastically different from what the authors and the media claimed.

[151] See https://jessesingal.substack.com/p/researchers-found-puberty-blockers?s=r

**The 2022 Chen study**[152] is a longitudinal observational study of patients receiving care at four gender centers in the United States. The primary conclusion made by the authors is that "GAH improved appearance congruence and psychosocial functioning." However, there are major limitations and weaknesses in the data that limit the conclusions that can be made. A revealing critique of the paper by de Vries and Hannema that was published alongside this article exposes some of these concerns.[153] The most glaring problem is that the study was observational and did not include a control group. Thus, there is no ability to draw causal conclusions. At best, the authors can find associations. Akin to many of the other papers in this field, there is no way to determine whether any of the changes were contributed by or due solely to psychiatric interventions. It is also notable that even though the study was designed to recruit only subjects in with good mental health at baseline, 48 of the 307 study subjects (15.6%) were described as having severe depression at this time point. At the end of the two year follow up, 30 of the 219 remaining subjects (13.7%) were reported to have major depression. Furthermore, two patients committed suicide during the time of observation. This is an outcome that in most

[152] Chen D, Berona J, Chan YM, Ehrensaft D, Garofalo R, Hidalgo MA, Rosenthal SM, Tishelman AC, Olson-Kennedy J. Psychosocial Functioning in Transgender Youth after 2 Years of Hormones. N Engl J Med. 2023 Jan 19;388(3):240-250. doi: 10.1056/NEJMoa2206297.
[153] de Vries ALC, Hannema SE. Growing Evidence and Remaining Questions in Adolescent Transgender Care. N Engl J Med. 2023 Jan 19;388(3):275-277. doi: 10.1056/NEJMe2216191

other situations would lead to a halt in study and detailed inquiry by an institutional review board.[154] The paper claims to present two year follow up data in this cohort. However, only half of the study participants were assessed at each study time point and 30% did not have 24 month data collected. Even if one accepted the follow up period, this is likely not long enough to make firm conclusions about long-term efficacy. Most of the measures are based upon subjective experience. There is no inclusion of more robust measures of psychological well-being such as the number on antidepressants and other psychotropic medications. The study effects for many of the measured parameters was very modest at best and, while statistically significant, do not have any meaningful clinical significance. For example, the depression scores, showed little change over two years in the highest severity group. There is also significant heterogeneity in responses with some subjects showing improvement, some no change, and others worsening. Despite the spin provided by the authors and media, these data do not alleviate the serious concerns raised regarding the safety and efficacy of gender affirming medical interventions.

121. Many conclusions in the above studies are drawn or characterized in fundamentally unscientific ways without apparent regard to the scientific process of disproving a null hypothesis. Instead, these studies suggest that the authors began with a conclusion and then looked for data to support that conclusion. That is

[154] https://grants.nih.gov/grants/guide/notice-files/NOT99-107.html

a vastly unsound way of doing science, and patients will not be aware of these methodological limitations and distortions when informed of these purported conclusions.

122. There remains a significant and unmet need to improve our understand of the biological, psychological, and environmental basis for the manifestation of patient reports of discordance of gender identity and biological sex in affected individuals, as well as the long-term effects of "affirming" interventions.[155] In particular, there is a concerning lack of randomized controlled trials or adequately controlled longitudinal studies comparing outcomes of youth with gender dysphoria who received psychological support, were encouraged to socially transition, or were put on medical interventions, and how these differential treatments affect the usual and natural progression to resolution of gender dysphoria and other variables. Such studies can be ethically designed and executed with provisions for other dignity affirming measures to all treatment groups.[156] But they have not been performed in the existing literature, leaving that literature in a state insufficient to enable sound conclusions about the efficacy of "affirming" treatments.

[155] Olson-Kennedy, J. et al. Research priorities for gender nonconforming/transgender youth: gender identity development and biopsychosocial outcomes. Current Opinion in Endocrinology, Diabetes and Obesity 23, 172-179, (2016).
[156] See Sugarman J. Ethics in the design and conduct of clinical trials. Epidemiol Rev. 2002;24(1):54-8. doi: 10.1093/epirev/24.1.54. PMID: 12119856; And https://clinicalcenter.nih.gov/recruit/ethics.html.

## International Responses

123. Recognizing the paucity of evidence supporting "affirming" treatments, along with the proven risks of those treatments, other countries are increasingly limiting use of those treatments.

124. **Finland**: The National Science Review in Finland carefully examined all relevant science and suspended transition treatments for minors under age 16.[157] The review determined that "[t]he first-line treatment for gender dysphoria is psychosocial support and, as necessary, psychotherapy and treatment of possible comorbid psychiatric disorders." According to the review, "[c]ross-sex identification in childhood, even in extreme cases, generally disappears during puberty." The review also found: "Potential risks of GnRH therapy include disruption in bone mineralization and the as yet unknown effects on the central nervous system"; "there are no medical treatments (for transitioning) that can be considered evidence-based"; and, "[t]he reliability of the existing studies with no control groups is highly uncertain." Thus, "because of this uncertainty, no decisions should be made that can permanently alter a still-maturing minor's mental and physical development," and "[n]o gender confirmation surgeries are performed on

[157] See 2020 Recommendation of the Council for Choices in Health Care in Finland (PALKO / COHERE Finland) Medical Treatment Methods for Dysphoria Related to Gender Variance In Minors.

minors." "Since reduction of psychiatric symptoms cannot be achieved with hormonal and surgical interventions, it is not a valid justification for gender reassignment. A young person's identity and personality development must be stable so that they can genuinely face and discuss their gender dysphoria, the significance of their own feelings, and the need for various treatment options. For children and adolescents, these factors are key reasons for postponing any interventions until adulthood…. In light of available evidence, gender reassignment of minors is an experimental practice."

125. **Sweden**: The world-renowned Karolinska Hospital reviewed the current research and suspended pediatric gender transitions for patients under 16 outside of experimental, monitored clinical trials settings as of May 2021. Treatment will focus on psychotherapy and assessment[158]. The "Dutch protocol" for treating gender dysphoric minors has been discontinued over concerns of medical harm and uncertain benefits.

Moreover, in a national policy review, a report commissioned by the Swedish government concluded that:

- We have not found any scientific studies which explains the increase in incidence in children and adolescents who seek the heath care because of gender dysphoria.

[158] See Sweden's Karolinska Ends All Use of Puberty Blockers and Cross-Sex Hormones for Minors Outside of Clinical Studies. https://segm.org/Sweden_ends_use_of_Dutch_protocol. See also, Karolinska Policy Change K2021-3343 March 2021 (in English).pdf; Karolinska Hospital Ends the Use of Puberty Blockers for patients under 16: New policy statement from the Karolinska Hospital.

- We have not found any studies on changes in prevalence of gender dysphoria over calendar time, nor any studies on factors that can affect the societal acceptance of seeking for gender dysphoria. There are few studies on gender affirming surgery in general in children and adolescents and only single studies on gender affirming genital surgery.
- Studies on long-term effects of gender affirming treatment in children and adolescents are few, especially for the groups that have appeared during the recent decennium…
- No relevant randomized controlled trials in children and adolescents were found.[159]

From these findings, the Swedish National Board of Heath in December of 2022 issued updated guidelines for the care of adolescents and children with gender dysphoria.[160] This medical board concluded that "the risks of puberty blockers and gender-affirming treatment are likely to outweigh the expected benefits of these treatment". Noting that there is uncertainty about the cause for the rapid rise in number of people being diagnosed with gender dysphoria, documented evidence of detransitioning young adults with uncertainty regarding the prevalence of this outcome, and lack of uniformity in experience-based knowledge among providers, GnRH analogues, gender affirming hormones and mastectomy should be provided only in exceptional cases and ideally as part of an experimental trial.

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[159] See Sweden Policy Review, Gender dysphoria in children and adolescents: an inventory of the literature, SBU Policy Support no 307, 2019 (https://www.sbu.se/307e).
[160] https://www.socialstyrelsen.se/globalassets/sharepoint-dokument/artikelkatalog/kunskapsstod/2023-1-8330.pdf

126. **United Kingdom**: The British official medical review office (National Institute of Health and Care Excellence, NICE) published reports on the use of both puberty blockers and hormones for transitioning purposes. The assessment of the evidence into the drugs was commissioned by NHS England. The review found that the evidence for using puberty blocking drugs to treat young people struggling with their gender identity is "very low certainty."[161] The review found that "all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using modified GRADE. They all reported physical and mental health comorbidities and concomitant treatments very poorly."

NICE also reviewed the evidence base for cross-sex hormones.[162] The review found the evidence of clinical effectiveness and safety of cross-sex hormones was also of "very low" quality. The review concluded: "Any potential benefits of gender-affirming hormones must be weighed against the largely unknown long-term safety profile of these treatments in children and adolescents with gender dysphoria."

[161] https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_GnRH-analogues_For-upload_Final.pdf
[162] https://cass.independent-review.uk/wp-content/uploads/2022/09/20220726_Evidence-review_Gender-affirming-hormones_For-upload_Final.pdf

A recent independent review of gender identity services in the United Kingdom, by Dr. Hillary Case, concluded that "Evidence on the appropriate management of children and young people with gender incongruence and dysphoria is inconclusive both nationally and internationally."[163] Dr. Cass notes that "[t]here is lack of consensus and open discussion about the nature of gender dysphoria and therefore about the appropriate clinical response."

Citing concerns from the Cass report that the Tavistok model of care placed affected youth at considerable risk of poor mental health, and is therefore "not a safe or viable long-term option," this clinic is being shut down. It will be replaced by a new regional hospital-based service where related services for mental health and autism can be provided by clinicians who have expertise in safeguarding, supporting looked-after children and children who have experienced trauma. Thus, gender-related distress will be addressed "within a broader child and adolescent health context."

This new model is in sharp contrast to recommendations made by WPATH in their "standards of care" (SOC8). Differences in approach include the prioritization of parent versus child expectations for care, recommendations against social

[163] https://cass.independent-review.uk/wp-content/uploads/2022/03/Cass-Review-Interim-Report-Final-Web-Accessible.pdf

affirmation of pre-pubertal youth, the provision of puberty blockers within the experimental setting, initial focus on exploration and treatment of mental health problems, and use of psychological support as a primary intervention.

## Conclusions

127. There are no long-term, peer-reviewed published, reliable and valid research studies documenting the reliability and validity of assessing gender identity by relying solely upon the expressed desires of a patient.

128. There are no long-term, peer-reviewed published, reliable, and valid research studies documenting any valid and reliable biological, medical, surgical, radiological, psychological or other objective assessment of gender identity or gender dysphoria.

129. A large percentage of children (over 80% in some studies) who questioned their gender identity will, if left alone, develop an acceptance of their natal (biological) sex.

130. A currently unknown percentage and number of patients reporting gender dysphoria suffer from mental illness(es) that complicate and may distort their judgments and perceptions of gender identity.

131. A currently unknown percentage and number of patients reporting gender dysphoria may be manipulated by a social contagion and social pressure

processes, including peer group, social media, YouTube role modeling, and parental pressures.

132. There are no long-term, peer-reviewed published, reliable and valid research studies documenting the number or percentage of patients receiving gender affirming medical interventions who are helped by such procedures.

133. There are no long-term, peer-reviewed published, reliable and valid research studies documenting the number or percentage of patients receiving gender affirming medical interventions who are injured or harmed by such procedures.

134. "Affirming" treatments have no known, peer reviewed and published error rates.

135. The gender affirming approach has limited, very weak scientific support for short-term alleviation of dysphoria and no long-term outcomes data demonstrating superiority over the other approaches.

136. Because of the major methodological limitations and weaknesses of the extent published literature in the field of gender dysphoria, one cannot make a conclusion that "affirming" treatments are justified as a safe and effective long-term solution to gender dysphoria in consideration of the significant risks and unsubstantiated long-term benefits.

137. With the limited and poor-quality data currently available about the purported efficacy of blocking normally timed puberty, administering cross-sex

hormones, and gender affirming surgeries in alleviating psychological morbidity for youth who experience sex-discordant gender identity and the associated serious medical risks associated with these interventions, it cannot be concluded that this approach is "medically necessary." Use of such medical interventions remains a largely experimental approach.

138. Experimentation on gender discordant youths is especially likely to cause harm to patients from historically marginalized communities. That is because children in such communities are disproportionally affected by gender discordance. These include:

- children with a history of psychiatric illness;[164]
- children of color;[165]
- children with mental developmental disabilities;[166]
- children on the autistic spectrum;[167] and,

[164] See, e.g., Kaltiala-Heino, R., Sumia, M., Työläjärvi, M., & Lindberg, N. (2015). Two years of gender identity service for minors: overrepresentation of natal girls with severe problems in adolescent development. *Child and adolescent psychiatry and mental health*, *9*, 9. https://doi.org/10.1186/s13034-015-0042-y.

[165] See, e.g., G. Rider et al. (2018), Health and Care Utilization of Transgender/Gender Non-Conforming Youth: A Population Based Study, Pediatrics at 4, DOI: 10.1542/peds.2017-1683.

[166] See, e.g., Bedard, C., Zhang, H.L. & Zucker, K.J. Gender Identity and Sexual Orientation in People with Developmental Disabilities. *Sex Disabil* 28**,** 165–175 (2010). https://doi.org/10.1007/s11195-010-9155-7.

[167] See, e.g., de Vries, A. L., Noens, I. L., Cohen-Kettenis, P. T., van Berckelaer-Onnes, I. A. & Doreleijers, T. A. Autism spectrum disorders in gender dysphoric children and adolescents. *J Autism Dev Disord* 40, 930-936, doi:10.1007/s10803-010-0935-9 (2010).

- children residing in foster care homes and adopted children.[168]

139. Patients suffering from gender dysphoria or related issues have a right to be protected from experimental, potentially harmful treatments lacking reliable, valid, peer reviewed, published, long-term scientific evidence of safety and effectiveness.

140. The treatment protocols and recommendations of politically influenced, non-science associations like WPATH and the American Academy of Pediatrics that engage in consensus-seeking methodologies by vote rather than science are not based on competent, credible, methodologically sound science, and have no known or published error rate.

141. Administering hormones to a child whose gender dysphoria is highly likely to resolve is risky, unscientific, and unethical. Iatrogenic damages from these interventions, including infertility, stunted growth, increased heart attack risk, and many more, are often irreversible.

142. Because of these concerns about the safety, efficacy, and scientific validity of controversial, unproven, and experimental treatment paradigms, I have not personally engaged in the delivery of gender affirming medical interventions to children with gender dysphoria. Given the unproven long-term benefits and the

[168] See, e.g., See e.g., D. Shumer et al. (2017), Overrepresentation of Adopted Adolescents at a Hospital-Based Gender Dysphoria Clinic, Transgender Health Vol. 2(1).

well-documented risks and harms of "transitioning" children, I decline to participate in such experimental treatments until the science has proven that the relative risks and benefits of this approach warrant such procedures.

143. My decision is strengthened by the knowledge that the vast majority of children who report gender dysphoria will, if left untreated, grow out of the problem — a natural coping-developmental process — and willingly accept their biological sex. Since there are no reliable assessment methods for identifying the small percentage of children with persisting sex-gender identity discordance from the vast majority who will accept their biological sex, and since puberty blocking treatments, hormone transition treatments, and surgical transition treatments are all known to have potentially life-long devastating, negative effects on patients, I and many colleagues view it as unethical to treat children with an unknown future by using experimental, aggressive, and intrusive gender affirming medical interventions.

I declare under penalty of perjury that the foregoing is true and correct.

Executed on February 15, 2023.

Paul W Hruz

Paul W. Hruz, M.D., Ph.D.

Exhibit "A"

# Curriculum Vitae

Date: 2/15/2023
Name: Paul W. Hruz, M.D., Ph.D.

## Contact Information


| | |
|---|---|
| Office: | Phone: 314-286-2797<br>Fax: 314-286-2892 |
| Mail: | Washington University in St. Louis<br>School of Medicine<br>Department of Pediatrics<br>Endocrinology and Diabetes<br>660 South Euclid Avenue<br>St Louis MO 63110 |
| Email: | Office: hruz_p@wustl.edu |


## Present Position

Associate Professor of Pediatrics, Endocrinology and Diabetes
Associate Professor of Pediatrics, Cell Biology & Physiology

## Education

| | |
|---|---|
| 1987 | BS, Chemistry, Marquette University, Milwaukee, WI |
| 1993 | PhD, Biochemistry, Medical College of Wisconsin, Milwaukee, WI<br>Elucidation of Structural, Mechanistic, and Regulatory Elements in 3-Hydroxy-3-Methlyglutaryl-Coenzyme A Lyase, Henry Miziorko |
| 1994 | MD, Medicine, Medical College of Wisconsin, Milwaukee, WI |
| 1994 - 1997 | Pediatric Residency, University of Washington, Seattle, Washington |
| 1997 - 2000 | Pediatric Endocrinology Fellowship, Washington University, Saint Louis, MO |
| 2017 | Certification in Healthcare Ethics, National Catholic Bioethics Center, Philadelphia, PA |

## Academic Positions / Employment

| | |
|---|---|
| 1996 - 1997 | Locum Tenens Physician, Group Health of Puget Sound Eastside Hospital, Group Health of Puget Sound Eastside Hospital, Seattle , WA |
| 2000 - 2003 | Instructor in Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO |
| 2003 - 2011 | Assistant Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO |
| 2004 - 2011 | Assistant Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO |
| 2011 - Pres | Associate Professor of Pediatrics, Cell Biology & Physiology, Washington University in St. Louis, St. Louis, MO |

| | |
|---|---|
| 2011 - Pres | Associate Professor of Pediatrics, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO |
| 2012 - 2017 | Division Chief, Endocrinology and Diabetes, Washington University in St. Louis, St. Louis, MO |

## Clinical Title and Responsibilities

| | |
|---|---|
| | General Pediatrician, General Pediatric Ward Attending: 2-4 weeks per year, St. Louis Children's Hospital |
| 2000 - Pres | Pediatric Endocrinologist, Endocrinology Night Telephone Consult Service: Average of 2-6 weeks/per yr, St. Louis Children's Hosptial |
| 2000 - Pres | Pediatric Endocrinologist, Inpatient Endocrinology Consult Service: 3-6 weeks per year, St. Louis Children's Hospital |
| 2000 - Pres | Pediatric Endocrinologist, Outpatient Endocrinology Clinic: Approximately 50 patient visits per month, St. Louis Children's Hospital |

## Teaching Title and Responsibilities

| | |
|---|---|
| 2009 - Pres | Lecturer, Markey Course-Diabetes Module |
| 2020 - 2020 | Facilitator, Reading Elective-Interdisciplinary/Miscellaneous Course #M80-800, Washington University School of Medicine |

## University, School of Medicine and Hospital Appointments and Committees

University

| | |
|---|---|
| 2012 - 2020 | Disorders of Sexual Development Multidisciplinary Care Program |

School of Medicine

| | |
|---|---|
| 2013 - 2020 | Molecular Cell Biology Graduate Student Admissions Committee |
| 2014 - Pres | Research Consultant, ICTS Research Forum - Child Health |

Hospital

| | |
|---|---|
| 2000 - Pres | Attending Physician, St. Louis Children's Hospital |

## Medical Licensure and Certifications

| | |
|---|---|
| 1997 - Pres | Board Certified in General Pediatrics |
| 2000 - Pres | MO Stae License #2000155004 |
| 2001 - Pres | Board Certified in Pediatric Endocrinology & Metabolism |

## Honors and Awards

| | |
|---|---|
| 1987 | National Institute of Chemists Research and Recognition Award |
| 1987 | Phi Beta Kappa |
| 1987 | Phi Lambda Upsilon (Honorary Chemical Society) |
| 1988 | American Heart Association Predoctoral Fellowship Award |
| 1994 | Alpha Omega Alpha |
| 1994 | Armond J. Quick Award for Excellence in Biochemistry |

| | |
|---|---|
| 1994 | NIDDK/Diabetes Branch Most Outstanding Resident |
| 1998 | Pfizer Postdoctoral Fellowship Award |
| 2002 | Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University |
| 2013 | Julio V Santiago, M.D. Scholar in Pediatrics |
| 2017 | Redemptor Hominis Award for Outstanding Contributions to the Study of Bioethics |
| 2018 | Eli Lilly Outstanding Contribution to Drug Discovery: Emerging Biology Award |
| 2018 | Scholar-Innovator Award, Harrington Discovery Institute |
| 2021 | Linacre Award |

## Editorial Responsibilities

Editorial Ad Hoc Reviews

| | |
|---|---|
| | AIDS |
| | AIDS Research and Human Retroviruses |
| | American Journal of Pathology |
| | American Journal of Physiology |
| | British Journal of Pharmacology |
| | Circulation Research |
| | Clinical Pharmacology & Therapeutics |
| | Comparative Biochemistry and Physiology |
| | Diabetes |
| | Experimental Biology and Medicine |
| | Future Virology |
| | Journal of Antimicrobial Chemotherapy |
| | Journal of Clinical Endocrinology & Metabolism |
| | Journal of Molecular and Cellular Cardiology |
| | Obesity Research |
| 2000 - Pres | Journal of Biological Chemistry |
| 2013 - Pres | PlosOne |
| 2016 - Pres | Scientific Reports |
| 2018 - Pres | Nutrients |

Editorial Boards

| | |
|---|---|
| 2014 - 2015 | Endocrinology and Metabolism Clinics of North America |

## National Panels, Committees

| | |
|---|---|
| 2017 - Pres | Consultant, Catholic Health Association |
| 2021 - Pres | Consulting Fellow, National Catholic Bioethics Center |

## National Boards

| | |
|---|---|
| 2020 - Pres | WU ICTS Clinical and Translational Research Funding Program (CTRFP) Review Committee |

## Community Service Contributions

Professional Societies and Organizations

American Diabetes Association
Endocrine Society
Pediatric Endocrine Society

## Major Invited Professorships and Lectures

| | |
|---|---|
| 2002 | Pediatric Grand Rounds, St. Louis Children's Hospital, St Louis, MO |
| 2004 | National Disease Research Interchange, Human Islet Cell Research Conference, Philadelphia, PA |
| 2004 | NIDA-NIH Sponsored National Meeting on Hormones, Drug Abuse and Infections, Bethesda, MD |
| 2005 | Endocrine Grand Rounds, University of Indiana, Indianapolis, IN |
| 2005 | The Collaborative Institute of Virology, Complications Committee Meeting, Boston, MA |
| 2006 | Metabolic Syndrome Advisory Board Meeting, Bristol-Meyers Squibb, Pennington, NJ |
| 2007 | American Heart Association and American Academy of HIV Medicine State of the Science Conference: Initiative to Decrease Cardiovascular Risk and Increase Quality of Care for Patients Living with HIV/AIDS, Chicago, IL |
| 2007 | Minority Access to Research Careers Seminar, University of Arizona, Tucson, AZ |
| 2007 | MSTP Annual Visiting Alumnus Lecture, Medical College of Wisconsin , Milwaukee, WI |
| 2007 | Pediatric Grand Rounds, St Louis Children's Hospital, St Louis, MO |
| 2008 | Division of Endocrinology, Diabetes and Nutrition Grand Rounds, Boston University, Boston, MA |
| 2009 | Pediatric Grand Rounds, St Louis Children's Hospital, St. Louis, MO |
| 2010 | American Diabetes Association Scientific Sessions, Symposium Lecture Orlando, FL |
| 2010 | School of Biological Sciences Conference Series, University of Missouri Kansas City, Kansas City, MO |
| 2011 | Life Cycle Management Advisory Board Meeting, Bristol-Myers Squibb,, Chicago, IL |
| 2013 | Pediatric Grand Rounds, St Louis Children's Hospital, ST LOUIS, MO |
| 2013 | Clinical Practice Update Lecture, St Louis Children's Hospital, St Louis, MO |
| 2014 | Pediatric Academic Societies Meeting,, Vancouver, Canada |
| 2014 | American Diabetes Association 74th Scientific Sessions, , San Francisco, CA |
| 2017 | Division of Pediatric Endocrinology Metabolism Rounds, University of Michigan, Ann Arbor, MI |
| 2017 | Catholic Medical Association National Conference, Denver, CO |
| 2018 | Obstetrics, Gynecology & Women's Health Grand Rounds, Saint Louis University, St. Louis, MO |
| 2018 | Medical Grand Rounds, Sindicato Médico del Uruguay, Montevideo, Uraquay |
| 2018 | Internal Medicine Grand Rounds, Texas Tech , Lubbock, TX |
| 2019 | Veritas Center for Ethics in Public Life Conference, Franciscan University, Steubenville, OH |
| 2019 | MaterCare International Conference, Rome, Italy |
| 2019 | Child Health Policy Forum, Notre Dame University, South Bend , IN |

| | |
|---|---|
| 2021 | Obstetrics & Gynecology Grand Rounds, University of Tennessee, Knoxville , TN |
| 2022 | The World Federation of Catholic Medical Associations (*FIAMC*), Rome, Italy |

## Consulting Relationships and Board Memberships

| | |
|---|---|
| 1996 - 2012 | Consultant, Bristol Myers Squibb |
| 1997 - 2012 | Consultant, Gilead Sciences |

## Research Support

Completed Governmental Support

| | |
|---|---|
| 2001 - 2006 | K-08 A149747, NIH<br>Mechanism of GLUT4 Inhibition by HIV Protease Inhibitors<br>Role: Principal Investigator |
| 2007 - 2012 | R01<br>Mechanisms for Altered Glucose Homeostasis During HAART<br>Role: Principal Investigator<br>Total cost: $800,000.00 |
| 2009 - 2011 | R01 Student Supp<br>Mechanisms for Altered Glucose Homeostasis During HAART<br>Role: Principal Investigator<br>Total cost: $25,128.00 |
| 2009 - 2014 | R01<br>Direct Effects of Antiretroviral Therapy on Cardiac Energy Homeostasis<br>Role: Principal Investigator<br>Total cost: $1,250,000.00 |
| 2017 - 2019 | R-21 1R21AI130584 , National Institutes of Health<br>SELECTIVE INHIBITION OF THE P. FALCIPARUM GLUCOSE TRANSPORTER PFHT<br>Role: Principal Investigator<br>Total cost: $228,750.00 |

Completed Non-Governmental Support

| | |
|---|---|
| 2015 | Novel HIV Protease Inhibitors and GLUT4<br>Role: Principal Investigator |
| 2008 - 2011 | II<br>Insulin Resistance and Myocardial Glucose Metabolism in Pediatric Heart Failure<br>Role: Co-Investigator<br>PI: Hruz<br>Total cost: $249,999.00 |
| 2009 - 2012 | Research Program<br>Regulation of GLUT4 Intrinsic Activity<br>Role: Principal Investigator<br>Total cost: $268,262.00 |
| 2010 - 2011 | Protective Effect of Saxagliptin on a Progressive Deterioration of Cardiovascular Function<br>Role: Principal Investigator |
| 2012 - 2015 | II<br>Solution-State NMR Structure and Dynamics of Facilitative Glucose Transport Proteins<br>Role: Principal Investigator<br>Total cost: $375,000.00 |

2017 - 2020 Prevention And Treatment Of Hepatic Steatosis Through Selective Targeting Of GLUT8
Role: Co-Principal Investigator
PI: DeBosch
Total cost: $450,000.00

2017 - 2021 Matching Micro Grant
Novel Treatment of Fatty Liver Disease (CDD/LEAP)
Role: Principal Investigator
Total cost: $68,500.00

2018 - 2021 LEAP Innovator Challenge
Novel Treatment of Fatty Liver Disease
Role: Principal Investigator
Total cost: $68,500.00

2019 - 2021 Scholar-Innovator Award HDI2019-SI-4555 , Harrington Foundation
Novel Treatment of Non-Alcoholic Fatty Liver Disease
Role: Principal Investigator
Total cost: $379,000.00

Current Governmental Support

2021 - 2025 R-01 DK126622 (Co-investigator), 8/25/2021-7/31/2025, NIH-NIDDK, , NIH
Leveraging glucose transport and the adaptive fasting response to modulate hepatic metabolism
Role: Co-Investigator
PI: DeBosch

## Trainee/Mentee/Sponsorship Record

2002 - 2002 Nishant Raj- Undergraduate Student, Other
Study area: Researcher

2002 - 2010 Joseph Koster, PhD, Postdoctoral Fellow
Study area: Researcher

2003 - 2004 Johann Hertel, Medical Student
Study area: Research
Present position: Assistant Professor, University of North Carolina, Chapel Hill, NC

2003 - 2003 John Paul Shen, Medical Student
Study area: Research

2004 - 2005 Carl Cassel- High School Student, Other
Study area: Research

2004 - 2004 Christopher Hawkins- Undergraduate Student, Other
Study area: Researcher

2004 - 2004 Kaiming Wu- High School Student, Other
Study area: Research

2005 - 2005 Helena Johnson, Graduate Student

2005 - 2005 Jeremy Etzkorn, Medical Student
Study area: Researcher

2005 - 2005 Dominic Doran, DSc, Postdoctoral Fellow
Study area: HIV Protease Inhibitor Effects on Exercize Tolerance

2006 - 2006 Ramon Jin, Graduate Student
Study area: Research

2006 - 2006 Taekyung Kim, Graduate Student
Study area: Research

2007 - 2007 Jan Freiss- Undergraduate Student, Other
Study area: Researcher

2007 - 2008 Kai-Chien Yang, Graduate Student
Study area: Research
Present position: Postdoctoral Research Associate, University of Chicago

2007 - 2007 Paul Buske, Graduate Student
Study area: Research

2007 - 2007 Randy Colvin, Medical Student
Study area: Researcher

2008 - 2011 Arpita Vyas, MD, Clinical Fellow
Study area: Research
Present position: Assistant Professor, Michigan State University, Lansing MI

2008 - 2009 Candace Reno, Graduate Student
Study area: Research
Present position: Research Associate, University of Utah

2008 - 2012 Dennis Woo- Undergraduate Student, Other
Study area: Researcher
Present position: MSTP Student, USC, Los Angeles CA

2008 - 2008 Temitope Aiyejorun, Graduate Student
Study area: Research

2009 - 2009 Anne-Sophie Stolle- Undergraduate Student, Other
Study area: Research

2009 - 2009 Matthew Hruz- High School Student, Other
Study area: Research
Present position: Computer Programmer, Consumer Affairs, Tulsa OK

2009 - 2009 Stephanie Scherer, Graduate Student
Study area: Research

2010 - 2014 Lauren Flessner, PhD, Postdoctoral Fellow
Present position: Instructor, Syracuse University

2010 - 2010 Constance Haufe- Undergraduate Student, Other
Study area: Researcher

2010 - 2011 Corinna Wilde- Undergraduate Student, Other
Study area: Researcher

2010 - 2010 Samuel Lite- High School Student, Other
Study area: Research

2011 - 2016 Thomas Kraft, Graduate Student
Study area: Glucose transporter structure/function
Present position: Postdoctoral Fellow, Roche, Penzberg, Germany

2011 - 2011 Amanda Koenig- High School Student, Other
Study area: Research

2011 - 2012 Lisa Becker- Undergraduate Student, Other

2011 - 2011 Melissa Al-Jaoude- High School Students, Other

2019 Ava Suda, Other, Pre-med

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A. Journal Articles


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3. Mitchell GA, Robert MF, Hruz PW, Wang S, Fontaine G, Behnke CE, Mende-Mueller LM, Schappert K, Lee C, Gibson KM, Miziorko HM. 3-Hydroxy-3-methylglutaryl coenzyme A lyase (HL). Cloning of human and chicken liver HL cDNAs and characterization of a mutation causing human HL deficiency. *J Biol Chem*. 1993;268(6):4376-81. PMID:8440722
4. Hruz PW, Anderson VE, Miziorko HM. 3-Hydroxy-3-methylglutaryldithio-CoA: utility of an alternative substrate in elucidation of a role for HMG-CoA lyase's cation activator. *Biochim Biophys Acta*. 1993;1162(1-2):149-54. PMID:8095409
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12. Murata H, Hruz PW, Mueckler M. Indinavir inhibits the glucose transporter isoform Glut4 at physiologic concentrations. *AIDS*. 2002;16(6):859-63. PMID:11919487
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C2. Chapters

1. Henderson KE, Baranski TJ, Bickel PE, Clutter PE, Clutter WE, McGill JB. Endocrine Disorders in HIV/AIDS. In: *The Washington Manual Endocrinology Subspecialty Consult* Philadelphia, PA; 2008:321-328.
2. Paul W Hruz. Medical Approaches to Alleviating Gender Dysphoria In: Edward J Furton, eds. *Transgender Issues in Catholic Health Care* Philadelphia PA; 2021:1-42.
3. Cara Buskmiller and Paul Hruz. A Biological Understanding of Man and Woman In: John Finley, eds. *Sexual Identity: The Harmony of Philosophy, Science, and Revelation* Steubenville OH; 2022:Chapter 2, pp 65-103.

C4. Invited Publications

1. Grunfeld C, Kotler DP, Arnett DK, Falutz JM, Haffner SM, Hruz P, Masur H, Meigs JB, Mulligan K, Reiss P, Samaras K, Working Group 1. Contribution of metabolic and anthropometric abnormalities to cardiovascular disease risk factors. *Circulation*. 2008;118(2):e20-8. PMCID: PMC3170411 PMID: 18566314
2. Hruz PW. HIV protease inhibitors and insulin resistance: lessons from in-vitro, rodent and healthy human volunteer models. *Curr Opin HIV AIDS*. 2008;3(6):660-5. PMCID: PMC2680222 PMID: 19373039
3. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*. 2011;25(3):459-68. PMCID: PMC3115529 PMID: 21663839
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5. Hruz PW. Commentary. *Clin Chem*. 2015;61(12):1444. PMID: 26614228

6. Hruz PW, Mayer LS, and McHugh PR. Growing Pains: Problems with Pubertal Suppression in Treating Gender Dysphoria *The New Atlantis*. 2017;52:3-36.
7. Hruz, PW. The Use of Cross-Sex Steroids in Treating Gender Dysphoria *Natl Cathol Bioeth Q*. 2018;17(4):1-11.
8. Hruz, PW. Experimental Approaches to Alleviating Gender Dysphoria in Children *Nat Cathol Bioeth Q*. 2019;19(1):89-104.

**Expert Witness Testimony**

2009 Rosas v. Astrazeneca

2012 O'Connor v. Stamford

2016 Carcaño et al. v. Patrick McCrory (United States District Court, M.D. North Carolina)

2016 Jane Doe v. Board of Education of the Highland School District (United States District Court For the Southern District of Ohio Eastern Division, Case No. 2:16-CV-, 524)

2017 Ward v. Janssen (Circuit Court of St Louis, Division 16, MO, Case No. 1522-CC00213-01)

2017 Adams v. St John's School Board (United States District Court For the Middle District of Florida, FL Civil Action No. 3:17-cv-00739-TJCJBT)

2017 Ashton Whitaker v. Kenosha Unified School District (United States District Court Eastern District of Wisconsin, Civ. Action No. 2:16-cv-00943)

2018 Terri Bruce v. State of South Dakota (The United States District Court District of South Dakota Western Division, Case No. 17-5080)

2019 Cause DF-15-09887-SD of the 255th Judicial Circuit of Dallas County, TX regarding the dispute between J.A. D.Y. and J.U. D.Y., Children

2021 Kadel vs. Falwell (The United States District Court For The Middle District Of North Carolina, Case No.: 1:19-cv-272-LCB-LPA)

2022 Brandt v Rutledge (The United States District Court Eastern District of Arkansas Central Division, Case No. 4:21-CV-00450-JM)

2022 Eknes-Tucker vs Ivey (United States District Court Middle District of Alabama Northern Division, Case 2:22-cv-00184-LCB-SRW)

2022 D.H. et al. v. Snyder (United States District Court For the District Court of Arizona, Case No. 4:20-cv-00335-SHR)