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,

and

L. W., BY AND THROUGH HER PARENTS AND NEXT FRIENDS, SAMANTHA WILLIAMS AND BRIAN WILLIAMS, *et al.*,

Respondents in Support of Petitioner.

ON WRIT OF CERTIORARI TO THE UNITED STATES COURT OF APPEALS FOR THE SIXTH CIRCUIT

BRIEF FOR *AMICI CURIAE* EXPERT RESEARCHERS AND PHYSICIANS IN SUPPORT OF PETITIONER

ALEXANDER SHALOM
Counsel of Record
NATALIE J. KRANER
LOWENSTEIN SANDLER LLP
One Lowenstein Dr.
Roseland, NJ 07068
(973) 597-2500
ashalom@lowenstein.com
nkraner@lowenstein.com

Counsel for Amici Curiae

130323

TABLE OF CONTENTS

Table of Contents

Table of Contents

TABLE OF CITED AUTHORITIES

Page

Statutes and Rules

Other Authorities

Cited Authorities

Page

Page

Cited Authorities

Page

Page

Page

INTEREST OF *AMICI CURIAE*[1]

Amici are scientists and clinicians based in the United States and Australia with expertise in the research and practice of treatment of transgender individuals with gender dysphoria. 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. The individualized care that amici clinicians provide is rooted in decades of research; it is accepted as standard clinical care in the world-class pediatric health centers where amici practice. All amici hold appointments at major universities and research organizations.[2]

- **Dr. Meredithe McNamara, MD, MSc**, is Assistant Professor of Pediatrics, Yale School of Medicine.

- **Dr. Kellan Baker, PhD, MPH, MA**, is Executive Director, Whitman-Walker Institute and Faculty Associate, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health.

- **Dr. Kara Connelly, MD, MCR**, is Associate Professor of Pediatrics, Division of Endocrinology,

1. No counsel for a party authored any part of this brief or made any monetary contribution to it. No one in addition to amici and their counsel made a monetary contribution to the preparation and submission of this brief. *See* S. Ct. R. 37.6.

2. In keeping with conventions in academia, amici join this brief as individuals; institutional affiliation is noted for informational purposes only.

School of Medicine, Oregon Health & Science University.

- **Dr. Aron Janssen, MD**, is Associate Professor of Psychiatry and Behavioral Sciences, Northwestern University Feinberg School of Medicine.

- **Dr. Johanna Olson-Kennedy, MD**, is Professor of Clinical Pediatrics, Keck School of Medicine of University of Southern California.

- **Dr. Ken C. Pang, FRACP, PhD**, is NHMRC Leadership Fellow and Senior Principal Research Fellow, Murdoch Children's Research Institute; Research Lead and Pediatrician, Royal Children's Hospital; Associate Professor, Department of Paediatrics, University of Melbourne, VIC Australia.

- **Dr. Ayden Scheim, PhD**, is Assistant Professor of Epidemiology, Dornsife School of Public Health, Drexel University.

- **Dr. Jack Turban, MD, MHS**, is Assistant Professor of Psychiatry & Behavioral Sciences and Affiliate Faculty at the Philip R. Lee Institute for Health Policy Studies, University of California, San Francisco.

In this brief, amici bring their expertise to bear to help the Court understand deep flaws in claims made by the Tennessee Respondents ("Tennessee") and their amici curiae that a United Kingdom report called the "Cass Review" provides authoritative evidence that supports

Tennessee legislation banning medications prescribed for some youth with gender dysphoria. Tenn. Code Ann. §§ 68-33-101 through -109 (the "Tennessee Ban"). Amici are well-poised to describe the solid medical research that supports gender-affirming medications for adolescents with gender dysphoria.

SUMMARY OF ARGUMENT

Central to Tennessee's case is the claim that the United States has become an outlier in permitting gender-affirming medical care for adolescents with gender dysphoria. Tennessee asserts that the United Kingdom and other countries have restricted such care based on their conclusions that "the harms associated with these interventions are significant, and the long-term benefits are unproven." Tennessee Resp'ts Br. in Opp. to Cert. ("Tenn. Resp'ts Cert. Br.") at 10 (Feb. 2, 2024). Tennessee and their experts, as well as other states with similar bans, repeatedly cite material produced by a United Kingdom ("U.K.") commission called the Cass Review as the authoritative assessment of the evidence on the treatment of adolescents with gender dysphoria, and they rely on the Cass Review to support the Tennessee ban and other similar laws.

As the Cass Review itself notes, it was commissioned to specifically address the problem of adolescents with gender dysphoria being unable to access appropriate care in the U.K. And it does provide a useful documentation of the serious shortages in the availability of care for young people with gender dysphoria in the U.K.; it does not, however, provide credible or authoritative scientific support for the Tennessee Ban.

First, the Cass Review contends that evidence on puberty blockers and cross-sex hormones (collectively "gender-affirming medications") for young people is "remarkably weak," but this assertion is based on its reliance on several literature reviews that repeatedly violate scientific standards for assessing medical evidence. *The Cass Review: Independent Review of Gender Identity Services for Children and Young People* 13 (2024) (the "Cass Review" or the "Review"), https://tinyurl.com/vvcu7rzy. These reviews are billed as "systematic reviews"—a rigorous type of literature search considered to be the gold standard for assessing the quality of medical evidence—and were conducted by authors affiliated with the University of York (the "York SRs"). However, the York SRs are unreliable, inter alia, because they arbitrarily exclude much of the evidence showing that gender-affirming medications are safe and effective treatments for gender dysphoria. Indeed, researchers have found that the York SRs inappropriately exclude nearly half of studies on puberty blockers and more than a third of studies on cross-sex hormone treatments. Thus, the Cass Review's recommendations are based on an assessment of only a subset of the full body of research, and that assessment is scientifically and fatally flawed.

The authors of the York SRs also violate scientific protocols by changing their methodology after they initiated their evidence reviews. Well-conducted reviews set standards and protocols at the outset that prevent researchers from changing their methodology to obtain a desired result. The authors of the York SRs deviate from this norm by changing the protocol for their reviews midstream, without explanation. Accordingly, the Cass Review departs from well-established standards for issuing recommendations for clinical care by relying on

systematic reviews that (1) improperly omit numerous important studies and (2) inexplicably change their methodology for evaluating the evidence after commencing their review.

The Cass Review commits another fundamental error by holding this area of medicine to an evidentiary standard that is not required or typical in pediatrics. The Review asserts that the evidence on gender-affirming medications provided to adolescents with gender dysphoria is "weak" because the research was not based on "high quality" evidence such as randomized controlled trials ("RCTs"). But this is true of many pediatric treatment recommendations. "High quality" is a scientific term of art and not an ordinary-language synonym for "reliable" or "sound." Studies deemed technically "moderate" or even "low" quality are ubiquitous and regularly used as the basis for clinical practice in medicine. If the Cass Review's arbitrary threshold for research quality were applied in pediatric medicine across the board, it would throw the field of pediatrics into chaos by casting doubt on many treatments that are critical to the well-being of children and youth.[3]

Indeed, these errors and others suggest that the authors and contributors to the Cass Review are not well-

3. In the interest of brevity, amici highlight for the Court the most critical flaws of the Cass Review to illustrate how it fails to provide reliable evidence in support of the Tennessee Ban. Amici detail additional fundamental flaws in the Cass Review's methodology and conclusions in their white paper. *See* Meredithe McNamara et al., *An Evidence-Based Critique of the Cass Review on Gender-Affirming Care for Adolescent Gender Dysphoria* (2024), https://tinyurl.com/mppm5cjz.

versed in making clinical recommendations in pediatric medicine, let alone gender-affirming medical care for adolescents with gender dysphoria.

Second, amici clarify for the Court that, contrary to the suggestion of Tennessee and its supporting amici, the Cass Review *does not* recommend banning gender-affirming medications. The Review recognizes that medical transition is the right choice for certain adolescents with gender dysphoria. Based on its problematic review of the evidence, the Cass Review recommends some changes in how treatment is provided, but it recognizes that gender-affirming medications are medically appropriate for certain youth and that they should continue to be available. In short, the Review endorses a holistic and individualized model for gender-affirming medical care that is aligned with the guidelines followed by U.S. gender clinics.

For all these reasons, the Cass Review does not provide credible, scientific support for the Tennessee Ban.

ARGUMENT

I. TENNESSEE REPEATEDLY CITES THE CASS REVIEW AS ESTABLISHING A LACK OF EVIDENCE ON THE SAFETY AND EFFICACY OF GENDER-AFFIRMING MEDICATIONS FOR ADOLESCENTS WITH GENDER DYSPHORIA.

Amici and other reputable clinicians provide treatment for transgender adolescents with gender dysphoria in accordance with the evidence-based guidelines published by the World Professional Association for Transgender

Health ("WPATH") and the Endocrine Society. *See* Eli Coleman et al., *Standards of Care for the Health of Transgender and Gender Diverse People, Version 8*, 23 Int'l J. Transgender Health S1 (2022) ("WPATH Standards of Care"), https://tinyurl.com/ycyr7c3r; Wylie C. Hembree et al., *Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline*, 102 J. Clinical Endocrinology & Metabolism 3869 (2017) ("Endocrine Society Guidelines"), https://tinyurl.com/mvvzyarm. Under the guidelines, treatment is individualized and may—or may not, depending on the individual—involve prescribing gonadotropin-releasing hormone agonists ("puberty blockers") and/or cross-sex hormones.

Tennessee, along with states defending medical care bans nationwide, claim that there is "scant scientific support" for the use of gender-affirming medications, Tenn. Resp'ts Cert. Br. at 2, which they characterize as "experimental in nature and not supported by high-quality, long-term medical studies." *Id.* (quoting Tennessee Ban). In the District Court, Tennessee contended that there was a "lack of reliable studies." Defs.' Resp. in Opp. to Plaintiff-Intervenor's Mot. for a Prelim. Inj. at 18, June 1, 2023, ECF No. 135. As explained more fully below, authoritative assessments of the evidence do indeed exist, including, inter alia, those conducted as part of the WPATH Standards of Care and the Endocrine Society Guidelines.

Nevertheless, to support their claims, Tennessee and its experts rely heavily on material produced by the U.K.'s Cass Review. Indeed, five of Tennessee's six expert reports filed with the District Court invoke the

Cass Review, citing the Review's written products in 18 separate discussions.[4]

As background, the Cass Review is named for its leader, Dr. Hilary Cass, a pediatrician and the former president of the Royal College of Pediatrics and Child Health. England's National Health Service ("NHS") appointed her in 2020 to lead a project examining access to gender-affirming health care for young people in the U.K., even though she has no prior expertise or experience in gender-affirming medications or treating adolescents with gender dysphoria. Terms of Reference Page, *The Cass Review*, https://tinyurl.com/4fb8wndd (last visited Aug. 26, 2024); *The Chair*, The Cass Review, https://tinyurl.com/2nzet3cs (last visited Aug. 26, 2024).

Dr. Cass and her staff produced several documents between 2020 and 2024, culminating in the final report issued in April 2024, which is accompanied by six systematic reviews (the York SRs) evaluating the research on the medical treatment of gender dysphoric adolescents. *See* Cass Review, *supra*, at 17, 53. The reviews most focused on gender-affirming medications are Jo Taylor et al., *Masculinising and Feminising Hormone Interventions for Adolescents Experiencing Gender Dysphoria or Incongruence: A Systematic Review*, Archives of Disease in Childhood (2024) ("Hormone Interventions"), https://tinyurl.com/3chxb8en; and Jo Taylor et al., *Interventions to Suppress Puberty in Adolescents Experiencing Gender Dysphoria or Incongruence: A Systematic Review*, Archives of Disease in Childhood (2024) ("Interventions to Suppress Puberty"), https://tinyurl.com/yc67s5k4.

4. *See generally* Decls. of Dr. Cantor, Dr. Hruz, Dr. Levine, Dr. Roman, and Dr. Laidlaw, May 19, 2023, ECF Nos. 113-3 to -7.

Amici address this final April 2024 report, which is the most comprehensive of the reports issued by the Cass Review. Although the final report postdates Tennessee's initial filings with this Court, amici expect that they—like state defendants in parallel cases in lower courts—will now rely heavily on this iteration of the Cass Review. The final Cass Review is consistent with the earlier documents on which Tennessee and their experts relied.

The Cass Review repeatedly states that the scientific evidence supporting gender-affirming medications is "weak." *See*, *e.g.*, Cass Review, *supra*, at 13, 20, 22, 25, 31, 33, 36, 44. Based on this characterization of the evidence, the Review recommends that puberty blockers be prescribed to transgender youth only in connection with a research study to be created by NHS England and that cross-sex hormones only be available from age 16 and subject to a "cautious clinical approach." *Id.* at 34.

In June 2024, the U.K. Department of Health and Social Care adopted emergency regulations that prohibit the supply of puberty blockers to new patients under 18 in England, Scotland, or Wales. *See* The Medicines (Gonadotrophin-Releasing Hormone Analogues) (Emergency Prohibition) (England, Wales and Scotland) Order 2024, SI 2024/727. This U.K. ban does *not* affect the prescription of cross-sex hormones to adolescents with gender dysphoria. *See id.* No action has been undertaken in the U.K. to restrict cross-sex hormones.

Notably, the Cass Review has been strongly criticized by experts in the U.K. and abroad. Members of the British Medical Association ("BMA"), which is a professional association representing doctors in the U.K., have

questioned the methodology and conclusions of the Cass Review. Press Release, *British Med. Ass'n*, BMA to Undertake an Evaluation of the Cass Review on Gender Identity Services for Children and Young People (July 31, 2024), https://tinyurl.com/43t7jtrr. The BMA has announced plans to undertake a thorough analysis of the Review to address "weaknesses in the methodologies used in the Review and problems arising from the implementation of some of the recommendations." *Id.* The BMA also called for a "pause" on the U.K. ban on puberty blockers, pending this review. *Id.*

As amici more fully explain below, the Cass Review is predicated on flawed methodology and unreliable evidence assessment that exclude much of the evidence supporting gender-affirming medical care for gender dysphoric adolescents. In fact, the evidence base for medical treatment for gender dysphoria in adolescents is sound and comparable to evidence supporting many other areas of pediatric medicine.

II. THE CASS REVIEW'S ASSESSMENT OF THE RESEARCH ON GENDER-AFFIRMING MEDICATIONS SHOULD NOT BE CREDITED.

The Cass Review is not the authoritative assessment of the evidence that Tennessee and its experts and supporting amici hold it out to be. The Review's methodology and conclusions are so deeply flawed that it should not be credited as reliable, scientific evidence in support of the Tennessee Ban. The Cass Review relies on the York SRs to conclude that the body of evidence supporting gender-affirming medications is "weak." Cass Review, *supra*, at 20. But systematic reviews are only as sound as their methodology. The York SRs repeatedly violate scientific

standards and introduce error into their results that are then transmitted to the Cass Review.

Given the glaring errors in the Cass Review and the systematic reviews it relies upon, it is not surprising that, like the BMA, many researchers have questioned its conclusions and reliability. For example, a recent study has quantified the errors in the York SRs and concluded that their assessment of the evidence is unreliable. *See* Chris Noone et al., *Critically Appraising the Cass Report: Methodological Flaws and Unsupported Claims* at 12-13 (2024) ("Noone Study"), https://tinyurl.com/bdxr5rv9. Using a well-regarded and routinely used assessment tool for systematic reviews, the Noone Study evaluated the York SRs across four domains and found a high risk of inaccuracy in every one: study eligibility criteria; identification and selection of studies; data collection and study appraisal; and synthesis and findings. *Id.* at 3-6; *see also* McNamara et al., *supra*, at 8-39; D. M. Grijseels, *Biological and Psychosocial Evidence in the Cass Review: A Critical Commentary*, Int'l J. Transgender Health 1 (2024), https://tinyurl.com/2m7fwm8v.

As more fully explained below, the York SRs are so unreliable that they do not support the conclusions drawn by the Cass Review about the purportedly "weak" quality of evidence supporting gender-affirming medications. By improperly and excessively excluding sound, peer-reviewed research, the Cass Review pre-determines its finding that there is "insufficient/inconsistent evidence about the effects of puberty suppression," Cass Review, *supra*, at 32, and "a lack of high-quality research assessing the outcomes of hormone interventions in adolescents with gender dysphoria," *id.* at 33 (quoting York SRs).

A. The York SRs Relied Upon by the Cass Review Violate Scientific Standards by Excluding Many Solid Studies on Gender-Affirming Medications for Adolescents with Gender Dysphoria.

The Cass Review cites the York SRs in claiming that the literature on gender-affirming medications "demonstrate[s] poor study design, inadequate follow-up periods and a lack of objectivity in reporting of results." *Id.* at 194. But the York SRs are scientifically unreliable because they arbitrarily and irrationally exclude major portions of the evidence demonstrating the positive effects of gender-affirming medications.

The Review is correct that systematic reviews can provide sound evaluations of the quality of medical evidence. *See id.* at 54-55. Systematic reviews combine the findings of multiple studies based on a thorough search of the scientific literature. *Id.* They are considered the strongest form of evidence in technical rating systems, *id.*, but *only* if they are well-conducted and include all relevant evidence without arbitrary exclusions. *See* Cochrane Library, *About Cochrane Reviews*, https://tinyurl.com/yc4n7cpn (last visited Aug. 26, 2024).

1. The York SRs exclude robustly conducted studies on the effects of gender-affirming medications.

Systematic reviews are vulnerable to many forms of error. They necessarily involve human judgment and subjective appraisals of quality, and they can produce unreliable results if researchers change methods

arbitrarily or select a methodology that is ill-suited to the subject matter. *See* Beverly J. Shea et al., *AMSTAR 2: A Critical Appraisal Tool for Systematic Reviews that Include Randomised or Non-Randomised Studies of Healthcare Interventions, or Both*, 358 British Med. J. 4008 (2017), https://tinyurl.com/2dd7f2pu.

To ensure reliable results, scientists use careful procedures and validated tools. But the York SRs deviate substantially from standard practices and, as a result, are flawed and error-prone. *See* McNamara et al., *supra*, at 29-39; Noone Study, *supra*, at 3-7.

The most serious error in the York SRs is that the authors chose an arbitrary and undefended methodology that resulted in the exclusion of much of the evidence supporting gender-affirming medications for adolescents with gender dysphoria. *See infra* Section II(A)(2).

To take just a few examples, among the valuable studies unjustifiably excluded by the York SR methodology are: Annelou L. C. de Vries et al., *Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment*, 134 Pediatrics 696 (2014) (finding that, after gender-affirming medications beginning in adolescence and surgery in young adulthood, "psychological functioning steadily improved" and that "well-being was similar to or better than same-age young adults from the general population."); Laura E. Kuper et al., *Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy*, 145 Pediatrics 1, 1 (2020), https://tinyurl.com/2y3xrwsc (finding that "youth reported large improvements in body dissatisfaction," "small to moderate improvements

in self-report of depressive symptoms," and "small improvements in total anxiety symptoms"); Diana M. Tordoff et al., *Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care*, 5 JAMA Network Open, e220978 (2022), https://tinyurl.com/yux5exxb (finding that "gender-affirming medical interventions were associated with lower odds of depression and suicidality over 12 months").

As another example of failing to consider valuable evidence, the York SR on puberty blockers disregards qualitative data, which shed important light on the impact of gender-affirming medications. For example, Carmichael and colleagues found that "[p]articipant experience of treatment as reported in interviews was positive for the majority, particularly relating to feeling happier, feeling more comfortable, better relationships with family and peers and positive changes in gender role." Polly Carmichael et al., *Short-Term Outcomes of Pubertal Suppression in a Selected Cohort of 12 to 15 Year Old Young People with Persistent Gender Dysphoria in the UK*, 16 PLoS One 1, 18 (2021), https://tinyurl.com/ysaxkwzz. But the York SRs categorically exclude such results and studies without explanation or justification. Notably, the exclusion of such qualitative research was apparently a post hoc decision, as the pre-registered protocol for the systematic reviews describes no such plan.

Moreover, the York SRs' search of the scientific literature is incomplete and outdated. Systematic reviews should always aim to search all relevant scientific literature. The York SR authors submitted their final manuscripts in October 2023 but did not systematically search literature published after April 2022. This left

18 months of the most contemporary scientific literature insufficiently examined. This is particularly important in a field of medical treatments for adolescents with gender dysphoria, which has seen more new research published in recent years than in years past.

While the York SRs recite that "more recent studies published from April 2022 until January 2024 also support the conclusions of this review," Interventions to Suppress Puberty, *supra*, at 1; Hormone Interventions, *supra*, at 1, the authors do not describe how those "recent studies" were identified or assessed, and they give only passing mention to new and highly impactful studies. For example, the longest and largest study to date, published in 2023, found that gender-affirming hormone treatments lead to improved mental health by helping align an individual's appearance with their gender identity. *See* Diane Chen et al., *Psychosocial Functioning in Transgender Youth After 2 Years of Hormones*, 388 New Eng. J. Med. 240 (2023), https://tinyurl.com/4h4zxhet, *as corrected*, 389 New Eng. J. Med. 1540 (2023), https://tinyurl.com/yeyj9u9t. This study, which was published in one of the most prestigious medical journals and funded by the National Institutes of Health, was particularly robust because its statistical analysis allowed strong causal inferences about the positive effects of gender-affirming medications on mental health. Yet this study receives only cursory mention in the York SRs. Hormone Interventions, *supra*, at 7.

Similarly, the York SR on puberty blockers did not substantively analyze a study presenting the longest outcome data regarding bone density. This study described normal bone density after 11 years of cross-sex hormone treatment. *See* Maria Anna Theodora Catharine van

der Loos, et al., *Bone Mineral Density in Transgender Adolescents Treated With Puberty Suppression and Subsequent Gender-Affirming Hormones*, 177 JAMA Pediatrics 1332, 1335-40 (2023). This study gets only a passing mention in the Review and no recognition of its key findings, despite the Review's repeated assertions about a need for long-term data in this field. *See* Cass Review, *supra*, at 171.

Newer studies, not analyzed by the York SRs or the Review, also demonstrate important findings: that avoiding a non-affirming puberty confers benefits in the years to come. *See* Kerry McGregor et al., *Association of Pubertal Blockade at Tanner 2/3 with Psychosocial Benefits in Transgender and Gender Diverse Youth at Hormone Readiness Assessment*, 74 J. Adolescent Health 801, 804-06 (2024); Priya Chelliah et al., *Changes in Gender Dysphoria, Interpersonal Minority Stress, and Mental Health Among Transgender Youth After One Year of Hormone Therapy*, 74 J. Adolescent Health 1106, 1109-10 (2024).

The Noone Study faulted the York SRs for, among other failures, excluding relevant scientific literature. In total, the York SRs excluded 48% of studies on puberty blockers and 36% of studies on cross-sex hormone treatments *without justification*. Noone Study at 5.

A related, serious error is that the York SRs treat puberty blockers and cross-sex hormones as distinct, review them separately, and improperly exclude studies that do not identify the independent impact of each therapy. This is deeply problematic because puberty blockers are not a sole treatment for gender dysphoria, but

rather are provided as part of a consistent, well-organized standard of care. 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. The attempt to strictly separate the impact of one set of medications from another led the York SR teams to inappropriately exclude numerous important studies that assess the overall impact of this care continuum on the well-being of transgender adolescents. *See*, *e.g.*, Kuper et al., *supra*, at 1-7; de Vries et al., *supra*, at 696.

The exclusion of valid evidence by the York SRs virtually guarantees their finding that there is a "lack of high-quality research" supporting gender-affirming medications. Interventions to Suppress Puberty, *supra*, at 1; Hormone Interventions, *supra*, at 1. The failure of the authors of the York SRs to understand and engage substantively with the full body of research led to flawed conclusions that were then transmitted to the Cass Review in its recommendations.

2. The York SRs violate scientific protocols by changing methods midstream.

An important step for any systematic review is to pre-register a precise research design. Pre-registration is standard practice designed to ensure that researchers adhere to their planned design and do not change their methodology to reach a desired result. *See What Is Registration?*, Nat'l Inst. Health & Care Rsch., https://tinyurl.com/5n99kjcm (last visited Aug. 26, 2024).

The York SR authors did develop one protocol for their six systematic reviews prior to embarking on their work, but that protocol bears no relation to the research the authors actually conducted. The pre-registered study design called for the use of a specific method (called the "Mixed Methods Appraisal Tool" or "MMAT") for appraising the quality of studies, which required inclusion of all studies. However, the authors switched midstream to a different scale (called the "Newcastle-Ottawa Scale" or "NOS"), which permitted exclusions of studies, and then made ad hoc modifications to the scale. *See generally* Quan Nha Hong et al., *Mixed Methods Appraisal Tool (MMAT) Version 2018 User Guide*, McGill Univ. (Aug. 1, 2018), https://tinyurl.com/yzannep5; *see also* Cass Review, *supra*, at App. 2 p.3-4. The published versions of the York SRs neither mention nor justify deviations from their pre-registered protocol.

This change in method causes major inaccuracies in the results of the York SRs. The pre-registered method (MMAT) would have encouraged the authors to include all studies, but the actual method used (NOS) permitted the York SR authors to exclude a substantial number of studies. By changing their methods midstream, the York SR authors not only ignored scientific guardrails but also smuggled in a flawed and arbitrary methodology that excluded reliable evidence supporting gender-affirming medications.

Curiously, and despite their professed commitment to evidence quality, the York SR authors even ignored the positive findings of a study that their adapted NOS scale deemed "high quality." *See*, *e.g.*, Anna I.R. 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, 702-03 (2020), https://tinyurl.com/4ctw43hy (finding significant improvements in various psychological outcomes, including suicidality, and peer relations).

B. The Cass Review Improperly Holds Gender-Affirming Medical Care to a Standard that Cannot Be Met by Many Areas of Pediatric Medicine.

The Cass Review repeatedly states that there is "a lack of high-quality evidence" supporting gender-affirming medications. Cass Review, *supra*, at 20; *see also id.* at 33, 175, 184. The Review then relies on these findings to make recommendations for clinical care. The result is that the Cass Review holds gender-affirming medical care to an unrealistic and inappropriate standard—and one that cannot be met by many areas of pediatric medicine.

"High quality" is a technical term that generally refers to randomized controlled trials ("RCTs"), which are rare in pediatric research. Indeed, the number of randomized controlled trials in adult medicine has always far outpaced those in pediatrics, and this discrepancy has worsened over the past decade. Michael L. Groff et al., *Publication Trends of Pediatric and Adult Randomized Controlled Trials in General Medical Journals, 2005-2018: A Citation Analysis*, 7 Child. 293, 297-98 (2020), https://tinyurl.com/3mntbuh2. "Moderate" and "low quality" studies do not mean that the evidence is of poor quality; to the contrary, they include many reliable, peer-reviewed studies and serve as the basis for strong clinical recommendations, particularly in pediatrics. Several

examples of such types of pediatric care are discussed in this section.

1. "High Quality" is a technical term that includes only a subset of research techniques and does not include many reliable, peer-reviewed studies.

Studies of evidence quality rely on a variety of technical measures. One widely used rating system is called "Grading of Recommendations, Assessment, Development, and Evaluations" ("GRADE"). *See* Gordon H. Guyatt et al., *What is "Quality of Evidence" and Why Is It Important to Clinicians?* 336 British Med. J., 995, 995 (2008), https://tinyurl.com/3esvyxpk. Under GRADE, there are four categories for evidence quality: very low, low, moderate, and high. *Id.* at 998.

The GRADE categories may sound like ordinary-language terms, but they have highly technical meanings and should not be used interchangeably (as the Cass Review does) with colloquialisms like "weak" and "poor." A key example is that evidence deemed technically "high quality" by systems like GRADE nearly always comes from RCTs. *See id.* at 995.

RCTs that compare treatment to placebo are ill-suited, however, to studying the effects of gender-affirming medications on psychological wellbeing and quality of life among transgender people. *See* Florence Ashley et al., *Randomized-Controlled Trials Are Methodologically Inappropriate in Adolescent Transgender Healthcare*, 25 Int'l J. Transgender Health, 407, 407 (2023), https://tinyurl.com/4t5fkufu.

It is impossible to blind participants and investigators in a study of puberty blockers and cross-sex hormones, because these medications produce obvious physical effects. *See id.* at 409. Both an individual and their provider would readily detect whether the physical changes of puberty occurred or if cross-sex hormones were administered as the individual observed (or did not see) feminizing or masculinizing changes in their breasts, voices, facial hair, and body shape.

There are also ethical barriers to RCTs. If participation in a research study is the only way to access medically affirming interventions that have substantial evidence demonstrating their effectiveness, the result is coercion, which is condemned by medical and scientific ethical rules. *See* World Med. Ass'n, *Declaration of Helsinki—Ethical Principles for Medical Research Involving Human Subjects* ⁋⁋ 25-27 (Sept. 6, 2022), https://tinyurl.com/5haue985. For this reason, restricting access to puberty blockers and cross-sex hormones to research settings, as the Cass Review recommends for puberty blockers, is unethical. Cass Review, *supra*, at 32.

2. Many areas of clinical practice in pediatrics are based on technically lower-quality evidence.

If the Cass Review's unrealistic standard for research quality were applied broadly, it would call into question many life-sustaining areas of pediatric medicine and create chaos in the day-to-day practice of pediatrics.

Many practices in pediatric medicine are based on evidence that is not "high quality." Yet, that evidence is

considered critical for guiding clinical recommendations. Like gender-affirming medications for transgender youth, use of these treatments are guided by robust clinical research. These practices are widely accepted in high-stakes scenarios even while decades worth of data are actively being collected.

In neonatology, which is the care of critically ill and, often, preterm infants, clinicians routinely make hundreds of high-stakes, evidence-informed, and guideline-driven decisions for their vulnerable patients each day. For example, should a premature infant with respiratory problems be supported with a breathing tube or a non-invasive ventilation method? The former can be more effective in the short term, but the latter may have the most long-term benefits.

The answers to these questions and so many others come from guidelines that are informed by evidence that is rarely "high quality." In fact, 92% of guideline recommendations for premature infants with severe breathing difficulty were based on expert consensus, "very low," "low," or "moderate" quality evidence. Yi Huang et al., *Guidelines for High-Flow Nasal Cannula Oxygen Therapy in Neonates (2022)*, 16 J. Evid. Based Med. 394, 408 (2023). And yet, clinical outcomes are only ever improving: more infants leave intensive care units better off than ever before. Edward F. Bell et al., *Mortality, In-Hospital Morbidity, Care Practices, and 2-Year Outcomes for Extremely Preterm Infants in the US, 2013-2018*, 327 JAMA 248, 250-60 (2022), https://tinyurl.com/rcsnh29m.

Other examples of pediatric care that are not grounded in "high quality" evidence are abundant. One

of the newest areas is the use of glucagon-like peptide-1 ("GLP-1") analogues for treatment of pediatric metabolic syndrome. These include familiar brand-names like Ozempic and Mounjaro. These medications are now recommended for children with pre-diabetes, metabolic-associated liver disease, and high blood pressure (among other health issues), even though the evidence base is far less robust than the evidence supporting gender-affirming medications. GLP-1s in children have only been studied for 1 to 2 years. We do not yet have decades' worth of evidence on the impact of significant weight loss in adolescence.

3. The Cass Review fixates on technical measures of evidence quality and ignores the many other factors that should guide day-to-day medical practice.

Scientists have recognized that clinical practice guidelines, like those developed by WPATH and the Endocrine Society for treatment of gender dysphoria, should consider evidence of a treatment's efficacy, the benefits and harms of both treatment and no treatment, patients' values and preferences, and the resources required to offer treatment. Robust and trustworthy guidelines follow protocols like the one set out in a landmark publication by the National Academy of Medicine (then known as the Institute of Medicine). *See generally* Inst. of Med., *Clinical Practice Guidelines We Can Trust* (Robin Graham et al. eds., 2011) ("National Academy of Medicine"), https://tinyurl.com/547kzrzk.

So widely accepted is this point that even the authors of evidence quality ratings systems agree that *evidence quality alone should not be the basis for clinical*

recommendations. Indeed, the GRADE authors state explicitly that technically "low quality" evidence can and does support strong recommendations for clinical care. Howard Balshem et al., *GRADE Guidelines: 3. Rating the Quality of Evidence*, 64 J. Clinical Epidemiology 401, 402-04 (2011). It may seem perplexing that clinical care is not *solely* based on the "quality" of medical evidence. But if this were the case, real patients would not receive appropriate care that aligns with their preferences and values, available resources, and the harms of not providing care. Here, amici offer three examples of how the Review violates scientific standards by fixating on evidence quality and ignoring or minimizing other factors that should motivate clinical recommendations.

First, the Cass Review fails to adequately and accurately describe the positive outcomes of gender-affirming medical treatments for transgender youth, including improved body satisfaction, appearance congruence, quality of life, psychosocial functioning, and mental health, as well as reduced suicidality. It is highly unusual for a document issuing clinical recommendations to barely engage with abundant evidence on the positive effects of treatment.

Second, the Cass Review fails to consider the harms of *denying treatment* to a young person with gender dysphoria. The most concrete effect would be the development of permanent physical characteristics that do not align with an individual's gender identity (e.g., voice deepening, hair growth, and breast tissue development). By ignoring these harms, the Review dismisses the significant psychological pain suffered by adolescents with gender dysphoria, for whom these permanent physical changes are highly distressing. The Review also ignores the future

consequences for adolescents who, left untreated, must present to the world a physical appearance that is at odds with their own identity. In adulthood, some (though not all) of these physical effects can be ameliorated to some degree with costly, invasive and painful treatments such as surgery, laser hair removal, and speech therapy, but these treatments do not erase the intervening and formative years of psychological distress.

Third, although the Cass Review conducted focus groups with transgender young people, its recommendations often conflict with their expressed values and preferences. *See* Cass Review, *supra*, at 61-62. Transgender youth conveyed that they want improved access to appropriate gender-affirming medical services from clinicians who have training and experience. *Id.* at 151, 166. The Review disregards these values and preferences in its most emphatic recommendation, which is to limit care to research settings that do not yet exist. *Id.* at 32.

C. The Cass Review's Fundamental Errors Suggest a Lack of Subject Matter Expertise Among the Authors.

Well-established standards for issuing clinical recommendations and conducting systematic reviews require the close involvement of true subject matter experts. *See* Toby J. Lasserson et al., *Chapter 1: Starting a Review*, *in* Cochrane Training Handbook ¶ 1.3, https://tinyurl.com/2zarrmk9 (last visited Aug. 26, 2024). Indeed, there are gold-standard scientific protocols—not followed by the Cass Review—that describe how to incorporate evidence into clinical recommendations and how to use expert input effectively and without bias. These standards

call for an expert panel to formulate research questions while a separate group conducts evidence quality reviews. *See* National Academy of Medicine, *supra*, at 93-97. The expert panel then weighs in again to translate evidence into clinical care. *Id.* at 97; *see also* Lasserson, *supra*, at ¶ 1.3.

Dr. Cass is an expert in Rett Syndrome and the care of children with complex developmental disabilities, but she is not an expert in the treatment of adolescents with gender dysphoria. *See Dr. Hilary Cass*, Royal Coll. Paediatrics & Child Health, https://tinyurl.com/346fjheh (last visited Aug. 26, 2024). Similarly, the authors of the York SRs do not have relevant expertise in managing gender-affirming medications and thus cannot engage substantively with the data they analyze. *See* Noone Study, *supra*, at 6 (explaining that "the Cass team specifically excluded content experts" except for one former clinical psychologist). The Review does not identify, either in its text or in the York SRs, who devised the research questions informing the evidence review—a failure to disclose authorship that violates scientific standards.

Amici cannot definitively assess whether the Review included subject matter experts because the Review breaks with scientific convention by not disclosing its full authorship. *See* McNamara et al., *supra*, at 3 n.9. However, the Review's numerous flaws suggest that the authors did not include subject matter experts. As an example, the Cass Review emphasizes that the York SR on puberty suppression demonstrated "no changes in gender dysphoria or body satisfaction." Cass Review, *supra*, at 32. This conclusion rests, however, on a lack of understanding of the goals of puberty blockers—an error that suggests a lack of relevant subject matter expertise.

Experts in treating youth with gender dysphoria would not expect that puberty blockers *alone* reduce gender dysphoria or increase body satisfaction, because these medications do not change the current physical characteristics of one's body. Rather, they only prevent future changes. Puberty blockers pause development of secondary sex characteristics that might be detrimental to the psychosocial well-being of a transgender young person. For example, puberty blockers halt growth of breasts, but they do not reverse any breast growth that has already occurred; they can prevent the deepening of one's voice, but they will not raise the pitch of a voice that has already deepened.

The true effects of puberty blockers are far more nuanced than the Review contends. Well-conducted studies show no change in certain mental health scores, which indicates *stability* rather than no effect. Carmichael et al., *supra*, at 15; van der Misen et al., *supra*, at 702-03. Stability is deeply meaningful for youth who are otherwise expected to experience increased gender-related distress without intervention.

The York SRs actually confirm that puberty blockers are effective in temporarily halting puberty and that cross-sex hormone therapy is effective in developing secondary sex characteristics that align with gender identity (e.g., a deepened voice in a transgender young man). *See* Interventions to Suppress Puberty, *supra*, at 12. The York SR authors—and the authors of the Cass Review itself—simply fail to understand that these are vital goals of gender-affirming medications for adolescent gender dysphoria.

Absence of expertise does not guarantee impartiality: it invites error. *See* National Academy of Medicine, *supra*, at 83-86 (recommending that experts from multiple disciplines be included when developing clinical practice guidelines).

III. THE CASS REVIEW *DOES NOT* CALL FOR A BAN ON GENDER-AFFIRMING MEDICATIONS.

As researchers and pediatric clinicians with experience in the field of transgender healthcare, amici read the Review with interest. The Review merits praise for gathering a great deal of data about youth gender services in the U.K. This information sheds light on the needs of the U.K.'s population of transgender youth and the barriers they face in the pursuit of care.

Importantly, notwithstanding its fundamental flaws and mischaracterizations of the evidence as "weak," the Cass Review *does not* recommend that gender-affirming medications for adolescent gender dysphoria be banned. Cass Review, *supra*, at 28-45.

Instead, the Review recognizes transgender identity as real and states that gender-affirming medical care is appropriate for certain transgender youth before age 18. For example, the Review notes that, "for some, the best outcome will be transition," while also acknowledging, as the WPATH Standards of Care and the Endocrine Society Guidelines do, that gender-affirming medical interventions are not appropriate for all transgender adolescents. Cass Review, *supra*, at 21; WPATH Standards of Care, *supra*, at S51; Endocrine Society Guidelines, *supra*, at 3871. The Review recommends that puberty blockers remain

available for minors via a research protocol to be designed by the NHS. Cass Review, *supra*, at 32. And the Review recommends that cross-sex hormones be available from age 16, albeit with a "cautious clinical approach" that individualizes care decisions. *Id.* at 34.

While amici believe these recommendations are more restrictive than warranted when the evidence is appropriately evaluated, it is notable that even based on its flawed, inexpert, and exceptionally harsh assessment of the evidence, the Cass Review did not recommend banning care as Tennessee has done.

The Cass Review also contains statements that favorably describe the kind of individualized, age-appropriate, and careful approach recommended by the WPATH Standards of Care and Endocrine Society Guidelines. For example, the Review endorses a holistic, comprehensive assessment of each adolescent and recommends that co-occurring mental health conditions be properly treated. *Id.* at 29-31; WPATH Standards of Care, *supra*, at S48; Endocrine Society Guidelines, *supra*, at 3871. Recommendations from WPATH and the Endocrine Society are followed for youth gender care in the United States.

While the WPATH Standards of Care, Endocrine Society Guidelines, and even the Cass Review recognize that gender-affirming medical interventions are indicated for some adolescents with gender dysphoria, the Tennessee Ban is a clear divergence from any medical consensus in this field.

CONCLUSION

When properly conducted, systematic reviews can shine important light on the appropriateness of certain medical care. However, the York SRs deviate so dramatically from established protocols and contain such critical methodological flaws that they fail to reliably assess the safety and effectiveness of gender-affirming medications for adolescents with gender dysphoria, and these fundamental errors were transmitted to the Cass Review.

Notwithstanding these flaws, even the Cass Review does not recommend a ban on gender-affirming medications. Rather, it recognizes that these treatments are essential medical care for some adolescents with gender dysphoria.

For all these reasons, the Cass Review provides no credible support for the Tennessee Ban. Amici join in the request of Petitioner and Respondents in Support of Petitioner that the decision below be vacated and the case remanded.

Respectfully submitted,

Alexander Shalom
Counsel of Record
Natalie J. Kraner
Lowenstein Sandler LLP
One Lowenstein Dr.
Roseland, NJ 07068
(973) 597-2500
ashalom@lowenstein.com
nkraner@lowenstein.com
Counsel for Amici Curiae

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