No. 23-477

In the Supreme Court of the United States

UNITED STATES OF AMERICA.,
Petitioner,

v.

JONATHAN SKRMETTI, ATTORNEY GENERAL AND REPORTER FOR TENNESSEE, *et al.*,
Respondents.

On Writ of Certiorari to the United States Court of Appeals for the Sixth Circuit

BRIEF OF THE MANHATTAN INSTITUTE AND DR. LEOR SAPIR AS *AMICI CURIAE* SUPPORTING RESPONDENTS

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QUESTION PRESENTED

Whether the Equal Protection Clause of the Fourteenth Amendment prohibits states from enacting laws protecting children from sex-transition medical interventions with risks of lifelong harm.

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INTEREST OF *AMICI CURIAE*[1]

The Manhattan Institute (MI) is a nonprofit policy research foundation whose mission is to develop and disseminate ideas that foster individual responsibility and agency across multiple dimensions. It has sponsored scholarship and filed briefs opposing regulations that interfere with constitutionally protected liberties.

Leor Sapir, Ph.D., is a fellow at MI, where his research focuses on pediatric gender medicine and medical policy in the U.S. and abroad. His academic work, including his dissertation on Title IX, investigated how America's political culture and constitutional government shape public policy on matters of civil rights. His scholarly work has appeared in numerous publications, including *Archives of Sexual Behavior*

Amici file this brief because the lack of robust or reliable evidence for the benefits of powerful medications like gonadotropin-releasing hormone agonists (puberty blockers) for youth gender dysphoria, alongside known and unknown risks, cautions against their use. *Amici* are also well-positioned to explain why some of petitioner's *amici* have misrepresented and overstated the medical literature to bolster the flimsy case for the long-term safety and efficacy of youth "gender-affirming" treatments.

BACKGROUND AND SUMMARY OF ARGUMENT

Well-established scientific evidence and a growing international consensus among medical professionals

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[1] Rule 37 statement: No part of this brief was authored by any party's counsel, and no person or entity other than *amici* funded its preparation or submission.

and authorities advise against the use of "gender-affirming" medications like puberty blockers and cross-sex hormones as first-line treatments for youth gender dysphoria. The most comprehensive assessment of the risks and benefits of pediatric gender medicine to date, conducted in the U.K. by Dr. Hilary Cass and finalized in April 2024, found "remarkably weak" evidence for the safety and efficacy of such medications. The Cass Review calls for a cautious, individualized approach to gender dysphoria that prioritizes psychotherapy. Medical organizations in the United States, however, have largely diverged from this cautious international approach, favoring aggressive "gender affirming" treatments.

Case in point: the brief by Dr. Meredithe McNamara and her fellow U.S-based *amici* ("McNamara et al." or the "McNamara Group") in this case. This brief casts doubt on the validity and ethical appropriateness of the Cass Review. Given the influence and prestigious positions that Dr. McNamara and her colleagues possess within the world of gender medicine and as expert witnesses in ongoing lawsuits, it is essential that the Court recognize and understand the flaws and misrepresentations in their arguments.

First, McNamara et al. conflate the overall quality of evidence with the quality of individual studies. According to the GRADE system—a widely accepted framework in evidence-based medicine (EBM)—"quality of evidence" reflects the degree of confidence that the estimate of effect of an intervention reflects the true effect. "Quality of individual studies," by contrast, indicates the risk of bias, such as when confounding factors can explain the observed outcome. In not differentiating between these concepts, the McNamara

Group sets the reader up for a second fallacy, when it misrepresents the evidence from individual studies. McNamara et al. cite specific studies as "robust" and "reliable," yet these studies suffer from serious methodological flaws. The studies' findings were mischaracterized by their own authors, who are gender clinicians with significant conflicts of interest. In one of the studies, two adolescents committed suicide after receiving "gender-affirming" treatments.

Third, McNamara et al. argue that requiring higher-quality evidence for gender-affirming interventions imposes an unrealistic burden compared to other areas of pediatric medicine. They warn that failure to rule in favor of petitioner would "create chaos in the day-to-day practice of pediatrics." But this claim is fearmongering, and the proof of this are the very examples they offer of other "low quality" evidence treatments. As we show, implicit in the McNamara Group's warning about "chaos in the field" is an assumption about suicide risk that numerous health authorities now reject.

Finally, the significant discrepancies among the McNamara Group, the American Academy of Pediatrics, and other U.S. medical organizations reveal a lack of consensus on core issues related to adolescent gender-affirming care. Disagreement over such questions as whether puberty blockers are diagnostic underscores the enduring confusions in the field.

Given these profound uncertainties and the untrustworthiness of clinicians who practice and claim special expertise in youth gender medicine, states like Tennessee are justified in taking steps to protect minors from potentially harmful medical interventions that are not supported by rigorous, reliable evidence.

ARGUMENT: NEITHER SCIENTIFIC EVIDENCE NOR GLOBAL HEALTH AUTHORITIES SUPPORT THE SAFETY AND EFFICACY OF PUBERTY BLOCKERS AND CROSS-SEX HORMONES FOR YOUTHFUL GENDER DYSPHORIA

This brief focuses on the arguments presented by Dr. Meredithe McNamara and her co-*amici* ("McNamara et al." or the "McNamara Group") because they purport to have unique expertise on questions of research and clinical care for gender dysphoric youth. "Amici have a total of 86 years of experience in caring for more than 4800 transgender youth and have published 278 peer-reviewed studies, 168 of which are in the field of gender-affirming health care." Br. Amici Curiae of Expert Researchers and Physicians ("McNamara Br."), at 1. The McNamara Group asserts that "gender-affirming" treatments are supported by "robust" and "reliable" evidence, and their analysis has been presented as authoritative in defending the current clinical practices in pediatric gender medicine. A close examination reveals significant misrepresentations of evidence-based medicine (EBM) principles, methodological flaws in the research they cite, and misleading claims about the safety and efficacy of these treatments.

I. THE MCNAMARA GROUP MISREPRESENTS BASIC CONCEPTS OF EVIDENCE-BASED MEDICINE

McNamara et al. misrepresent EBM in numerous ways. Most glaringly, they describe only part of an EBM concept or principle and then use that partial description to draw convenient but misleading conclusions. This method makes the McNamara Group's

analysis appear technical and thus convincing to lay readers—and possibly even to more informed readers whose understanding of EBM is incomplete.

A. Evidence-Based Medicine Requires Quality Evidence and Quality Studies

A good example is the McNamara Group's assertion that term "low quality evidence" has a "highly technical meaning[]" in EBM and "should not be used interchangeably . . . with colloquialisms like 'weak' and 'poor.'" McNamara Br. at 20. McNamara et al. are correct that "low quality" has a technical meaning not synonymous with its lay meaning, but they are incorrect or at least misleading when they go on to say that "low quality" can describe "robust clinical research," *id.* at 22, and, more broadly, "reliable, peer-reviewed studies [that] serve as the basis for strong clinical recommendations, particularly in pediatrics," *id.* at 19.

When McNamara et al. write that "'[m]oderate' and 'low quality' studies do not mean that the evidence is of poor quality", *id.*, they conflate quality of evidence with quality of individual studies. Quality of studies means risk of bias, i.e., systemic error or deviation from truth in research. *See, e.g.*, Julian Higgins & Sally Green, *Cochrane Handbook for Systematic Reviews of Interventions* 188 (2008). Quality of evidence includes, but is not limited to, quality of studies. According to a seminal EBM article that McNamara et al. themselves cite, "'Quality' as used in GRADE [Grading of Recommendations Assessment, Development, and Evaluation] means more than risk of bias and so may also be compromised by imprecision, inconsistency, indirectness of study results, and publication bias." Howard Balshem et al., *GRADE Guidelines: 3. Rating the Quality of Evidence*, 64 J. Clinical

Epidemiology 401, 401 (2011); *see also* McNamara Br. at 24. Publication bias, for instance, happens when studies that yield null or negative findings do not make it into the medical literature because the publisher believes they will not receive enough attention from the scholarly community or because the findings are politically inconvenient. *See, e.g.*, Ana Mlinarić et al., *Dealing with the Positive Publication Bias: Why You Should Really Publish Your Negative Results*, 27 Biochemia Medica 1, 1–3 (2017). If there is publication bias in an area of research, a systematic review of evidence can find that the quality of evidence is low, even if individual studies may be at low risk for bias.

According to the GRADE developers cited by McNamara et al., low quality evidence means that "Our confidence in the effect estimate is limited: The true effect may be substantially different from the estimate of the effect." Balshem et al., *supra*, at 404. "Very low" quality means "The true effect is likely to be substantially different from the estimate of effect." *Id.* By failing to quote these definitions from the sources they themselves cite and by failing to accurately explain the key distinction in EBM between quality of evidence and quality of individual studies, the McNamara Group commits the very fault they accuse others of committing. That is, they use "highly technical meanings . . . interchangeably . . . with colloquialisms." McNamara Br. at 20.

Importantly, McNamara et al. conveniently fail to mention that the systematic reviews of evidence for puberty blockers and cross-sex hormones that used the GRADE system found "very low" quality evidence. *See id.* at 19, 24. In GRADE's terms, these systematic reviews found that "the true effect" of puberty blockers

and cross-sex hormones is "likely to be substantially different from the estimate of effect," Balshem et al., *supra*, at 404, as reported by the authors of the research in question. This is critical to an area like gender-medicine research, where authors are often gender clinicians with financial as well as non-financial (*e.g.*, intellectual) conflicts of interest who exaggerate or "spin" their findings *See* E. Abbruzzese et al., *The Myth of "Reliable Research" in Pediatric Gender Medicine: A Critical Evaluation of the Dutch Studies—and Research that Has Followed*, J. Sex & Marital Therapy 673, 673 (2023).

To say that the "the true effect may be [or is likely to be] substantially different from the estimate of effect," Balshem et al., *supra*, at 404, means precisely the opposite of what McNamara et al. say it means. It means that the supposedly positive findings of gender medicine research are *un*reliable and may present clinicians and patients with a highly misleading picture about the benefits and risks of a drug.

B. Is There "Reliable" and "Robust" Research in Pediatric Gender Medicine?

In their brief, McNamara et al. critique the Cass Review and the systematic reviews of the medical literature conducted by the University of York that informed the Cass Review's conclusions. *See* McNamara Br. at 12–19. They argue that the York systematic reviews on puberty blockers and cross-sex hormones should be disregarded in part because they "exclude robustly conducted studies on the effects of gender-affirming medications." *Id.* at 12.

That the York reviews' findings are consistent with all previous systematic reviews of the evidence,

including one commissioned by the World Professional Association for Transgender Health (WPATH), makes the McNamara Group's argument suspicious on its face. *See* Kellan E. Baker, *Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review*, 5 J. Endocrine Soc. 1, 1, 8, 12–13 (2021) ("The strength of the evidence . . . is low due to concerns about bias in study designs, imprecision . . . and confounding by factors such as gender-affirming surgery status"). McNamara et al. cannot substantiate their claims about the state of the evidence as a whole, so instead they merely assert it and list (without analyzing) a few examples of "valuable studies" they believe demonstrate credible benefits from hormonal treatments.

Among the "valuable studies" mentioned, two are given special weight in the original white paper on which the McNamara Group's brief is based. These are Diana M. Tordoff et al., *Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care*, 5 JAMA Network Open 1 (2022), and Diane Chen et al., *Psychosocial Functioning in Transgender Youth After 2 Years of Hormones*, 388 New Eng. J. Med. 240 (2023) (as corrected, 389 New Eng. J. Med. 1540 (2023)). Since McNamara et al. cite these studies as prime examples of "robust" and "reliable" research, it is worth asking what these studies found and whether the McNamara Group brief accurately represent those findings.

1. Tordoff et al.

McNamara et al. quote the Tordoff study's chief finding from its abstract: "gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months." Tordoff et

al., *supra*, at 2. But the study found no such thing. The Tordoff study divided participants—patients at Seattle Children's Hospital—into two groups, one that received endocrine interventions and another that did not. *Id.* at 1, 6. The treatment group showed no improvement in depression and suicidality by the end of the study. *Id.* at 6–9.

As it turns out, Tordoff et al. inferred that treatment was "associated with lower odds of depression and suicidality," *id.* at 2, from the apparent deterioration in mental health of the non-treatment group. However, that inference was also unwarranted given the high drop-out rate in the non-treatment group. Drop-out rates of 20% or above pose "serious threats to [the] validity of a study." Mary S. Fewtrell et al., *How Much Loss to Follow-up is Acceptable in Long-Term Randomised Trials and Prospective Studies?*, 93 Archives Disease Childhood 458, 458 (2008). In the Tordoff study, a whopping 80 percent of the non-treatment group (28 out of 35 participants) dropped out before the end of the study. Tordoff et al., *supra*, at Supplemental Online Content eTable 3, https://tinyurl.com/hdap7336. The Occam's Razor explanation for this result is that the adolescents who did not receive hormones got better—due perhaps to psychotherapy, regression to the mean, or some other factor—and no longer sought gender-related services at Seattle Children's Hospital.

The authors of the Tordoff study thus egregiously misrepresented their findings. By using the misleading language "associated with lower odds of depression and suicidality," Tordoff et al., *supra*, at 2, the authors anticipated that ideologically aligned journalists, clinicians, and researchers would accept the finding at face

value. That is exactly what happened. As one peer-reviewed critique of the study observed, "The spin of Tordoff is dramatic" Abbruzzese et al., *supra*, at 688. The fact that McNamara et al. cite this study as "valuable," McNamara Br. at 13–14, and uncritically present its self-reported findings to the Court is a good illustration of the problems of bias and activism that plague the field of pediatric gender-medicine research.

2. Chen et al.

According to the McNamara Group, this study "was particularly robust because its statistical analysis allowed strong causal inferences about the positive effects of gender-affirming medications on mental health." *Id.* at 15. The study's authors, among whom is one member of the McNamara Group, reported that they found "improved appearance congruence and psychosocial functioning," Chen et al., *supra*, at 240, as a direct result of cross-sex hormone therapy. Again, these terms must be understood in context.

The authors of the Chen study had initially planned to study eight outcome measures of mental health but ended up reporting only on two. *Id.* at 242–45. Outcomes for gender dysphoria, self-injury, trauma, suicidality, body esteem, and quality of life were registered in the study protocol but never appeared in the final publication. Questions about the "safety" of puberty blockers and cross-sex hormones (for "metabolic and physiological parameters" such as "bone health") also appeared in the original hypotheses but not in the published results. *See* Johanna Olson-Kennedy et al., *Impact of Early Medical Treatment for Transgender Youth: Protocol for the Longitudinal, Observational Trans Youth Care Study*, 8 JMIR Rsch. Protocols 1, 5 (2019). Curiously, the authors wrote that

they "vouch for . . . the fidelity of the study to the protocol." Chen et al., *supra*, at 241.

Not only did the Chen study's authors disappear most of their intended outcome measures, but they added new ones that were not initially registered—a practice known as hypothesizing after results are known (HARKing) and strongly discouraged in scientific research. *See* Norbert L. Kerr, *HARKing: Hypothesizing After the Results are Known*, 2 Personality & Soc. Psych. Rev. 196, 196–97 (1998). The new outcome measures included the dubious "appearance congruence," a cosmetic (and surrogate) rather than clinical outcome measure indicating how treated adolescents believe others see them in terms of conformity to male- or female-typical appearance. *See* Chen et al., *supra*, at 241–42.

The methodology of Chen et al. alone should raise suspicion, but a close examination of the study's findings simply does not support the McNamara Group's claim that it allows for "strong causal inferences about the positive effects of gender-affirming medications on mental health." McNamara Br. at 15. Foremost, the Chen study was neither randomized nor properly controlled, making it definitionally incapable of furnishing "causal inferences," let alone "strong" ones. Its authors say so themselves: "our study lacked a comparison group, which limits our ability to establish causality." Chen et al., *supra*, at 249.

Natal males (who were 111 of the 315 participants) receiving feminizing hormones had statistically significant improvement in "appearance congruence" and "positive affect" but no improvement in the key mental health outcomes of anxiety, depression, and life satisfaction (underscoring the risks of using surrogate

outcomes). *See id. at* 245–49. The McNamara Group, like the Chen study's authors, assume that any benefit to mental health is caused by the (small) improvement in "appearance congruence," but the causal relationship could equally be in reverse: those with better mental health worry less about their appearance. Because the study wasn't controlled, there is no way to know how even this modest gain in a dubious surrogate measure can be explained.

The natal females in the study (204/315) showed improvement in life satisfaction, depression, and anxiety, but the improvements were tiny and clinically insignificant. *Id.* For all participants in the study, the following changes over the two-year study period were recorded: life satisfaction improved by 4.64 out of 100 points; depression decreased by 2.54 out of 63 points; anxiety decreased by 2.92 out of 100 points. *Id.* at 243.

Chen et al. called these "significant within-participant changes," Chen et al., *supra,* at 243, which they technically were. However, even very small effect sizes can produce statistically significant variations. What truly counts is whether statistically significant variations have clinical relevance for patients. A statistically significant but clinically insignificant reduction in depression, for instance, is a weak benefit that must be traded off against serious and lifelong risks associated with testosterone use.

McNamara et al. thus misrepresent the findings of Chen et al. when they write that the study "found that gender-affirming hormone treatments lead to improved mental health by helping align an individual's appearance with their gender identity." McNamara Br. at 15. This statement is highly misleading as it

relates to the natal females in the study and outright false as it pertains to the natal males.

Even more concerning than their distortion of the Chen study's methodology and findings, McNamara et al. fail to mention that two of the 315 adolescents who enrolled in the study committed suicide after receiving cross-sex hormone therapy—a troubling outcome that has been noted in critiques of the Chen study. Chen et al., *supra*, at 240; *see also* Jesse Singal, *The New, Highly Touted Study On Hormones For Transgender Teens Doesn't Really Tell Us Much Of Anything*, Singal-Minded (Feb. 7, 2023), https://tinyurl.com/48xhfthm. It is not clear why these adolescents committed suicide, but psychiatric distress associated with high dose exposure and not receiving adequate psychotherapy are possible explanations.

II. PEDIATRIC GENDER MEDICINE IS UNIQUELY EXPERIMENTAL AND OUT OF STEP WITH PEDIATRIC RESEARCH

McNamara et al. argue that the Cass Review unfairly holds pediatric gender medicine to "a standard that cannot be met by many areas of pediatric medicine." McNamara Br. at 19. That is, they say, because "high quality" evidence can only come from randomized controlled trials (RCTs), which are neither feasible nor ethical for pediatric gender medicine. *See id.* at 19–21. RCTs are not feasible because the effects of endocrine interventions cannot be blinded to adolescents or their providers, which makes placebo controls impossible. *See id.* And they are not ethical because endocrine interventions for gender dysphoria are already shown to have positive impacts on mental health, which makes withholding them harmful for

adolescents in the control arm of an RCT. *See id.* If the Court adopts a standard of judicial review that allows states to restrict medical practices that rely on "low quality evidence," the McNamara Group argues, it could "create chaos in the day-to-day practice of pediatrics." *Id.* at. 21. That assertion fails for at least three reasons.

A. Research Quality in Youth Gender Medicine Is Poor by Any Rigorous Scientific Standard

Once again, McNamara et al. describe only part of an EBM concept or principle and then using that partial description to draw convenient but highly misleading conclusions. First, and as a preliminary matter, there is an absence of quality RCTs in adult as well as pediatric gender medicine. Moreover, as explained by the Society for Evidence-Based Gender Medicine in its critically important amicus brief for this case, the field of pediatric gender medicine was launched because "gender transition in adults failed to yield the intended positive outcomes." Br. Amicus Curiae at 2 of Society for Evidence-Based Gender Medicine (SEGM) ("SEGM Br."). Had adult transition been more successful, there would have been little reason to initiate it in adolescence. When McNamara et al. write that "the number of randomized controlled trials in adult medicine has always far outpaced those in pediatrics," McNamara Br. at 19, they conveniently omit this critical context.

But McNamara et al. are also wrong about the feasibility and ethics of RCTs in pediatric gender medicine. Their assertion that it would be "coerci[ve]" and thus "unethical" to condition access to "gender-affirming" interventions on participation in clinical trials, *id.* at 21, presupposes the very thing that RCTs are

supposed to confirm—namely, that (in this case) puberty blockers and cross-sex hormones are safe and effective. Regarding feasibility, McNamara et al. set up a false choice between double-blinded, placebo-controlled RCTs, and the low-quality observational research that already exists. Randomization need not be double-blinded and placebo-controlled; participants could be randomly assigned to alternative treatments arms such as psychotherapy or SSRI medications (*i.e.*, "active controls").

Moreover, even non-randomized (*i.e.*, observational) studies can be significantly improved. The systematic review of evidence undertaken in Sweden proposed a checklist for improving observational research in this field. *See* Jonas Ludvigsson et al., *A Systematic Review of Hormone Treatment for Children with Gender Dysphoria and Recommendations for Research*, 112 Acta Paediatrica 2279, 2289 tab.5 (2023).

It is not the case, as McNamara et al. imply, that the current research underpinning youth gender medicine is as good as it can be short of an RCT. "In youth gender medicine, it is not only the lack of RCTs that is the issue but it also the dearth of high-quality longitudinal observational studies." Alison Clayton et al., *Implications of the Cass Review for Health Policy Governing Gender Medicine for Australian Minors*, Australasian Psychiatry 1, 5 (2024).

Research in youth gender medicine is poor even by the already lower standards of observational studies. It likely for this reason that the University of York systematic reviews, which McNamara et al. criticize, ultimately used the more forgiving study-rating scale "Newcastle-Ottawa Scale" rather than the more commonly used and rigorous "Risk of Bias in Non-

Randomized Studies—of Interventions." *See* Josep-Maria Losilla, et al., *Three Risk of Bias Tools Lead to Opposite Conclusions in Observational Research Synthesis*, 101 J. Clinical Epidemiology 61, 68–70 (Sept. 2018) (discussing the differences).

B. Pediatric Gender Medicine Cannot Be Compared to Other "Low Quality" Evidence Interventions

McNamara et al. provide examples of other low-quality evidence practices that they believe demonstrate the consistency of "gender-affirming care" with the broader field of pediatric medicine. Their first example, recommending breathing tubes versus non-invasive ventilation methods for "critically ill and, often, preterm infants," McNamara Br. at 22, doesn't hold up because infants in these circumstances face imminent risk of death if not treated. Gender dysphoria, by contrast, is not a fatal condition. Adolescents with gender dysphoria do have elevated risk of suicide and suicidal ideation relative to non-dysphoric adolescents, but the risk of suicide is still very low. *See, e.g.*, Michael Biggs, *Suicide by Clinic-Referred Transgender Adolescents in the United Kingdom*, Archives Sexual Behav. 685, 687 (2022) (estimating the suicide rate at London's pediatric gender clinic at 13 per 100,000). The best available evidence suggests that it is attributable to comorbid mental health conditions, not to gender dysphoria itself. *See* Sami-Matti Ruuska et al., *All-Cause and Suicide Mortalities Among Adolescents and Young Adults Who Contacted Specialised Gender Identity Services in Finland in 1996–2019: A Register Study*, 27 BMJ Mental Health 1, 4–5 (2024).

In addition, a study from Sweden using national health data over three decades found that gender

transition did not reduce morbidity to the levels of matched controls; gender "reassigned" individuals were 19.1 times more likely to die by suicide after undergoing sex-trait modification procedures. Cecilia Dhejne et al., *Long-Term Follow-Up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden*, 6 PLoS One 1, 1, 5 (2011). As health authorities in other countries have said, the suicide rhetoric used in transgender medicine is not only scientifically unfounded, but it is also unethical because it can itself drive suicidal behavior. *See, e.g.*, Louis Appleby, *Review of Suicides and Gender Dysphoria at the Tavistock and Portman NHS Foundation Trust: Independent Report*, U.K. Nat'l Health Serv. (July 19, 2024), https://tinyurl.com/4vyy9sfm ("One risk is that young people and their families will be terrified by predictions of suicide as inevitable without puberty blockers—some of the responses on social media show this.")

The McNamara Group's comparison to the use of glucagon-like peptide-1 (GLP-1) analogues (e.g., Ozempic) for treating childhood metabolic syndromes (CMS), McNamara Br. at 23, is also inapt. The choice of this example is puzzling, considering that there has been a double-blinded, placebo-controlled RCT for GLP-1 drugs in obese adolescents. *See* Daniel Weghuber et al., *Once-Weekly Semaglutide in Adolescents with Obesity*, 387 New Eng. J. Med. 2245, 2245 (2022). Childhood diabetes and obesity indeed carry long-term risks to health and functioning, but just as with neonatal respiratory dysfunction, CMS conditions have a scientific basis and objective diagnosis. In contrast, the diagnosis of gender dysphoria in adolescents is based on the subjective experiences and feelings of individuals who are in the throes of puberty—by definition a

tumultuous period of identity consolidation and change—and who have not yet reached cognitive maturity (which happens around age 25). Hence, the risk-to-benefit profile in the former two treatments is fundamentally different than in the latter.

C. Pediatric Gender Medical Interventions Based on "Low Quality" Evidence Are Not Justified Because Gender Dysphoria Is Not Fatal

While evidence-based medicine generally discourages clinical practice guideline (CPG) developers from making strong treatment recommendations based on low- or very-low-quality evidence, exceptions can be made. These are known as "discordant recommendations," and must be justified by CPG developers. Liang Yao et al., *Can We Trust Strong Recommendations Based on Low Quality Evidence?*, 375 BMJ 1, 1 (2021).

The exception that McNamara et al. implicitly invoke, and the only one of the five recognized in EBM that would apply here, is where non-treatment is likely to lead to death. For obvious reasons, low-quality evidence interventions, even ones that carry risks, may be recommended in these circumstances. The McNamara Group's entire argument about consistency with the field of pediatrics thus hinges on accepting their assumption that the expected alternative to "gender-affirming" endocrine interventions is death by suicide. But as mentioned above, research does not support this assumption.

It is important to put all this in its proper context. While the benefits of puberty blockers and cross-sex hormones are profoundly uncertain, the risks to health are potentially serious. Infertility and sexual

dysfunction are the most widely acknowledged risks, especially when pubertal suppression is followed by cross-sex hormone therapy, which it almost always is.

But there are many others, including: cognitive impairment, *see* Sallie Baxendale, *The Impact of Suppressing Puberty on Neuropsychological Function: A Review*, 113 Acta Paediatrica 1156, 1164 (2024); bone-density problems, *see, e.g.*, Maria Anna Theodora Catharina van der Loos et al., *Bone Mineral Density in Transgender Adolescents Treated With Puberty Suppression and Subsequent Gender-Affirming Hormones*, 177 JAMA Pediatrics 1332, 1332 (2023); and heightened chance of cancer and cardiovascular disease are also risks, *see* Natalie J. Nokoff et al., *Body Composition and Markers of Cardiometabolic Health in Transgender Youth on Gonadotropin-Releasing Hormone Agonists*, 6 Transgender Health 111, 115–17 (2021).

Regret is another harm, although the true regret rate is not known and will likely not be known for years to come. J. Cohn, *The Detransition Rate Is Unknown*, 52 Archives Sexual Behav. 1937, 1944–46 (2023). Some research suggests a current detransition rate of up to 30 percent. Christina M. Roberts et al., *Continuation of Gender-affirming Hormones Among Transgender Adolescents and Adults*, 107 J. Clinical Endocrinology & Metabolism e3937, e3939 (2022).

The McNamara Group's suggestion that "gender-affirming care" is in line with other pediatric practices is thus absurd on its face. There is no other example in pediatrics of treating a mental-health condition with invasive, life-altering, experimental drugs and surgeries—especially when the diagnosis relies on an adolescent's subjective feelings, and even more so when a

stipulation of treatment is that those feelings must never be questioned (*see infra* Section III.D). If there is one lesson to learn from pediatric gender medicine, it is that the field has operated outside the bounds of medical science and ethics. In Hilary Cass's words, "Children and young people with gender related distress have been poorly served because we've exceptionalised them." Kamran Abbasi, *"Medication Is Binary, but Gender Expressions Are Often Not"—the Hilary Cass Interview*, 385 BMJ q794 (2024).

III. THE CASS REVIEW REJECTS WIDESPREAD "GENDER-AFFIRMING" MEDICALIZATION

According to McNamara et al., "the Cass Review *does not* recommend that gender-affirming medications for adolescent gender dysphoria be banned." McNamara Br. at 28 (emphasis in original). The Review acknowledges that puberty blockers and cross-sex hormones are medically indicated "for certain transgender youth before age 18." *Id*. For this reason, McNamara et al. argue, its recommendations "describe the kind of individualized, age-appropriate, and careful approach recommended by the WPATH Standards of Care and Endocrine Society Guidelines." *Id.* at 29. Once again, the McNamara Group fastens onto a true observation that it takes out of context, thus painting a false picture. It is true that the Cass Review does not explicitly recommend legislative bans and that it states that for adolescents, "the best outcome will be transition." Hilary Cass et al., *The Cass Review Independent Review of Gender Identity Services for Children and Young People: Final Report* 21, 150 (2024). But there are some crucial caveats here.

A. State Legislative Bans Reflect the U.S. Healthcare System's Decentralized Nature

First, the Cass Review recommended a complete overhaul of NHS youth gender services, with psychotherapy being the first line of treatment for adolescent gender dysphoria and endocrine intervention reserved for exceptional cases and under research protocols. *Id.* at 196. NHS England has since limited the prescription of puberty blockers to adolescent males who are over age 16 and already on estrogen. NHS England, *Prescribing of Gender Affirming Hormones (Masculinising or Feminising Hormones) as part of the Children and Young People's Gender Service* 1, 5 (2024). Access to cross-sex hormones is conditioned on approval by a centralized, multidisciplinary team and participation in research. *Id.* at 3.

In the United States, state legislative bans are largely a reaction to the reality that Americans lack a centralized healthcare system that would allow the same kind of expert-driven systemic overhaul. Our decentralized healthcare system has many advantages, but one disadvantage is that reversing medical practices shown to be ineffective or net-harmful is harder. *See* Eric M. Patashnik et al., *Unhealthy Politics: The Battle over Evidence-Based Medicine* 205 (2017); Vinayak K. Prasad & Adam S. Cifu, *Ending Medical Reversal: Improving Outcomes, Saving Lives* 59–61 (2015). That is due in part to the constellation of interests—pharmaceutical companies, NGOs, clinicians with financial conflicts of interest, etc.—that become invested in a medical practice and defend it against reversal. The U.S. system is very good at launching innovative clinical practices but very bad at pumping the brakes when those practices are shown to be net-

harmful (or non-beneficial). When Florida tried to accomplish what European countries accomplished through its Boards of Medicine and Osteopathic Medicine, gender-medicine advocacy groups successfully challenged the Boards' new standard of care in court. *See Doe v. Ladapo*, No. 4:23cv114-RH-MAF 1, at *99–105 (N.D. Fla., June 11, 2024).

In short, the Cass Review's recommendation that endocrine interventions be available to some adolescents within research settings is likely intended for a medical system with centralized oversight and control.

B. The Cass Review's Recommendations Diverge from Those of WPATH and the Endocrine Society

The McNamara Group's assertion that the Cass Review's recommendations are fundamentally in alignment with those of WPATH and the Endocrine Society is easily disproven. A systematic review of guideline quality published alongside the Cass Review found both guidelines to be of low quality using a tool known as AGREE II, "the most commonly applied and comprehensively validated appraisal tool." Cass, *supra*, at 128. In the most important category of guideline assessment, "rigour of development," the systematic review gave WPATH SOC-8 a score of 35/100 and the 2017 Endocrine Society guideline a score of 42/100. *Id.* at 129. (A score below 70% is generally regarded as inadequate.) Neither guideline was recommended by the authors of the systematic review. *Id.* at 129–32.

The only two guidelines recommended by the Cass Review were those by Finland's Council for Choices in Healthcare (2020) and Sweden's National Board of Health and Welfare (2022). *See id.* at 130.

Indeed, the Cass Review noted that the WPATH and Endocrine Society's guidelines, "are also closely interlinked, with WPATH adopting Endocrine Society recommendations, and acting as a co-sponsor and providing input to drafts of the Endocrine Society guideline. . . . The circularity of this approach may explain why there has been an apparent consensus on key areas of practice despite the evidence being poor." *Id.* Amazingly, McNamara et al. mention none of this critical information.

C. The Cass Review Insists on Differential Diagnosis While Recognizing That Even Proper Diagnoses Have Low Predictive Value

McNamara et al. fail to grapple with a key dilemma in the Cass Review. Although the Review says that for some adolescents "the best outcome will be transition," *id.* at 21, it also says that mental-health therapies should be the first line of treatment and, crucially, that there is no reliable way for clinicians to tell who will benefit and who will be harmed by endocrine interventions, *id.* at 134, 155.

Differential diagnosis is the process of identifying the cause of illness when the symptoms are known to have more than one possible cause. *See id.* It is at the heart of all good medicine, and an organizing principle of the Cass Review's 32 recommendations. *Id.* at 144.

Importantly, however, the final Cass Review observes that "Although a diagnosis of gender dysphoria has been seen as necessary for initiating medical treatment, it is not reliably predictive of whether that young person will have longstanding gender

incongruence in the future, or whether medical intervention will be the best option for them." *Id.* at 29.

The field of pediatric gender transition is founded on the belief that although prepubertal gender dysphoria almost always desists on its own, adolescent gender dysphoria almost never does. But this belief was never properly tested, *see* Abbruzzese, *supra*, at 687, and there is mounting evidence to negate it. A recent Dutch study on "gender non-contentedness," measured by answers to the question "I wish to be of the opposite sex" (an imperfect proxy for GD), found, "In early adolescence, 11% of participants reported gender non-contentedness. The prevalence decreased with age and was 4% at the last follow-up (around age 26)" Pien Rawee et al., *Development of Gender Non-Contentedness During Adolescence and Early Adulthood*, 53 Archives Sexual Behav. 1813, 1813 (2024). A German study based on national insurance data from 2013 to 2022 found that over 60 percent of adolescents with a GD diagnosis no longer had that diagnosis 5 years later. Christian Bachmann et al., *Gender Identity Disorders Among Young People in Germany: Prevalence and Trends, 2013–2022*, 121 Deutsches Ärzteblatt Int'l 370, 370–71 (2024). This important finding was then replicated (42.2 percent persistence rate after seven years) in an analysis of an all-claims, all payers U.S. national insurance database. Leor Sapir, *Adolescent Gender Dysphoria Is a Temporary Diagnosis for Most Teens*, City Journal (Aug. 30, 2024), https://tinyurl.com/t8jedpys.

The McNamara Group, which includes gender clinicians, believe that gender clinicians have the unique capacity to look into an adolescent's future and intuit whether the purported benefits of early intervention

will outweigh the negative health impacts. Some clinicians may believe that they possess this ability, but that belief is more hubris than reality.

D. The Prevailing U.S. Model of "Gender-Affirming" Care Rejects Differential Diagnosis

Even under the best circumstances, when clinicians try to perform differential diagnosis, youth gender medicine is fraught with risk due to the inherent uncertainty of predicting adult outcomes. But the "gender affirming" model of care as practiced in the U.S. does not even try to exercise caution. Its core assumption is that transgender identity is innate and that children can know they are transgender from a very early age. In this child-led approach, differential diagnosis—conducted through exploratory therapy—amounts to trying to figure out if a young person's rejection of his or her body might not stem from some other cause, such as history of sexual trauma. Indeed, exploration—the bedrock of mental health care—is cast as a form of "conversion therapy" because it withholds active "gender affirmation." *See, e.g.*, Florence Ashley, *Interrogating Gender-Exploratory Therapy*, 18 Perspectives on Psych. Sci. 472, 475–78 (2022).

Gender clinicians and supportive medical groups say this explicitly when they are not presenting arguments to courts. In its 2018 policy statement on youth gender transition, the American Academy of Pediatrics states that "children who are prepubertal and assert an identity of [transgender] know their gender as clearly and as consistently as their developmentally equivalent peers who identify as cisgender." Jason Rafferty et al., *Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children*

and Adolescents, 142 Pediatrics 1, 4 (2018). The AAP contrasts its preferred approach to "outdated approach in which a child's gender-diverse assertions are held as 'possibly true' until an arbitrary age (often after pubertal onset) when they can be considered valid." *Id.*

A subsequent peer-reviewed fact-check of these claims found that the sources the AAP cites in support of them say just the opposite. James M. Cantor, *Transgender and Gender Diverse Children and Adolescents: Fact-Checking of AAP Policy*, J. Sex & Marital Therapy 307, 307 (2019). The author of the AAP statement later clarified that the essence of the "gender-affirming" approach is "'affirming and validating the child's sense of identity from day one through to the end.' Its main principle is that when a patient says, 'I'm X,' we operate under the assumption that what they're telling us is their truth, that the child's sense of reality and feeling of who they are is the navigational beacon to sort of orient treatment around." Jennifer Block, *Youth Gender Medicine Has Become a Hall of Mirrors*, Boston Globe, (Nov. 7, 2023), https://tinyurl.com/4j5msskh.

Evidence from U.S. healthcare settings confirms that gender clinicians are using this child-led approach in which the sufficient indication for treatment is an adolescent's desire for it. The director of the gender clinic at Boston Children's Hospital admitted in a private video that they were giving out puberty blockers "like candy." Spencer Lindquist, *WATCH: Director of Boston Children's Gender Clinic Says Puberty Blockers Cause Infertility, Are Given Out 'Like Candy*,' Breitbart (Oct. 10, 2022), https://tinyurl.com/24z4wsju. Even the founding psychologist of that clinic sounded the alarm that assessment was being abandoned in

favor of self-diagnosis and that adolescents were consequently being inappropriately "rushed toward the medical model." Laura Edwards-Leeper & Erica Anderson, *The Mental Health Establishment Is Failing Trans Kids*, Wash. Post (Nov. 24, 2021), https://tinyurl.com/4x3wz3ka. Other whistleblowers, including one who worked in a pediatric gender clinic for over four years, have come forward with evidence showing that there is almost no situation in which a gender clinician will refuse to approve an adolescent for endocrine treatments. *See, e.g.*, Jamie Reed, *I Thought I Was Saving Trans Kids. Now I'm Blowing the Whistle*, Free Press (Feb. 9, 2023), https://tinyurl.com/549736zk.

Indeed, even one of the members of the McNamara Group, Dr. Jack Turban of UCSF, has admitted in interviews and in writing that mental-health assessments are at best pointless and at worst harmful. *See* GenderGP, *How Many People Detransition? Exploring Detransition—Jack Turban*, GenderGP Podcast (March 2, 2021), https://tinyurl.com/yc343zas. In an interview in 2021, Turban said that "if you set up this assessment, gatekeeping protocol, people are just going to figure out the answers and then tell you what you want to hear. And you've set up this . . . argumentative relationship with your patient or client . . . And you're like, why, why even bother?" *Id.*

IV. THE LACK OF CLEAR RATIONALES FOR INTERVENTION EXPLAINS THE MCNAMARA GROUP'S CONTRADICTORY CLAIMS

The deep contradictions in the field of gender medicine, including over what diagnosis indicates

treatment, are acknowledged in the medical literature by the field's own founders. *See* William Byne et al., *Report of the APA Task Force on Treatment of Gender Identity Disorder*, 41 Archives Sexual Behav. 759, 769 (2012); Jack Drescher, *Controversies in Gender Diagnoses*, 1 LGBT Health 9, 12 (2014). Two examples of these contradictions are visible in the briefs of the McNamara Group and the American Association of Pediatrics, respectively. Together, they demonstrate that even among the leading authorities in the field there are profound disagreements over core issues.

A. Are Puberty Blockers Part of Diagnosis or Treatment?

As the Society for Evidence-Based Gender Medicine notes in its *amicus* brief, the Dutch clinicians who pioneered early intervention were trying to solve a specific problem: for adult "transsexuals," and natal males in particular, "sex reassignment" was not enough to undo the effects of puberty on the body and did not allow adults to pass socially as members of their claimed gender. SEGM Br. at 11, 13. Early intervention was designed to bypass the effects of natal sex puberty, with the assumption that the generally poor psychosocial outcomes post-transition the Dutch observed in adults were a consequence of failure to pass as the other sex or enduring psychopathology from a severely distressing puberty. *Id.* at 14–19.

Despite their belief that GD persisting from childhood into adolescence was a reliable indication of a future struggle, the Dutch team acknowledged that puberty was a time of identity development. *See id.* at 16–19. They posited that puberty blockers would allow adolescents a critical window of time to think about their gender identity and consider whether transition

was in their best interests. *See id.* This is the origin of the claim found in the AAP *amicus* brief that puberty blockers are "fully reversible." By this, the AAP means that "when a patient discontinues their use, the patient resumes endogenous puberty." Br. Amici Curiae at 13 of Am. Academy of Pediatrics and Additional National and State Medical and Mental Health Orgs.

The Dutch articulated several rationales for pubertal suppression. Among other things, puberty blockers would enable better cosmetic outcomes in adulthood—particular for natal males—without the need for invasive surgeries. They would provide adolescents with short-term relief from anxiety caused by puberty-related physical changes. And importantly, they would serve as a critical diagnostic tool, giving patients, caregivers, and clinicians "more time to explore" the potential permanence of a cross-gender identity. Peggy T. Cohen-Kettensis et al., *The Treatment of Adolescent Transsexuals: Changing Insights*, 5 J. Sexual Med. 1892, 1894 (2008). The AAP brief's assurance about the "general" reversibility of puberty blockers' effects makes sense only in light of this third (diagnostic) rationale, that is, only if patients have the agency to resume puberty in accordance with their biological sex.

In contrast to the AAP, McNamara et al. explicitly reject the diagnostic/"time to think" rationale for puberty blockers. Unlike the AAP, McNamara et al. acknowledge the body of research showing that 93 to 100 percent of adolescents who are put on puberty blockers proceed to cross-sex hormones—meaning, proceed with the transition protocol. McNamara Br. at 17. Unlike the AAP, McNamara view puberty blockers as the first step in a cascade of interventions that together constitute "gender-affirming" medical care. *See*

id. at 16–17. They criticize the University of York systematic reviews (commissioned as part of the Cass Review) in part because these reviews examined the evidence for puberty blockers and for cross-sex hormones separately, rather than acknowledge that they are two parts in a single "consistent, well-organized standard of care." *Id.* As McNamara et al. write, "The vast majority of adolescents with gender dysphoria who receive puberty blockers progress to cross-sex hormone therapy—because they are indeed transgender and because their diagnosis of gender dysphoria is accurate." *Id.* at 17.

Set aside the astonishing confidence of this statement. The McNamara Group plainly concedes that puberty blockers are not diagnostic but are instead prescribed to "transgender adolescents." *Id.* But because McNamara et al. are convinced that virtually all adolescents who undergo puberty suppression "are indeed transgender," *id.*, the lack of diagnostic value from puberty blockers does not pose a problem for them.

This profound disagreement between self-proclaimed experts in youth gender medicine shows, at minimum, that even among medical *amici* who criticize Tennessee's law, there is no consensus over the most basic aspects of this controversial medical intervention, including over how to conduct diagnosis and the effects of pharmaceutical intervention Where health authorities abroad see potential for iatrogenesis—medical treatment that induces illness, in this case by causing temporary gender dysphoria to persist artificially—McNamara et al. see clinician infallibility. It is precisely in the face of such medical hubris, where the health of children is at stake, that

lawmakers in Tennessee have resolved not to trust gender clinicians to regulate themselves.

B. How Common Should Medical Interventions Be for Adolescents with Gender Dysphoria?

A further example of confusion in the field concerns the value of mental-health assessment. The McNamara Group asserts the importance of "holistic, comprehensive assessment of each adolescent," *id.* at 29, prior to medical intervention. Yet, as noted above, one of its members, Jack Turban, has repeatedly argued that assessments are at best unhelpful and at worst harmful.

An extension of the prevarication over the value of assessment is the disagreement between the AAP and WPATH over how many adolescents who seek gender transition should receive it. In 2022, the president of the AAP wrote that "for the vast majority" of children with gender-related distress, the "gender-affirming" approach recommends "the opposite" of endocrine interventions. Moira Szilagyi, *Academy of Pediatrics Responds on Trans Treatment for Kids*, Wall St. J. (Aug. 21, 2022). Presumably, that means psychotherapy and social support.

By contrast, in its response to the Cass Review, WPATH said the report "is rooted in the false premise that non-medical alternatives to care will result in less adolescent distress *for most adolescents* and is based on a lack of knowledge of and experience working with this patient population." Press Release, *WPATH Responds to Cass Report Publication*, WPATH (Apr. 12, 2024), https://tinyurl.com/43kyj9cn (emphasis added). Whether most adolescents who identify as transgender

or experience gender-related distress should get puberty blockers and cross-sex hormones as opposed to psychotherapy is not a minor point of disagreement. It goes to the heart of the question of what mental health assessments are all about, and it is yet more evidence that lawmakers can reasonably distrust gender clinicians to regulate themselves.

CONCLUSION

Given the profound uncertainties that persist in the field of pediatric gender medicine, states like Tennessee are justified in enacting measures to protect minors from potentially harmful medical interventions that lack a rigorous and reliable evidence base.

The Court should affirm the decision below.

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