No. 23-477

In the Supreme Court of the United States

UNITED STATES,
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 DO NO HARM AS AMICUS CURIAE IN SUPPORT OF RESPONDENTS

DAVID H. THOMPSON
Counsel of Record
BRIAN W. BARNES
JOHN D. RAMER
COOPER & KIRK, PLLC
1523 New Hampshire Avenue, N.W.
Washington, D.C. 20036
(202) 220-9600
dthompson@cooperkirk.com

Counsel for Amici Curiae

October 15, 2024

TABLE OF CONTENTS

TABLE OF AUTHORITIES

INTEREST OF AMICUS CURIAE[1]

Do No Harm, Inc., is a nonprofit membership organization that includes over 10,000 physicians, nurses, medical students, patients, and policymakers. Do No Harm is committed to ensuring that the practice of medicine is driven by scientific evidence rather than ideology. In recent years, the practice of biology-denying interventions, euphemistically known as "gender affirming care," has become more common despite the serious harm caused by those medical interventions and the complete lack of reliable evidence for any benefit caused by them. Indeed, Do No Harm has recently released a database demonstrating that nearly 14,000 minors were subjected to biology-denying interventions in the United States between 2019 and 2023. *See Do No Harm Launches First National Database Exposing the Child Trans Industry*, DO NO HARM (Oct. 8, 2024), https://bit.ly/4f2AJPt. Part of Do No Harm's mission is to ensure that courts have a proper understanding of the dangers of these medical interventions and the lack of evidence supporting them. To that end, Do No Harm submits this brief to provide the Court with an accurate analysis of the lack of evidence justifying the use of puberty blockers, cross-sex hormones, and surgeries as treatments for gender dysphoria.

---

[1] Pursuant to SUP. CT. R. 37.6, amicus certifies that no counsel for any party authored this brief in whole or in part, no party or party's counsel made a monetary contribution to fund its preparation or submission, and no person other than amicus or its counsel made such a monetary contribution.

SUMMARY OF THE ARGUMENT

"Gender affirming care" is a medical scandal. This purported "treatment" calls for a host of biology-denying medical interventions from puberty blockers to cross-sex hormones to genital surgeries. All this to treat a *psychological* condition. These interventions inflict grave harms, and there is no reliable evidence demonstrating that they resolve gender dysphoria.

Some States, like Tennessee, are doing something about it. Led by the scientific evidence, Tennessee has prohibited the use of puberty blockers, cross-sex hormones, and surgeries to treat gender dysphoria in minors. This decision is justified by the known harms of these interventions—including the sterilization of healthy boys and girls—and the complete lack of evidence showing that they do anything to resolve gender dysphoria. Most significantly, despite statements by some that this care is "life saving," there is no reliable evidence whatsoever that biology denying interventions reduce the risk of suicide.

The lack of evidence of benefit from these interventions has been established in every systematic review to analyze the question. These reviews—which represent the highest form of medical evidence—have been conducted by health authorities in Finland, Sweden, the U.K. and by expert researchers hired by the health authority in the State of Florida and the U.K.'s National Health Service. All of them have concluded that no reliable evidence demonstrates that these interventions help resolve gender dysphoria.

Petitioner and its *amici* largely ignore not only these systematic reviews, but also the basic principles of evidence-based medicine. Instead, they rely on

either doctors' clinical experience (the *lowest* form of medical evidence) or on individual studies that are unreliable due to their high risk of scientific bias (as found in the systematic reviews described above). In addition, Petitioner and its *amici* resort to conflating biology-denying interventions with the treatment for conditions that carry *vastly* different risks and benefits. This too ignores principles of not only evidence-based medicine, but also common sense. Based on the medical evidence, Tennessee was wholly justified in banning the use of puberty blockers, cross-sex hormones, and surgeries to treat gender dysphoria in minors. The Court should affirm.

ARGUMENT

I. In The Practice Of Evidence-Based Medicine, Systematic Reviews Are The Highest Form of Medical Evidence.

The proper practice of medicine is driven by evidence, but not all medical evidence is created equal. Researchers have thus spent decades refining the process that clinicians use to assess the medical evidence supporting a particular medical intervention. That process—often referred to as the practice of "evidence-based medicine"—outlines a hierarchy of medical evidence based on the confidence a clinician can place in a particular source of evidence. At the top of this hierarchy are "systematic reviews," which are essentially studies of studies on a particular topic. At the bottom of the hierarchy is clinical experience—*i.e.*, the untested observations and anecdotes of clinicians. Systematic reviews provide the greatest insight into the medical evidence underpinning a particular intervention because they scan for all relevant studies, assess

those individual studies for areas of potential scientific bias, and thus provide visibility on the *reliability* of the *entire* evidence base.

A. The Hierarchy Of Medical Evidence Places Systematic Reviews At The Top And Clinical Experience At The Bottom.

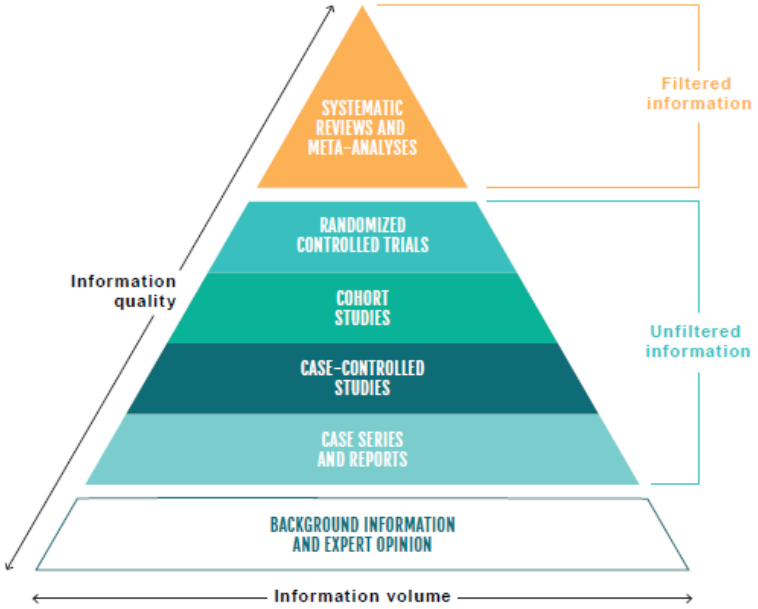
Proper healthcare must be driven by medical evidence because patients "will suffer if clinicians fall prey to muddled clinical reasoning" or to a "misunderstanding of research findings." GORDON GUYATT, ET AL., USERS' GUIDES TO THE MEDICAL LITERATURE: A MANUAL FOR EVIDENCE-BASED CLINICAL PRACTICE 10 (2015) ("Evidence-Based Medicine User Guide"). Healthcare providers must therefore "strive for a clear and comprehensive understanding of the evidence underlying their clinical care." *Id.* That understanding includes the ability to differentiate between different types of medical evidence.

Medical evidence comes in different forms. For example, expert opinion and so-called "clinical experience"—*i.e.*, "the unsystematic observations of individual clinicians"—is one form of medical evidence. *See id.* at 15. So too is a "[r]andomized [c]linical [t]rial"—a type of study "in which individuals are randomly allocated to receive or not receive" an intervention. *Id.* at 474. And as discussed below, there are additional types of studies that fall somewhere between clinical experience and randomized controls.

These different forms of medical evidence vary in terms of reliability. Unsurprisingly, evidence resting on the unsystematic observations of individual clinicians—*i.e.*, clinical experience—is not as reliable as

evidence resulting from a randomized controlled trial. *See id.* at 15. Therefore, a clinician cannot place as much confidence in evidence resulting from clinical experience as compared to evidence resulting from a randomized controlled trial. *See id.* And this commonsense principle—that less reliable evidence leads to less confidence in the outcome—applies to all forms of medical evidence.

The principles of evidence-based medicine guide clinicians in how to determine the reliability of the different forms of medical evidence. Specifically, evidence-based medicine "provides guidance to decide whether evidence is more or less trustworthy—that is, how confident can we be of the properties of diagnostic tests, of our patient's prognosis, or of the impact of our therapeutic options?" *Id.* at 10 (emphasis omitted). Most notably, the "pyramid of standards of evidence" reflects the hierarchy of reliability for evidence in medicine:



See Independent Review of Gender Identity Services for Children and Young People: Final Report, NAT'L HEALTH SERV. ENG. 55 (Apr. 2024) ("Cass Review"); *see also* Evidence-Based Medicine User Guide at 15.

As the pyramid shows, the following types of medical evidence are arranged in descending order of reliability—with the most reliable form (systematic reviews) at the top and the least reliable (clinical experience) at the bottom.

Systematic Reviews: A systematic review, which will be explained in more detail below, is a study that involves the "identification, selection, appraisal, and summary of primary studies that address a focused clinical question using methods to reduce the likelihood of bias." Evidence-Based Medicine User Guide at 484.

Randomized Clinical Trials: A randomized controlled trial is "an experiment in which individuals are randomly allocated to receive or not receive an experimental diagnostic, preventive, therapeutic, or palliative procedure and then followed up to determine the effect of the intervention." *Id.* at 474.

Cohort Studies: A cohort study, sometimes also called a "longitudinal study" in this context, "is an investigation in which a cohort of individuals who receive the intervention is compared with a concurrent cohort who does not receive the intervention," while "both cohorts are followed forward to compare the incidence of the outcome of interest." *Id.* at 430. Cohort studies can be either "prospective" (*i.e.*, rely on data that will be gathered over the course of the study) or "retrospective[]" (*i.e.*, rely on data that was previously gathered and recorded).

Case-Control Study: A case-control study is a study where those "with the outcome (cases) are compared" to "those without the outcome (controls) with respect to exposure to the suspected harmful agent." *Id.* at 427. For example, a case-control study would compare those with a disease (cases) to those without a disease (controls) to determine whether the cases were exposed to a particular agent that may have played a role in the development of the disease.

Case Series and Reports: A case-series is a "report of a study of a collection of patients treated in a similar manner, without a control group." *Id*. For example, a clinician might describe the characteristics of an outcome for a group of patients who all received the same intervention. *See id.*

Background Information and Expert Opinion: As mentioned above, given "the limitations of human intuition," evidence-based medicine "places the unsystematic observations of individual clinicians lowest on the hierarchy." *Id.* at 15. This category includes so-called "clinical experience." *Id.*

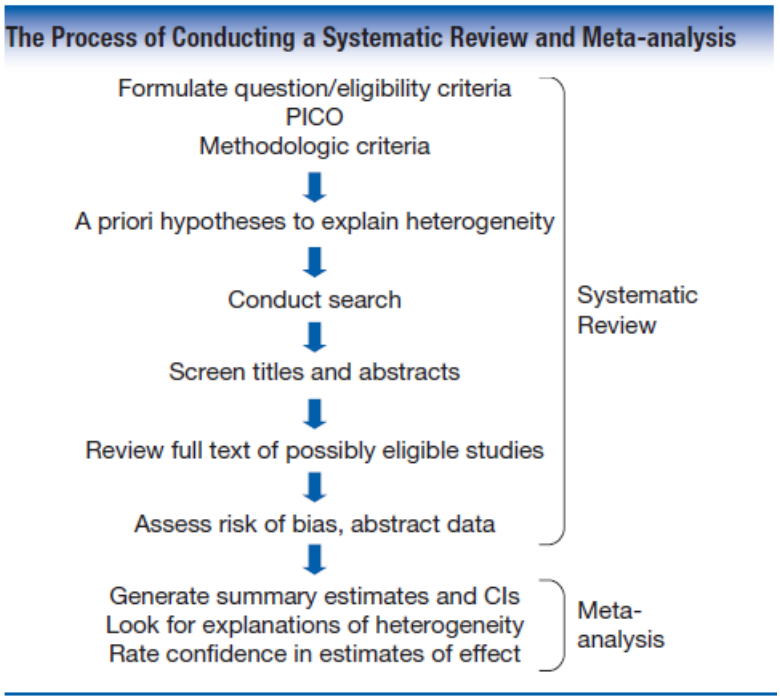
Although it is not even on the pyramid due to its unreliability for purposes of assessing benefit, another design—a "cross-sectional" study—bears mention. *See* Peter McNair & Gwyn Lewis, *Levels of Evidence in Medicine*, 7 INT'L J. SPORTS PHYSICAL THERAPY 474, 478 (2012) (describing cross-sectional studies as "the lowest level of the aetiology hierarchy"). A "cross-sectional study" is the "observation of a defined population at a single point in time or during a specific interval." Evidence-Based Medicine User Guide at 437. A cross-sectional study would therefore assess how many patients taking a drug have high blood pressure at a particular point in time. *See id.*

Because "optimal clinical decision making requires awareness of the best available evidence," *id.* at 10, providers should "[s]tart [their] searches by using resources at the top of the pyramid," *id.* at 60. "When searching for evidence to answer a clinical question," therefore, "it is preferable to seek a systematic review." *Id.* at 274. Consulting systematic reviews over the less reliable forms of medical evidence protects clinicians from providing potentially harmful interventions based on a "misunderstanding of research findings." *Id.* at 10. Without systematic summaries of the evidence, "clinicians—expert or otherwise—will be unduly influenced by their own preconceptions and by unrepresentative and often lower-quality evidence." *Id.* at 14. In sum: "Efficient and optimally

effective evidence-based practice dictates bypassing the critical assessment of primary studies and, if they are available, moving straight to the evaluation of rigorous *systematic reviews*." *Id.* at 4 (emphasis in original).

B. Systematic Reviews Are The Highest Form Of Evidence In Part Because They Account For The Risk Of Bias In Individual Studies.

"A systematic review is a summary of research that addresses a focused clinical question in a systematic, reproducible manner." *Id.* at 272. Accordingly, there is a well-defined process for conducting a systematic review:



Id. at 275. As the above figure demonstrates, the process begins with formulating the relevant question to be researched, which is typically done by identifying the patient population, the intervention, and the outcome that the researchers are interested in studying. *See id.* at 274-75. "Having specified their selection criteria, reviewers will conduct a comprehensive search of the literature in all relevant medical databases, which typically yields a large number of potentially relevant titles and abstracts." *Id.* at 275. "They then apply the selection criteria to the titles and abstracts, arriving at a smaller number of articles that they retrieve." *Id.*

"Having completed the culling process, the reviewers assess the risk of bias of the individual studies and abstract data from each study." *Id.* This stage of the systematic review process—assessing individual studies for bias—is a critical part of understanding the evidence base for a particular intervention. As a general matter, "bias" in this context means a study's results are a "deviation from the underlying truth because of a feature of the design or conduct of a research study." *Id.* at 422. If the data is coming from studies with a high risk of bias, then the data is less reliable. And "[e]ven if the results of different studies are consistent, determining their risk of bias is still important" because "[c]onsistent results are less compelling if they come from studies with a high risk of bias than if they come from studies with a low risk of bias." *Id.* at 283. Thus, it does not matter if one has several studies coming out the same way if those studies have a high risk of bias: Five times zero still equals zero.

There are multiple methods for assessing the reliability of individual studies. A well-known method is the Newcastle-Ottawa Scale (NOS). *See Yangqin* Xun, et al., *Characteristics of the Sources, Evaluation, and Grading of the Certainty of Evidence in Systematic Reviews in Public Health: A Methodological Study*, 11 FRONTIERS PUB. HEALTH 1, 3 (2023) ("The Newcastle-Ottawa Scale (NOS) tool is commonly used for cohort studies and case-control studies[.]"). The systematic reviews performed by researchers at York University in support of the Cass Review Final Report utilized this method. *See* Jo Taylor, et al., *Interventions To Suppress Puberty in Adolescents Experiencing Gender Dysphoria or Incongruence: A Systematic Review*, ARCHIVES DISEASE CHILDHOOD 1 (2024), https://bit.ly/402E7WC ("Taylor – Puberty Blockers"); Jo Taylor, et al., *Masculinising and Feminising Hormone Interventions for Adolescents Experiencing Gender Dysphoria or Incongruence: A Systematic Review*, ARCHIVES DISEASE CHILDHOOD 1 (2024), https://bit.ly/4dE9Pws ("Taylor – Cross-Sex Hormones"). Another frequently used method is the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) method. *See* Evidence-Based Medicine User Guide at 16. The systematic reviews performed by researchers at the U.K.'s National Institute for Health and Care Excellence in support of the Cass Reviews' interim report used this methodology. *See Evidence Review: Gonadotrophin Releasing Hormone Analogues for Children and Adolescents with Gender Dysphoria*, NAT'L INST. HEALTH & CARE EXCELLENCE 4 (Oct. 2020), https://bit.ly/3NnivfV ("NICE – Review of Puberty Blockers"); *Evidence Review: Gender-Affirming Hormones for Children and Adolescents with Gender Dysphoria*, NAT'L INST.

HEALTH & CARE EXCELLENCE 4 (Oct. 2020), https://bit.ly/3YnzzZH ("NICE – Review of Cross-Sex Hormones").

In the GRADE system, researchers rate the evidence using specified criteria. "In the context of a systematic review, the ratings of the quality of evidence reflect the extent of our confidence that the estimates of the effect are correct." Howard Balshem, et al., *GRADE Guidelines: 3. Rating the Quality of Evidence*, 64 J. CLINICAL EPIDEMIOLOGY 401, 403 (2011). This rating demonstrates the researchers' "confidence in estimates of the effects of health care interventions (also referred to as quality of evidence) as high, moderate, low, or very low." Evidence-Based Medicine Users Guide at 16. The following definitions explain what the various levels mean:

High Quality Evidence: "We are *very confident* that the true effect lies close to that of the estimate of the effect." Balshem, *supra*, at 404 (emphasis added).

Moderate Quality Evidence: "We are *moderately confident* in the effect estimate: The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different." *Id.* (emphasis added).

Low Quality Evidence: "Our *confidence* in the effect estimate *is limited*: The true effect may be *substantially different* from the estimate of the effect." *Id.* (emphasis added).

Very Low Quality Evidence: "We have *very little confidence* in the effect estimate: The true effect *is likely to be substantially different* from the estimate of effect." *Id.* (emphasis added).

Thus, when evidence is deemed "low" or "very low" quality, that means researchers have "limited" or "very little confidence" that the results of the study reflect the truth; indeed, the truth may or *likely* will turn out "to be substantially different" from what the studies are telling us.

Finally, after analyzing all relevant studies, the researchers will "summarize the results." Evidence-Based Medicine User Guide at 275. This process can include a quantitative synthesis or "meta-analysis" of data that provides an overview to clinicians. *See id.* at 275-76. The end result is a study of studies—a comprehensive look at the evidence on a given question that accounts for the reliability of the studies forming the evidence base.

In sum, systematic reviews are the most reliable form of medical evidence. And they are substantially more reliable than narrative reviews (such as a clinician's experiences recounted in an *amicus brief* or expert witness report) for several reasons. First, unlike systematic reviews, narrative reviews "have no explicit criteria for selecting the included studies." *Id.* at 273. Thus, narrative reviews can cherry-pick examples and individual studies—discussing only those that support their conclusions and ignoring those that do not. Systematic reviews do not suffer from this flaw. Second, narrative reviews "do not include systematic assessments of the risk of bias associated with primary studies." *Id.* (emphasis omitted). Thus, narrative reviews may stress that several studies all support the same conclusion, but "[c]onsistent results are less compelling if they come from studies with a high risk of bias than if they come from studies with a low risk of bias." *Id.* at 283. Systematic reviews account

for this principle; narrative reviews do not. For these reasons (among others), systematic reviews represent the highest form of medical evidence, and optimal clinical care requires consulting systematic reviews to assess the evidence justifying a particular intervention.

II. Every Systematic Review Of Medicalized Interventions For Minors With Gender Dysphoria Has Concluded The Evidence Is Weak.

Several entities and institutions have conducted systematic reviews to assess the evidence underlying the use of puberty blockers and cross-sex hormones as a treatment for minors with gender dysphoria. All have concluded that the evidence underlying medical interventions for gender dysphoria in minors is weak; zero have come out the other way.

Finland. The first systematic review came in 2019 when Finland's Ministry of Social Affairs and Health completed its review of the medical evidence. *See* J.A. 331. In light of this evidence review, Finland's healthcare authority concluded that "gender reassignment of minors is an experimental practice." *See* J.A. 583-84. This conclusion was based on the fact that "[t]he reliability of the existing studies" is "highly uncertain." *Id.* at 583.

The Cass Review Interim Report. Next, in 2020, the United Kingdom's National Institute for Health and Care Excellence (NICE) completed its review of the evidence for using puberty blockers and cross-sex hormones on minors with gender dysphoria to aid the

Cass Review, an independent review commissioned by the United Kingdom's National Health Service. *See* J.A. 364. The result was two separate systematic reviews—one for puberty blockers and one for cross-sex hormones. *See* J.A. 364-66. The review of puberty blockers concluded that the relevant studies were "all small, uncontrolled observational studies, which are subject to bias and confounding, and all the results are of very low certainty using [a] modified GRADE" methodology. NICE – Review of Puberty Blockers at 13. Similarly, in the review of cross-sex hormones, the reviewers concluded that the relevant studies were "uncontrolled observational studies, which are subject to bias and confounding and were of very low certainty using [a] modified GRADE" methodology. NICE – Review of Cross-Sex Hormones at 13.

The State of Florida. In 2022, researchers at McMaster University—a world-renowned institution in evidence-based medicine—completed a systematic review at the request of the Florida Agency for Health Care Administration. J.A. 361-62. They also found that the evidence supporting these interventions was weak. "'Due to the important limitations in the body of evidence," they concluded, "there is great uncertainty about the effects of puberty blockers, cross-sex hormones, and surgeries in young people with gender dysphoria.'" J.A. 362 (quoting Romina Brignardello-Petersen & Wojtek Wiercioch, *Effects of Gender Affirming Therapies in People with Gender Dysphoria: Evaluation of the Best Available Evidence* 5 (May 16, 2022), https://bit.ly/4dE7ZM9).

Sweden. In 2023, Swedish researchers published a systematic review that was commissioned by Sweden's Agency for Health Technology and Assessment

of Social Services. J.A. 338. The review concluded that the "[e]vidence to assess the effects of hormone treatment" on (among other things) "mental health" in minors "with gender dysphoria is insufficient." J.A. 280-82 (providing Jonas F. Ludvigsson, et al., *A Systematic Review of Hormone Treatment for Children with Gender Dysphoria and Recommendations for Research*, 112 ACTA PAEDIATRICA 2279, 2280 (2023)). Specifically, it noted that "[l]ong-term effects of hormone therapy on psychosocial health are unknown," and using puberty blockers to treat gender dysphoria "should be considered experimental treatment." *See* J.A. 283; *see also* J.A. 338.

The Cass Review Final Report. Most recently, researchers from York University published a series of systematic reviews as part of the Cass Review. The York University researchers conducted systematic reviews of the evidence for both puberty blockers and cross-sex hormones. *See generally* Taylor – Puberty Blockers; Taylor – Cross-Sex Hormones. In their review of puberty blockers, the researchers concluded that their "findings add to other systematic reviews in concluding there is insufficient and/or inconsistent evidence about the effects of puberty suppression on gender dysphoria, body satisfaction, psychological and psychosocial health, cognitive development, cardiometabolic risk and fertility." Taylor – Puberty Blockers at 12. Similarly, in their review for cross-sex hormones, the researchers concluded that their "findings add to other systematic reviews in concluding there is insufficient and/or inconsistent evidence about the risks and benefits of hormone interventions in this population." Taylor – Cross-Sex Hormones at 6.

In sum, all these systematic reviews concluded the same thing: There is no reliable evidence to justify the use of puberty blockers and cross-sex hormones as a treatment for gender dysphoria in minors.

III. Petitioner And Its *Amici* Either Misunderstand Or Misrepresent The Principles Of Evidence-Based Medicine.

Petitioner and its *amici* have no answer to the systematic reviews described above. So instead, they try to change the subject. First, they point to various individual studies that, they say, show these interventions are safe and effective. But the systematic reviews above *already analyzed* those studies and concluded they did not provide reliable evidence. Next, they say that providing interventions based on low quality evidence is no big deal. For interventions with low risks, that may be true; for interventions that involve sterilization and stunting of brain development in minors, that is plainly false. Finally, they attempt to conflate biology-denying interventions with the use of puberty blockers and surgical procedures to treat *other* conditions. But those other treatments carry risks and benefits that *vastly* differ from the treatments Tennessee has banned for minors; Petitioner's attempt to conflate them is meritless.

A. Petitioner And Its *Amici* Rely On Evidence That Systematic Reviews Have Already Concluded Are Unreliable.

Petitioner and its *amici* do not cite any systematic reviews in support of their argument—because there are none. Instead, they rely on clinical experience—*i.e.*, the *lowest* form of medical evidence—and the very studies that numerous systematic reviews have

concluded are subject to high risk of bias. For example, Petitioner expressly invokes "clinical experience" as evidence in support of its position. *See* U.S. Br. 5-6. And the pages it cites of the petition appendix recount one doctor's "observations based on her clinical experience" in practice. *See* Pet. App. 194-95a.

The American Bar Association's brief perhaps best exemplifies why it is wrong to bypass systematic reviews and begin reading individual studies instead. *See generally* Br. of the Am. Bar Ass'n as *Amicus Curiae*. On page 10 of its brief, the ABA (an "association of attorneys and legal professionals," *id.* at 1) opines that "[e]xtensive scientific literature" supports the purported consensus that these interventions are beneficial. *Id.* at 10. In support of that sentence, the ABA cites five studies. *See id.* at 10 n.21. Every single one was reviewed by one of the systematic reviews above that concluded the evidence is weak. Indeed, 4 of the 5 studies were so poorly designed, and thus subject to such a high risk of bias, that they had to be excluded from the analysis entirely in multiple systematic reviews.[2] And the fifth study was analyzed in York

---

[2] *See* NICE – Review of Cross-Sex Hormones at 72 (listing among its excluded studies Annelou L.C. de Vries, et al., *Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment*, 134 PEDIATRICS 696 (2014); NICE – Review of Puberty Blockers at 74-75 (listing among its excluded studies Christal Achille, et al., *Longitudinal Impact of Gender-Affirming Endocrine Intervention on the Mental Health and Well-being of Transgender Youths: Preliminary Results*, INT'L J. PEDIATRIC ENDOCRINOLOGY (2020); Jack L. Turban, et al., *Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation*, 2 Pediatrics 145 (2020)); Ludvigsson, *supra*, app'x 2, https://bit.ly/4gYTQvN (excluding for high risk of bias Achille,

University's systematic review of the benefits of puberty blockers—a systematic review that concluded there is "insufficient and/or inconsistent evidence about the effects of puberty suppression" on minors with gender dysphoria. Taylor – Puberty Blockers at 12. Perhaps most notably, the study itself stated that it could "'not provide evidence about the direct benefits of puberty suppression over time and long-term mental health outcomes.'" J.A. 421 (quoting Van der Miesen, et al., *Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared with Cisgender General Population Peers*, 66 J. ADOLESCENT HEALTH 699, 703 (2020)).

But lawyers are not the only ones making this error. Brief after brief of medical professionals who should know better cite the same studies that the systematic reviews have already analyzed. *See, e.g.*, Br. of Am. Acad. of Pediatrics, et al., as *Amici Curiae* 17-18; Br. of Am. Psychological Assoc., et al., as *Amici Curiae* 16-18. A glaring example comes from the brief of "Expert Researchers and Physicians," which fault the York Systematic Reviews for "excluding" studies that *amici* think they should not have excluded. Br. of Expert Researchers and Physicians as *Amici Curiae* 13-14. But these *amici* fail to explain *why* the reviewers excluded those studies—which is because they were of such low quality that they were unreliable. *See* Taylor – Puberty Blockers at 2 ("Due to high risk of bias in low-quality studies, these were excluded from

---

supra, and Luke Allen, et al., *Well-Being and Suicidality Among Transgender Youth After Gender-Affirming Hormones*, 7 CLINICAL PRAC. PEDIATRIC PSYCH. 302 (2019)).

the synthesis."). This exclusion was entirely appropriate since it is well accepted that a systematic review "may restrict studies to those that minimize the risk of bias." Evidence-Based Medicine User Guide at 274. Thus, the studies that Petitioner and its *amici* rely on are *already* accounted for and assessed in the systematic reviews above. And it bears repeating: Every single systematic review on this subject has concluded the evidence is poor.

Choosing a different tack, several *amici* offer shrugging indifference that the evidence is either low or very low quality under GRADE. *See, e.g.*, Br. of Clinical Guideline Experts as *Amici Curiae* 27-30; Profs. of Law, Med., & Pub. Health as *Amici Curiae* 10-11. They purport to warn the Court that "low" or "very low" doesn't really mean what it says. It is true that "low" or "very low" quality has a specialized meaning in the GRADE methodology. But how that helps Petitioner is a mystery because the specialized meaning of "low" or "very low" quality evidence is that we have "limited" or "very little" confidence that the results are accurate, and the truth "may be" or "is likely to be substantially different from" what the study says. Balshem, *supra*, at 404. It is difficult to see how one could say a drug has been proven to be effective if the doctor tells you that she has "limited" or "very little confidence" that the drug will work.

Next, some *amici* highlight the fact that, in some circumstances, the GRADE methodology permits "strong" recommendations when the evidence is "low quality." *See* Br. of Expert Researchers & Physicians as *Amici Curiae* 24; Profs. of Law, Med., & Pub. Health as *Amici Curiae* 12. But the *amici* fail to explain two critical points: (1) the "strong"

recommendation that GRADE sometimes permits in the face of low-quality evidence includes making a strong recommendation *against* the intervention; and (2) GRADE offers five paradigmatic situations where a strong recommendation can be made based on low-quality evidence—and none of them applies here. As an initial matter, GRADE recommends a strong recommendation *against* an intervention based on low-quality evidence in four of the five paradigms—meaning the provider should *refuse* to offer the intervention that is supported by low-quality evidence. *See* Ming C. Chong, et al., *Strong Recommendations from Low Certainty Evidence: A Cross-Sectional Analysis of a Suite of National Guidelines*, 23 BMC MED. RSCH. METHODOLOGY 1, 3 (2023). The only situation in which GRADE permits a strong recommendation *in favor* of an intervention based on low-quality evidence is when a patient is facing a "[l]ife-threatening (or catastrophical) situation." *Id.* The example provided is when there is an "absence of effective alternatives" for a disease with a "high mortality" rate. *Id.* Gender dysphoria does not have a "high mortality" rate; as explained below, there is no reliable evidence suggesting that these interventions have any effect on suicide. And gender dysphoria can be treated through psychotherapy as health officials in Finland, Sweden, the U.K., and Norway all recommend. *See* Resp. Br. 9-10.

B. Petitioner And Their *Amici* Conflate Medicalized Transitions With Interventions That Present Vastly Different Risks And Benefits.

The risks and benefits associated with different interventions for different conditions should not be conflated. *See* Evidence-Based Medicine User Guide

at 6 (noting that providers must determine "the tradeoff among the benefits, risks, and burdens of alternative management strategies" (emphasis omitted)). It is common sense that uncertainty about the *benefit* of a drug is less significant when the *risks* associated with taking that drug are low. For example, if there is low *risk* in brushing one's teeth with fluoride, then one need not be concerned if there is low quality evidence of the *benefit* of brushing with fluoride toothpaste. Relatedly, it is common sense that uncertainty about the benefit of a drug is less significant when the *marginal* risk associated with taking that drug is low. For example, if there is little marginal risk in prescribing an experimental drug to a patient suffering from an aggressive form of life-threatening cancer, then uncertainty about the benefit is less concerning. This principle—close to a "nothing-to-lose" situation—is reflected in the lone situation where GRADE permits a strong recommendation in favor of an intervention supported by low-quality evidence. *See* Chong, *supra*, at 3. The upshot is that using interventions to treat different conditions carries different risks and benefits that must be analyzed separately.

Petitioner and their *amici* ignore this fundamental principle in two ways. First, *amici* suggest that, because medical treatments are provided based on low-quality evidence, then providers should be permitted to offer biology denying interventions based on low-quality evidence. *See, e.g.*, Br. of Clinical Guideline Experts as *Amici Curiae* 27-30; Br. of Profs. of Law, Med., & Pub. Health as *Amici Curiae* 10-11. Second, Petitioner and its *amici* contend that, because providers offer puberty blockers to treat central precocious puberty or surgery to treat gynecomastia in

boys, then providers should be permitted to offer puberty blockers or mastectomies to treat gender dysphoria. *See, e.g.*, U.S. Pet. Br. 7, 46-47; Br. of Resp. *in Support of Pet.* 6-7; Br. of Experts on Gender Affirming Care as *Amici Curiae* 18.

The critical flaw in this argument is that there are no interventions—including the ones *amici* highlight—that share a similar risk-benefit profile with the ones at issue in this case. Take central precocious puberty for example. That treatment involves delaying puberty until the normal age, at which point the boy or girl will proceed through his or her *natural* puberty. *See* J.A. 358. With biology denying interventions, however, the patient's natural puberty is permanently suppressed. *See id.* The harms and risks of *never* going through natural puberty are vastly different from merely delaying one's natural puberty until the normal age. *See id.* For example, unlike a child who takes puberty blockers to treat central precocious puberty, a gender dysphoric child whose puberty is suppressed and then continues on cross-sex hormones will be sterilized. *See* J.A. 428-29. In addition, the effects of pubertal suppression on brain development are entirely unknown, and puberty blockers are administered far later into adolescence when used to treat gender dysphoria than when used to treat central precocious puberty. *See* J.A. 430-32.

The same is true of *amici*'s other leading example of gynecomastia. In rare circumstances, that treatment can call for the surgical removal of chest tissue in a boy. *See* J.A. 780. But removing chest tissue from a boy to treat gynecomastia is not the same as performing a mastectomy on an adolescent girl to treat a psychological disorder. Performing a mastectomy on

an adolescent girl means that she will never have the ability to breastfeed a child, J.A. 429; it should go without saying, but a boy does not have the ability to breastfeed a child anyway. Thus, the harms of these procedures are *vastly* different.

In sum, the use of puberty blockers, cross-sex hormones, and surgeries to treat gender dysphoria carries a *host* of known harms and risks and has no reliable evidence of benefit. The treatments that petitioners and their *amici* attempt to analogize to biology-denying interventions at issue here have no comparable risk-benefit profile. For example, permitting the treatment of central precocious puberty is no argument for permitting providers to sterilize a boy or girl through puberty blockers and cross-sex hormones. Tennessee is entirely justified in banning these dangerous and unproven interventions.

C. There Is No Reliable Evidence That Puberty Blockers And Cross-Sex Hormones Reduce The Risk Of Suicide.

The briefs seeking reversal are shot through with assertions that puberty blockers and cross-sex hormones are "life saving" or reduce the risk of suicide. This language is grossly irresponsible in light of the actual *evidence* on this question. As WPATH's own researcher admitted: "There is insufficient evidence to draw a conclusion about the effect of hormone therapy on death by suicide among transgender people." J.A. 375 (quoting Kellan E. Baker, et al., *Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review*, 5 J. ENDOCRINE SOC. 1, 13 (2021)); *see also* Baker, *supra*, at 12 ("It was impossible to draw conclusions about the

effects of hormone therapy on death by suicide."). And just months ago, in what is likely the most controlled environment that is currently feasible, a researcher in the U.K. concluded that there was no evidence of a rise in suicides after the country's health service had restricted the use of puberty blockers as a treatment for gender dysphoria. *See Puberty Blocker Curb Has Not Led to Suicide Rise—Review*, BBC (July 20, 2024), https://bbc.in/3BQ7yRn.

Thus, the briefs to the Court in this case are reminiscent of the emotional blackmail that a small number of doctors blinded by ideology have inflicted on parents of children suffering from gender dysphoria: "Would you rather have a dead daughter or a live son?" J.A. 905 (quotations omitted). This reprehensible language is completely unsupported by the evidence. And Tennessee has done the right thing in ensuring that gender ideology is not allowed to displace the principles of evidence-based medicine when doctors treat vulnerable young people suffering from gender dysphoria.

CONCLUSION

For these reasons, the Court should affirm the judgment below.

October 15, 2024

Respectfully submitted,

DAVID H. THOMPSON
Counsel of Record
BRIAN W. BARNES
JOHN D. RAMER
COOPER & KIRK, PLLC
1523 New Hampshire
Avenue, N.W.
Washington, D.C. 20036
(202) 220-9600
dthompson@cooperkirk.com

Counsel for Amicus Curiae