

IN THE UNITED STATES DISTRICT COURT FOR  
THE EASTERN DISTRICT OF ARKANSAS

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DYLAN BRANDT, et al.,		:
	Plaintiffs,	:
		:
	v.	:
		:
LESLIE RUTLEDGE, et al.,		:
	Defendants.	:
		:
-----X		:

Case No.: 4:21-CV-00450-JM-01

**SUPPLEMENTAL DECLARATION OF ARMAND H. MATHENY AN TOMM MARIA,  
MD, PhD, FAAP, HEC-C IN SUPPORT OF PLAINTIFFS’ MOTION FOR  
PRELIMINARY INJUNCTION**

I, ARMAND H. MATHENY AN TOMM MARIA, MD, PhD, FAAP, HEC-C, declare as follows:

1. I have personal knowledge of the matters stated in this declaration.
2. As set forth in greater detail in my previously submitted declaration dated June

11, 2021, my background and credentials include the following: I am the Director of the Ethics Center, the Lee Ault Carter Chair of Pediatric Ethics, and an Attending Physician in the Division of Hospital Medicine at Cincinnati Children’s Hospital Medical Center. I am also a Professor in the Departments of Pediatrics and Surgery at the University of Cincinnati College of Medicine. My CV is attached as Exhibit A.

3. I reviewed the Defendants’ Combined Brief in Opposition to Plaintiffs’ Motion for Preliminary Injunction and Reply in Support of Defendants’ Motion to Dismiss (“Opposition Brief”), and the declarations of Drs. Stephen Levine, Paul Hruz, Mark Regnerus, and Paul Lappert. Here, I respond to some of the central points in the brief and declarations. I do not



specifically address each and every point made and study or article cited, but instead explain the problems with the major conclusions the Defendants and their experts draw and provide data showing why such conclusions are in error. I reserve the right to supplement my opinions if necessary as the case proceeds.

4. While the Defendants assert that the Plaintiffs' filings leave a false impression, Defendants' brief and their expert witnesses' declarations consistently mischaracterize the current treatment paradigm for adolescents with gender dysphoria as experimental, mislead the court by suggesting that parts of the treatment paradigm not being approved by the US Food & Drug Administration (FDA) is intrinsically problematic, and suggesting that the treatment paradigm is politically biased and not evidence-based. They, by way of just one example, state, "When used as a gender transition procedure to indefinitely halt the normal progression of puberty in a child, puberty blockers are *not* FDA approved. That is, the use of such drugs as gender-transition procedure on children is experimental and unsupported by data." Opposition Brief, at 9. These claims are misleading and false. They also erroneously claim that the current treatment paradigm is inconsistent with the standards of informed consent.

The prohibited treatments are not experimental

5. The Defendants use the term "experimental" in the colloquial sense rather than in the technical sense of the subject of research. These two uses should not be conflated. The Belmont report states, "The fact that a procedure is 'experimental,' in the sense of new, untested or different, does not automatically place it in the category of research (National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*:

*Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* [Bethesda, MD]: The Commission; 1978).”

6. Regardless of which meaning Defendants intend, neither the colloquial nor the technical use of the term “experimental” applies to the current treatment paradigm. It is not new or untested; the Endocrine Society’s recommendation regarding pubertal suppression, for example, is supported, in part, by a clinical trial published 10 years ago. See Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3869-3903 and 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.* 2011;8(8):2276-2283. The current treatment paradigm is also not experimental in the technical sense. See National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research.* [Bethesda, MD]: The Commission; 1978. The interventions are designed to promote the well-being of individual patients. They are not administered to contribute to generalized knowledge or as part of a formal research protocol.

The use of drugs for uses other than indications for which they were approved by the FDA does not mean the use is experimental, untested, or unsafe

7. For the FDA to approve a drug, the company must show that it is safe and effective for its intended use. (Safe does not mean that the drug is without side effects, but rather that the benefits outweigh the potential risks.) Once a drug is approved, healthcare providers may prescribe the drug for other uses that they believe are medically appropriate. They may, for example, prescribe it for another disease or medical condition. This is called off-label use. See

U.S. Food & Drug Administration. Understanding unapproved use of approved drugs “off label” February 5, 2018. Available at <https://www.fda.gov/patients/learn-about-expanded-access-and-other-treatment-options/understanding-unapproved-use-approved-drugs-label>. Accessed July 12, 2021.

8. Off-label use does not mean that the use is experimental, untested, or unsafe. The American Academy of Pediatrics Committee on Drugs states, “It is important to note that the term ‘off-label’ does not imply an improper, illegal, contraindicated, or investigational use” and “[t]he administration of an approved drug for a use that is not approved by the FDA is not considered research and does not warrant special consent or review if it is deemed to be in the individual patient’s best interest (Frattarelli DA, Gailinkin JL, Green TP et al. Off-label use of drugs in children. *Pediatrics* 2014;133:565).” The off-label use may be well-supported by evidence. For example, the off-label use of tricyclic antidepressants (amitriptyline and nortriptyline) and calcium channel alpha(2)-delta ligands (gabapentin and pregabalin) are supported by randomized controlled trials. See Dworkin RH, O’Connor AB, Audette J, et al. Recommendations for the pharmacological management of neuropathic pain: An overview and literature update. *Mayo Clin Proc.* 2010;85(3 Suppl):S3-14. Companies nevertheless may choose not to seek FDA approval for additional indications for a drug because it is not cost effective. Companies are, however, generally prohibited from advertising off-label uses. See Wittich CM, Burkle CM, Lanier WL. Ten common questions (and their answers) about off-label drug use. *Mayo Clin Proc.* 2012;87(10):982-990.

9. Off-label use of drugs is common in many areas of medicine, including pediatrics. For example, morphine, an opioid that is indicated for the management of pain that is not adequately treated by non-narcotic pain medication, although widely used, is not FDA approved

for individuals under 18 years of age. See Morphine Sulfate injection label. November 2011. Available at [https://www.accessdata.fda.gov/drugsatfda\\_docs/label/2011/202515s000lbl.pdf](https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202515s000lbl.pdf) Accessed July 12, 2021. A recent study of children’s hospitals found that in 28.1% of encounters, at least one off-label drug was prescribed. The study only included 76 preselected medications. It also only included one type of off-label use: use in patients younger than the lower limit of the FDA-approved age range. If the investigators had included more medications and other types of off-label use, e.g., use of these drugs for unapproved indications or unapproved dosages, the actual percentage of off-label use would be even higher. See Yackey K, Stukus K, Cohen D, Kline D, Zhao S, Stanley R. Off-label medication prescribing patterns in pediatrics: An update. *Hosp Pediatr*. 2019;9(3):186-193. The rate of off-label use may be significantly higher in certain age groups, categories of drugs, and clinical settings. For example, a recent study of patients in pediatric cardiac wards and intensive care units found that 75% of treatments were off-label. See Back J, Wahlander H, Hanseus K, Bergman G, Naumburg E. Evidence of support used for drug treatments in pediatric cardiology. *Health Sci Rep*. 2021;4(2):e288.

The Endocrine Society Guideline on the banned care is based on accepted scientific methodology

10. The Defendants’ brief asserts that while clinical practice guidelines have increasingly become a familiar part of clinical practice, “[u]nlike standards of care, which should be authoritative, unbiased consensus positions designed to produce optimal outcomes, practice guidelines are suggestions or recommendations to improve care that, depending on their sponsor, may be biased.” Opposition Brief, at 12. It goes on to say that “because guidelines represent a political, consensus-seeking process (i.e., voting)—a process with no known error rate—as

opposed to an evidence-seeking scientific research process, they have never been accepted by the scientific community as establishing what practices are or are not experimental. (See Hruz Decl. at pp. 46-48; Levine Decl. ¶ 52.) (12-13).” *Id.*

11. As an initial matter, the Defendants’ brief and the expert declarations upon which it relies confuse standard of care and clinical practice guidelines. While healthcare providers may use the term “standard of care” in a colloquial manner, it is a technical legal term that refers to “what a minimally competent physician in the same field would do in the same situation, with the same resources (Moffett P, Moore G. The standard of care: Legal history and definitions: The bad and good news. *West J Emerg Med.* 2011;12(1):111.)” It is a decision regarding the care of a particular patient in a particular context. Clinical practice guidelines in contrast are intended to assist clinicians and patients in medical decision-making and improve the quality of care. See Murad MH. Clinical practice guidelines: A primer on development and dissemination. *Mayo Clin Proc.* 2017;92(3):423-433. Guidelines are not intended to dictate the treatment of a particular patient. See Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3869-3903.

12. More importantly, Defendants and their experts incorrectly suggest that the Endocrine Society’s clinical practice guidelines are developed by a political process as opposed to a scientific method. In developing clinical practice guidelines, the Endocrine Society follows the Grades of Recommendation Assessment, Development and Evaluation (GRADE) methodology. GRADE provides systematic and explicit methods of grading the quality of evidence and the strength of recommendations.<sup>1</sup> See Atkins D, Best D, Briss PA, et al. Grading

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<sup>1</sup> Woolf et al.’s analysis of the potential benefits, limitations, and harms of clinical guidelines, Defendants Exhibit 18, was published in 1999 before GRADE.

quality of evidence and strength of recommendations. *BMJ*. 2004;328(7454):1490. Research has shown that the methodology is reliable—different individuals using the method reach similar conclusions about the quality of evidence. See Mustafa RA, Santesso N, Brozek J, et al. The GRADE approach is reproducible in assessing the quality of evidence of quantitative evidence syntheses. *J Clin Epidemiol*. 2013;66(7):736-742. It has been adopted by more than 100 organizations and is considered the gold standard. See Murad MH. Clinical practice guidelines: A primer on development and dissemination. *Mayo Clin Proc*. 2017;92(3):423-433. The Endocrine Society funds the development of its guidelines; the guideline task forces receive no commercial funding. The Society has rules for disclosing and managing potential conflicts of interest. Endocrine Society. Methodology. 2021. Available at <https://www.endocrine.org/clinical-practice-guidelines/methodology>. Accessed July 12, 2021. This is not, therefore, “a political, consensus-seeking process (i.e., voting).”

The banned treatments are supported by medical evidence

13. The Defendants continue to falsely assert that there is no evidence supporting the current treatment paradigm. They, for example, state, “But contrary to Plaintiffs’ claim, there is no evidence whatsoever that such procedures are beneficial.” Opposition Brief, at 2. The Endocrine Society Guideline identifies and evaluates the relevant evidence, including longitudinal clinical trials. See Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab*. 2017;102(11):3869-3903. While the evidence has limitations—as is often the case in medicine, and particularly in pediatrics—it is erroneous to state that there is no evidence.



14. To the extent that the Defendants' expert witnesses address individual studies, their criticisms are largely irrelevant. Dr. Levine and Professor Regnerus, for example, are critical of Bränström R, Pachankis JE. Reduction in mental health treatment utilization among transgender individuals after gender-affirming surgeries: A total population study. *Am J Psychiatry*. 2020;177(8):727-734. While not conceding any of these criticisms, they are beside the point as the Endocrine Society Guideline does not cite this article and the Guideline's recommendations are not dependent upon it. Dr. Levine and Professor Regnerus do not specifically analyze the studies on which the Society's recommendations are based.

15. The Defendants suggest that mental health treatment for gender dysphoria is sufficient, at least until individuals turn 18 years old. This recommendation fails to acknowledge the substantial dysphoria that may remain, even with mental health treatment, and which motivates individuals to seek other medical treatment. *See, e.g.* Levine Decl., ¶ 81 (characterizing the pain of gender dysphoria as "relatively minor"). It also does not acknowledge the development of secondary sexual characteristics inconsistent with the individual's gender identity that may make treatment in adulthood more difficult. The Defendants' experts also fail to support their recommended alternative treatment regime with the same level of evidence to which they hold others. They, for example, provide no randomized controlled trials comparing "watchful waiting" and psychotherapy with what they refer to as "affirmation."

The banned treatments follow accepted principles of informed consent

16. The Defendants suggest, based on solely anecdotal evidence, that treatment is being performed without adequate informed consent. Dr. Levine, for example, intimates that



health care providers “[w]ithhold[] accurate information from patients or parents about alternative approaches and risks and benefits of transition, or misrepresent[] the current state of research in this field.” Levine Decl, ¶ 8(1). The Endocrine Society Guideline in fact emphasizes the importance of informed consent and is clear about alternatives, potential risks, and the available evidence.

17. The Guideline emphasizes the importance of informed consent. The criteria for sex hormone treatment for adolescents, for example, include the following:

1. A qualified MHP [mental health provider] has confirmed:

...

- the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment.

2. And the adolescent:

- has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
- has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on the applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in support the adolescent through the treatment process (Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3878).

18. It acknowledges alternatives. It, for example, states, “In some forms of GD/gender incongruence, psychological intervention may be useful and sufficient (Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3880.)”

19. The Guideline discusses the risks of treatment including the potential effects on fertility. It, for example, states, “Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of

transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option (Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3879).”

20. Finally the Guideline acknowledges the current state of research in the field. It, for example, states, “We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 | ++OO) (Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3871).” “We suggest” is a weak, compared to a strong, recommendation and “++OO” designates low, compared to very low, moderate, and high quality evidence. As explained in my opening declaration (par. 20), these descriptions of the evidence are relative, and “low quality” evidence may be sufficient to make a recommendation.

21. The Defendants do not provide empirical evidence of widespread inadequacy of informed consent. Even if inadequate informed consent were frequent, there are mechanisms other than banning the procedures to address this hypothetical problem. Patients and parents could, for example, sue providers for inadequate informed consent and state medical boards could discipline providers for not obtaining adequate informed consent.

22. The Defendants and their expert witnesses also emphasize minors’ inability to provide informed consent and to appreciate the long-term consequences of medical decisions. But that is not unique to gender-affirming medical care, and such care, like most other medical care, is only provided to minors with parental consent.

23. The Endocrine Society Guideline acknowledges the role of parents in the informed consent process. It, for example, states, “Because young adolescents may not feel qualified to make decision about fertility and many not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent support group (Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: An Endocrine Society clinical practice guideline. *J Clin Endocrinol Metab.* 2017;102(11):3879).” The Guideline also acknowledges the role of parents, other caretakers, or guardian in providing informed consent for adolescents who have not reached the age of legal medical consent.

24. Dr. Levine asks rhetorically, “Do parents have a right to determine their child’s future sterility, for instance?” Levine Decl., ¶ 8(1). Yes, patients and parents may make medical decisions that cause infertility. This is not unique to the banned treatments. Parents of children with some types of differences of sex development or intersex conditions may choose to have their children’s gonads removed due to the risk of malignancy. See Abaci A, Catli G, Berberoglu M. Gonadal malignancy risk and prophylactic gonadectomy in disorders of sexual development. *J Pediatr Endocrinol Metab.* 2015;28(9-10):1019-1027. Parents of children with some types of malignancies may also choose treatments which may damage their children’s gonads and result in infertility. See Delessard M, Saulnier J, Rives A, Dumont L, Rondamino C, Rives N. Exposure to chemotherapy during childhood or adulthood and consequences on spermatogenesis and male fertility. *Int J Mol Sci.* 2020;21(4) and Blumenfeld Z. Chemotherapy and fertility. *Best Pract Res Clin Obstet Gynaecol.* 2012;26(3):379-390. Professor Regnerus’ reference to judicial review does not apply to these types of treatments; it applies to involuntary sterilization, e.g., performing a hysterectomy on an adolescent with an intellectual disability in

order to prevent pregnancy. See Diekema DS. Involuntary sterilization of persons with mental retardation: An ethical analysis. *Ment Retard Dev Disabil Res Rev.* 2003;9(1):21-26.

25. Dr. Levine's comparison of the treatment of adolescents with gender dysphoria to the Tuskegee study and the Nazi and Imperial Japanese wartime experimental research is offensive. These activities were clearly research rather than practice; they sought to generate knowledge rather than to improve the subjects' health. The Tuskegee study was a study of untreated syphilis in Black men from whom effective treatment was withheld. Nazi research included studies of death by freezing on concentration camp prisoners and Japanese research included studies of gas gangrene on prisoners of war. Such experiments were unethical for multiple reasons including the lack of free and adequately informed consent, the disproportionate risks, and the inequitable selection of participants. See Freedman B. Research, unethical. In: Reich WT, Editor in Chief. *Encyclopedia of Bioethics* Vol 4. Rev Ed. New York: Macmillan Library Reference USA;1995:2258-2261.

26. The Defendants and their experts consistently falsely and erroneously characterize the current treatment paradigm for the care of adolescents with gender dysphoria to justify state prohibition of that care. Decisions to provide and receive gender-affirming care are nonetheless evidence-based and consistent with medical ethics and should remain in the purview of patients, their parents and guardians, and their health care providers.

I declare under penalty of perjury under the laws of the United States of America that the foregoing is true and correct.

Executed on JULY 15, 2021

  
ARMAND H. MATHENY AN TOMM MARIA, MD, PhD