Documents for the Record – 06/14/23

Majority:

- June 14, 2023 statement by Brett Giroir, MD, Sickle Cell Disease Partnership
- June 14, 2023 letter from the Sickle Cell Disease Partnership
- June 14, 2023 letter from Sick Cells
- June 14, 2023 written testimony from Michael J. Fox Foundation
- June 14, 2023 statement from Troy Burns, MD, Direct Primary Care Coalition
- June 14, 2023 article submitted by Rep. Crenshaw

Minority:

- Yale School of Medicine article on "Flawed Medicaid Report in Florida"
- April 28, 2022 article on "Biased Science.."
- June 14, 2023 letter from Gillette Children's Specialty Healthcare
- June 9, 2023 letter from coalition on PREEMIE reauthorization
- August 2022 study on "A Surgical Simulation Module on Pediatric Femoral Osteotomies for Orthopedic Surgery Residents"
- June 14, 2023 letter from the Healthcare Leadership Council
- June 14, 2023 statement from the Children's Hospital Association
- June 14, 2023 statement from Rep. Pascrell
- June 14, 2023 statement from interACT
- June 14, 2023 statement from Rep. Wexton
- June 14, 2023 statement from American Dental Association

June 14, 2023

SICKLE CELL DISEASE PARTNERSHIP

Statement by Brett Giroir, M.D.

"The time for Congress to act is now. For too long, our nation's efforts to address this painful, debilitating disease have been woefully inadequate, leaving patients and families behind – without access to high-quality care and without sufficient progress toward new treatments and cures. Sickle cell disease affects African Americans at a disproportionate rate, with one in 13 African Americans carrying the gene that causes sickle cell disease.

There are three important things Congress can do to help preserve and improve access to care this session.

- First, Congress should reauthorize the HRSA Treatment Centers Program to enable HRSA to continue to provide specialized care for our fellow Americans.
- Second, Congress should ensure stable funding for the CDC's data program which helps support state efforts in sickle cell disease; having consistent data is fundamental.
- Finally, Congress should adopt H.R. 1672, *The Sickle Cell Disease Comprehensive Care Act,* to help ensure comprehensive, patient-centered care for the more than half of Americans with this disease who are served by Medicaid.

For far too long, policymakers have stood on the sidelines. Policy inaction has made it harder for individuals with sickle cell disease to stay engaged in their jobs, homes, communities and places of worship. There is more Congress can and should do, but these foundational actions are targeted, timely, bipartisan and common-sense policies that would help ensure that Sickle Cell Warriors get the care and the support they need now."

Brett Giroir, M.D.
Senior Advisor, Sickle Cell Disease Partnership

SICKLE CELL DISEASE PARTNERSHIP

June 14, 2023

The Honorable Cathy McMorris Rodgers
Chair
Subcommittee on Health
House Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member
Subcommittee on Health
House Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

Statement for the Record on "Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases"

Dear Chair Rodgers and Ranking Member Eshoo,

The Sickle Cell Disease Partnership ("The Partnership") is a multi-sector collaboration of more than a dozen healthcare organizations working together to advance federal policies to improve the lives of Americans with sickle cell disease (SCD) – a rare, genetic blood disorder that disproportionately impacts Black Americans and Hispanic Americans.[1] SCD causes a myriad of debilitating acute and chronic health issues and severely impacts quality of life.[2]

The Partnership applauds the Committee for holding this hearing on providing access to care for patients and supporting research for rare diseases. For far too long, individuals with SCD have lacked access to high-quality, comprehensive care and treatment and data collection and research efforts have been inadequate, compared to other rare diseases.

The Partnership also applauds Representatives Burgess, Davis and Carter for their recent introduction of the *Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act of 2023* (H.R. 3884) and applauds the Committee for including this bill in the hearing discussion. This bill reauthorizes the critically important Health Resources and Services Administration (HRSA) Sickle Cell Disease Treatment Demonstration Program (SCDTDP) beyond FY2023, through 2028. SCDTDP is a HRSA grant program aiming to:

(1) increase the number of clinicians knowledgeable about SCD care,
(2) improve the quality of care provided to individuals with SCD,
(3) improve care coordination with other providers; and
(4) developing best practices for coordination of services during pediatric to adult transition.

[1] The Partnership is comprised of sickle cell disease patient and community organizations, healthcare providers who have experience caring for sickle cell patients, manufacturers of medical products, health plans, researchers, and others interested in improving the lives of patients living with sickle cell disease.
[2] https://www.cdc.gov/ncbddd/sicklecell/data.html#:~:text=SCD%20occurs%20among%20about%201,sickle%20cell%20trait%20(SCT).

Throughout its existence, the centers involved in the SCDTDP have made progress in improving SCD care across the nation; however, without reauthorization, this progress may come to a halt. The Partnership strongly supports the SCDTDP program and encourages lawmakers to reauthorize the SCDTDP at the appropriated level.

While the *Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act of 2023* marks a tremendous step forward in Congress' commitment to SCD, the Partnership encourages the Committee to consider additional actions that are necessary to support the SCD population. One of these actions includes providing adequate funding to the Centers for Disease Control and Prevention (CDC) SCD data collection program. Through its SCD data collection program, the CDC awards grants to states, academic institutions, and non-profit organizations to gather information on the prevalence of SCD and health outcomes, complications, and treatment that people with SCD experience. Currently, 11 states participate in the program, with data being collected from multiple sources. However, these 11 states only account for an estimated 35 percent of the population of Americans living with SCD. The Partnership supports authorizing $25 million for the CDC to continue to support data collection efforts in all of the states participating in the program and expand the program to additional states, with the goal of covering the majority of the SCD population in the next few years.

In addition to timely reauthorization of the SCDTDP and adequately funding the CDC SCD data collection program, Congress also must enact the following SCD-related pieces of legislation:

- **Sickle Cell Disease Comprehensive Care Act (S.904, H.R.1672).** This bill authorizes the federal government to establish a demonstration program in up to ten states to provide comprehensive care to Medicaid SCD beneficiaries.
- **The Sickle Cell Care Expansion Act (S.1423 , H.R.3100).** This bill would authorize a scholarship and loan repayment program to incentivize medical physicians to enter into the field of SCD research and treatment.

By reauthorizing the SCDTDP and enacting the legislation, Congress will have taken the steps necessary to ensure individuals with sickle cell disease in the United States have the timely, sustained access to high-quality, equitable, coordinated care and treatment that they deserve.

We look forward to working with you, other Energy and Commerce Committee members, and our Congressional champions on this issue. Should you have any questions, please contact Clay Alspach at [redacted] or Josh Trent at [redacted]. Thank you.

SICKLE CELL DISEASE PARTNERSHIP

The Honorable Brett Guthrie
Chair
Subcommittee on Health
House Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member
Subcommittee on Health
House Energy and Commerce Committee
United States House of Representatives
Washington, DC 20515

June 14, 2023

Dear Chair Guthrie and Ranking Member Eshoo,

Sick Cells is a national sickle cell disease organization with the mission of elevating the voices of the sickle cell community to ultimately influence decision-makers and project positive change.[1] Sick Cells works with a wide variety of stakeholders including individuals and families living with sickle cell disease (SCD), medical providers, payers, manufacturers, government agencies, academic research centers, and other community-based organizations. Our vision is to ignite public interest in SCD, humanize the disease, inspire the public to take action, and empower the SCD community to share their stories to know that they are not alone.

SCD is an inherited blood disorder that disproportionately affects Black and Brown populations in the United States, including roughly 1 in 365 Black and African Americans, and 1 in 14,000 Hispanic Americans.[2] Due to racism and patterns of health inequities in the United States, the SCD population has been marginalized in the realms of research, data collection, education, and access to quality care across the healthcare continuum. Because of the lack of robust funding for research and treatment, the lives of those living with SCD are approximately 40 years shorter than the average U.S. adult lifespan.

Sick Cells is pleased to see the Committee hold a hearing on important legislation that will impact the lives of tens of thousands Americans living with SCD. This population has historically been overlooked in federal funding, access to life-saving treatments, and cures. We applaud Representative Burgess, Davis, and Carter for their introduction of the *Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act of 2023* and truly appreciate their continued support of the SCD community's priorities.

The federal government, through legislation and program funding, is uniquely positioned to support and address the needs of the sickle cell disease community and design and coordinate a longitudinal

[1] "About Us." *Sick Cells*, 8 Feb. 2023, sickcells.org/.
[2] "Data & Statistics on Sickle Cell Disease." *Centers for Disease Control and Prevention*, 2 May 2022, www.cdc.gov/ncbddd/sicklecell/data.html#:~:text=SCD%20occurs%20among%20about%201,sickle%20cell%20trait%20(SCT).

understanding of the SCD community to improve health outcomes, quality of life, and reduce the cost of care.

There is an opportunity to build on the current efforts and (1) expand identification of individuals living with SCD through the CDC Sickle Cell Data Collection (SCDC) Program; and (2) enhance education about SCD and improve on quality of care through ECHO program and provide much-needed funding and support to federally qualified healthcare centers and community-based organization who directly serve the community through HRSA's programming.

Despite important advances in federal priorities for SCD, health disparities in the treatment of individuals with sickle cell in the United States continue. The financial and economic burden for an individual with SCD is unimaginably costly. The average annual cost caring for a child with SCD with insurance can cost up to $10,000. As an insured adult with SCD, the annual cost can be three-times as much as a child costing $30,000, annually.[3] An individual with SCD in America will pay four-times as much as an adult without a chronic condition in out-of-pocket expenses, totaling up to $44,000 in their lifetime.[4] Furthermore, the lack of coordination and proper preventative care provided by the medical system results in roughly $2.98 billion in annual healthcare costs.[5] The COVID-19 health crisis has only exacerbated the disparities and inequities found in the SCD community.

To date, there still is not a universal standard of care for people living with SCD. Furthermore, individuals with SCD have less access to comprehensive care than others living with genetic disorders, such as hemophilia and cystic fibrosis. Project ECHO and other educational efforts are designed to improve knowledge about care administration for individuals with SCD. While the intention of the education programs is clear, there is a disconnect in coordination between the existing federal programs and a need for more robust funding. Therefore, barriers still exist to quality healthcare.

With much innovation, including cutting edge treatments like gene therapy for SCD on the horizon, this legislation provides an opportunity to enhance resources to programs that work towards improving access to care. Sick Cells hopes to see improved coordination among the services offered through the federal government. Each service builds upon the next, thus resulting in the services leaving individuals from the SCD community behind, when the services are not aligned.

In 2018, the SCD community unified in our request to pass the *Sickle Cell Disease and other Heritable Blood Disorders Research, Surveillance, Prevention, and Treatment Act*. We worked closely with the same key champions who are still supporting us today. We were overjoyed to see Public Law No. 115-327. In 2020, the 116th Congress made history by being the first Congress to appropriate $2 million funding

[3] Kauf, Teresa L., et al. "The Cost of Health Care for Children and Adults with Sickle Cell Disease." *American Journal of Hematology*, vol. 84, no. 6, 2009, pp. 323–327, https://doi.org/10.1002/ajh.21408

[4] Johnson, Kate M., et al. "Lifetime Medical Costs Attributable to Sickle Cell Disease among Nonelderly Individuals with Commercial Insurance." Blood Advances, vol. 7, no. 3, 2023, pp. 365–374, https://doi.org/10.1182/bloodadvances.2021006281.

[5] Huo, J, et al. "The Economic Burden of Sickle Cell Disease in the United States." *Value in Health*, vol. 21, 2018, https://doi.org/10.1016/j.jval.2018.07.826.

towards the SCDC Program. These steps were important steps to begin addressing the disparities the SCD community has faced for over 110 years. Nonetheless, more action is needed to address the challenges of SCD, and Sick Cells is happy to continue to help the Committee to develop and enact policies to ultimately solve these challenges.

The sickle cell community continues to advocate for robust funding for the SCDC Program as there is a historical need for this data collection. Improvements for the SCD community require a longitudinal understanding of the unique needs of the patient with ongoing coordination of care and services. Prior to the expansion of the data collection program, Georgia and California were the first and only two states to be actively collecting SCD data. Currently, the SCDC program has expanded to 11 states, however these states do not cover the majority of the Americans living with SCD. The total 13 states only address 35% of the national SCD population and excludes individuals that identify as non-African-American or Native American.[6]

The ongoing support of funding SCD related programs roughly impacts 100,000 Americans who unfortunately are slipping through the cracks of a system; a system that we are confident is capable of making the much-needed change that the sickle cell disease community requires to eliminate health disparities and save lives.

We thank you for including the sickle cell disease community in important advances in public health policy. As leaders in the SCD space, we are looking forward to working with you, members of the Energy and Commerce Committee, and our Champions on this matter. If you have any questions, please contact **Emma Andelson** at [redacted] or **Ashley Valentine** at [redacted].

[6] Snyder, Angela B., et al. "Surveillance for Sickle Cell Disease — Sickle Cell Data Collection Program, Two States, 2004–2018." *MMWR. Surveillance Summaries*, vol. 71, no. 9, 2022, pp. 1–18, https://doi.org/10.15585/mmwr.ss7109a1.

Written testimony of The Michael J. Fox Foundation for Parkinson's Research
Submitted to:
Subcommittee on Health
House Committee on Energy and Commerce
Regarding the Hearing: *"Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases"*
June 14, 2023

Chair Rodgers, Chair Guthrie, Ranking Member Pallone, Ranking Member Eshoo, and Members of the House Energy and Commerce Subcommittee on Health, thank you for providing the opportunity to submit testimony in support of today's hearing entitled "Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases." We are thankful for the opportunity to support the National Plan to End Parkinson's Act and highlight the hope it brings to the Parkinson's community.

"The Michael J. Fox Foundation launched with one goal: to end Parkinson's. Since our start in 2000, we've made tremendous progress. We have funded more than $1.75 billion in research. And the recent discovery of a biomarker is our biggest breakthrough yet. But we're not slowing or stopping to congratulate ourselves — much more work is needed ahead. And we can't do it alone. The Foundation endeavors to partner effectively with the government to leverage federal research investments and keep good ideas moving forward toward patients, and to ensure those living with the disease have access to the care they need. I urge you to keep the National Plan to End Parkinson's Act moving through Congress, and to pass it. We stand ready to work together to make Parkinson's a thing of the past." — Michael J. Fox, actor, advocate, founder of The Michael J. Fox Foundation for Parkinson's Research

The Michael J. Fox Foundation (MJFF) is the world's largest nonprofit funder of Parkinson's research and an organization dedicated to accelerating a cure for Parkinson's and developing improved therapies for those currently living with the disease. MJFF pursues its goals through an aggressively funded, highly targeted research program coupled with active global engagement of scientists, Parkinson's patients and their families, business leaders, clinical trial participants, donors and volunteers. To date, MJFF has funded $1.75 billion in research and has fundamentally altered the trajectory of progress toward a cure.

On April 12, 2023, MJFF announced an enormous research breakthrough, opening a new chapter for Parkinson's research — with the promise of better drug development and care for all people and families living with the disease.[i] The new tool called the α-synuclein seeding amplification assay (αSyn-SAA), validated by the Foundation's landmark brain health study, the Parkinson's Progression Markers Initiative (PPMI), can reveal a key pathology of the disease: abnormal alpha-synuclein — known as the "Parkinson's protein" — in brain and body cells. This new biological test can detect the disease at the molecular level, even before the onset of symptoms. It does so by detecting abnormal alpha-synuclein in spinal fluid not only in people diagnosed with Parkinson's, but also in individuals who have not yet been diagnosed or shown clinical symptoms of the disease but are at a high risk of developing it.[ii] We have long known that abnormal alpha-synuclein clumps in the brains of people living with Parkinson's through post-mortem analysis, but this is the first time where we can detect it in a living human person.

This breakthrough heralds a new era of research with the promise of speeding faster, cheaper and smarter clinical trials. It also opens a world of opportunities to treat the disease earlier and prevent it altogether.

Parkinson's is a chronic, progressive neurological disorder with no cure or treatment to slow, stop or reverse the progression of the disease. Parkinson's occurs when brain cells that make dopamine, a chemical that coordinates movement, stop working or die. Since Parkinson's can cause tremor, slowness, stiffness, and walking and balance problems, it is referred to as a "movement disorder." However, there are many non-movement symptoms that can be associated with Parkinson's, such as constipation, depression and dementia. Parkinson's is a lifelong and progressive disease, which means that symptoms worsen over time, and the experience of living with Parkinson's over the course of a lifetime is unique to each person, with symptoms and progression of the disease varying from person to person.

Parkinson's also has the unfortunate distinction of being the fastest-growing neurological disease and second most common after Alzheimer's. Over 1 million Americans, including over 110,000 military veterans, currently live with the disease — a number that is expected to double by 2040.[iii,iv] To put that into context, there are 90,000 new diagnoses each year in the United States, which equates to 1 person every six minutes. In addition, it costs our country $52 billion every year to care for people with Parkinson's, half of which is paid by Medicare and Social Security, with the other $26 billion being paid for by American taxpayers, state and local governments, and through lost wages of patients and caregivers.[v] Even more concerning is that, by 2037, the

annual cost and financial burden of Parkinson's is projected to balloon to $80 billion.[vi]

However, despite Parkinson's staggering economic toll, the National Institutes of Health (NIH) only invested an estimated $260 million in annual support for Parkinson's disease research in 2022.[vii] In other words, the federal government spends approximately 100 times more caring for people with Parkinson's than the NIH spends researching the disease. This is alarming because Parkinson's is the 11th leading cause of death for Americans 65 and older, and disparities in resource allocations for Parkinson's disease become exponentially more concerning as we look to the future.[viii] The largest risk factor for developing Parkinson's disease is aging, so as the U.S. population ages, many more of our friends and family members will be diagnosed with Parkinson's. We simply cannot afford to wait. We must act now to prevent and cure this disease.

We thank the Subcommittee for its consideration of H.R.2365, the National Plan to End Parkinson's Act, and urge you to advance the bill through Committee and to the House floor. Introduced by Representative Gus Bilirakis (R-FL) and Representative Paul Tonko (D-NY), this bipartisan, no-cost legislation will, for the first time, unite the federal government and non-federal partners in a mission to treat, prevent and cure Parkinson's, alleviate financial and health burdens on American families, and reduce government spending over time. This legislation establishes an advisory council comprising representatives from federal agencies supporting Parkinson's-related research and services, as well as patients, care partners, researchers, clinicians, and

other non-federal experts, all charged with creating a national plan to coordinate and maximize efforts to prevent and cure Parkinson's disease.

The advisory council will host meetings throughout the year and provide biannual reports to Congress and the Secretary of Health and Human Services containing evaluations of all federally funded programs related to Parkinson's. The reports will include recommendations on priority actions to prevent and cure Parkinson's, improve health outcomes, reduce the financial impact of the disease on patients and the federal government, and limit exposures to environmental risk factors. The goal of the advisory council is to ensure efficient and effective coordination among all federal entities with responsibility for managing, treating, and curing Parkinson's disease. Importantly, this coordination of efforts across the federal government and non-federal stakeholders will create efficiencies by maximizing research opportunities, avoiding duplicative efforts, and allocating resources and expertise where they will be the most impactful.

The National Plan to End Parkinson's Act is a game-changing piece of legislation that provides the pathway for federal agencies, private organizations, the medical community, people and families living with Parkinson's and caregivers to unite in a singular mission to end Parkinson's, alleviate its medical, financial, and emotional burdens on American families, and ease the pressure on public programs like Medicare and Social Security. By advancing this critical legislation, you are supporting the first step in what will be a truly historic and transformative period for those living with Parkinson's disease and their loved ones.

On behalf of the Parkinson's community, we thank the Subcommittee for its support and for the opportunity to submit this testimony. As the Subcommittee looks to advance legislation in the 118th Congress, we urge you to prioritize the National Plan to End Parkinson's Act to find a cure for Parkinson's and improve the quality of life of millions of Americans. On behalf of the more than one million people in the United States living with the disease, thank you for your time and attention. We hope you will consider The Michael J. Fox Foundation a trusted resource as the Subcommittee continues its important work this Congress.

# # #

[i] Michael J. Fox Foundation. Breaking News: Parkinson's Disease Biomarker Found. April 13, 2023. Available at: https://www.michaeljfox.org/news/breaking-news-parkinsons-disease-biomarker-found

[ii] Siderowf A, Concha-Marambio L, Lafontant DE, Farris CM, Ma Y, Urenia PA, Nguyen H, Alcalay RN, Chahine LM, Foroud T, Galasko D, Kieburtz K, Merchant K, Mollenhauer B, Poston KL, Seibyl J, Simuni T, Tanner CM, Weintraub D, Videnovic A, Choi SH, Kurth R, Caspell-Garcia C, Coffey CS, Frasier M, Oliveira LMA, Hutten SJ, Sherer T, Marek K, Soto C; Parkinson's Progression Markers Initiative. Assessment of heterogeneity among participants in the Parkinson's Progression Markers Initiative cohort using α-synuclein seed amplification: a cross-sectional study. Lancet Neurol. 2023 May;22(5):407-417. doi: 10.1016/S1474-4422(23)00109-6. PMID: 37059509.

[iii] Parkinson's Foundation. Statistics. Available at: https://www.parkinson.org/Understanding-Parkinsons/Statistics#:~:text=Approximately%2060%2C000%20Americans%20are%20diagnosed,are%20diagnosed%20before%20age%2050.

[iv] Mantri S, Duda JE, Morley JF. Early and Accurate Identification of Parkinson Disease Among US Veterans. Fed Pract. 2019 Jun;36(Suppl 4):S18-S23. PMID: 31296979; PMCID: PMC6604980

[v] Yang, W., Hamilton, J.L., Kopil, C. et al. Current and projected future economic burden of Parkinson's disease in the U.S.. npj Parkinsons Dis. 6, 15 (2020). https://doi.org/10.1038/s41531-020-0117-1

[vi] Ibid.

[vii] National Institutes of Health. Focus On Parkinson's Disease Research. Available at: https://www.ninds.nih.gov/current-research/focus-disorders/focus-parkinsons-disease-research

[viii] Centers for Disease Control and Prevention, National Center for Health Statistics. National Vital Statistics System, Mortality 1999-2020 on CDC WONDER Online Database, released in 2021. Data are from Multiple Cause of Death Files, 1999-2020, as compiled from data provided by the 57 vital statistics jurisdictions through the Vital Statistics Cooperative Program. Available at: https://wonder.cdc.gov/ucd-icd10.html.

Statement of Troy Burns, MD

House Energy and Commerce Subcommittee Legislative Hearing:

Improving Access to Care for Patients and Supporting Research for Rare Diseases

June 14, 2023

Chairs Rodgers and Guthrie, Ranking Members Pallone and Eshoo, thank you for the opportunity to testify today on ways to improve access to great primary care for patients. I am Dr. Troy Burns, a practicing primary care physician from Leawood, Kansas and founder and Medical Director of ProPartners Healthcare, Kansas City's first Direct Primary Care (DPC) medical practice. I am pleased to present this testimony on behalf of the Direct Primary Care Coalition and the views I express are also my own. Let me begin by offering my special thanks to Representatives Dan Crenshaw, and Kim Schrier, MD for introducing the Medicaid Primary Care Improvement Act, which will be the focus of my remarks today.

Primary care is generally accepted to be the foundation of any effective healthcare system. Efficient healthcare begins with a primary physician who has an ongoing relationship with the patient, full knowledge of their medical and personal history, and is trusted by the patient to be the first source of information, advice, diagnosis, and treatment of their health needs. In the context of this relationship, patients are statistically more likely to receive timely preventive screenings, early detection and treatment of diseases, and are more likely to be encouraged in healthy lifestyle. Primary care improves health, prevents illness and death, and is associated with a more equitable distribution of health in populations.

Unfortunately, in today's post-pandemic world, Americans are experiencing a crisis in access to primary care which leads to unnecessary overutilization of expensive specialty and emergency services and to poorer health outcomes. USA Today reported in February 2023 that more than 100 million Americans are currently without a primary care doctor. And this problem is widespread among Medicaid recipients. In January, a Commonwealth Fund report found "Medicaid's low payment rates for office-based visits have long led to concerns about the quality of care" in fee for service (FFS) based Medicaid managed care practices. So, this legislation is timely and much needed.

H.R. 3836, the Medicaid Primary Care Improvement Act would help clear federal regulatory hurdles at CMS to allow states to innovate in Medicaid by offering low income individuals in Medicaid the choice to have a lasting relationship with a primary care doctor in a DPC practice. Several states, such as Washington and Michigan have tried to do Medicaid pilot programs with DPC. But CMS' denial of a waiver, or a state's concerns that the waiver process would be too difficult, has been a significant barrier to entry into DPC for many states. I would also like to thank Rep. Crenshaw and Dr. Schrier for joining Representatives Smucker and Blumenauer on the Ways and Means Committee in sponsoring the Primary Care Enhancement Act, a bill that clarifies long standing issues in the tax code that keep many Americans with High Deductible Health Plans (HDHP) from choosing a DPC doctor. Together, these two regulatory hurdles are among the most significant policy barriers facing Americans trying to access better, more humane, and more personal primary care from a doctor of their choice with DPC.

What is Direct Primary Care? Direct Primary Care (DPC) is a value-based care delivery model that is growing rapidly and organically among practicing primary care physicians across America. DPC is a membership-based primary care payment model in which patients, their employers or a health benefits payer like Medicaid pay a flat monthly/periodic fee directly to the DPC physician practice in exchange for unrestricted access to their personal physician. Physician services are never billed to a third party on a fee-for-service basis, which eliminates all of the time and expenses associated with filing and refiling insurance claims, negotiating disputed claims, balance billing, adjusting off unpaid charges, and satisfying the insurance

carriers' complex requirements for documentation and coding in order to be reimbursed. As a result of eliminating this significant administrative overhead, DPC physicians provide unparalleled access to their patients including same or next day appointments, visits up to an hour face-to-face with their doctor, virtual visits and direct access to the physician's personal cell phone.

DPC is recognized as an advanced payment model (APM) in which a patient choses a personal primary care physician. As a result of this value-based direct payment model, the DPC physician is uniquely able to offer their patients ample time and accessibility that is required to fulfill the breadth of primary care services, including continuity and accountability of care, proactive preventive care, efficient disease management and assistance in navigating the overall healthcare system. This access to a doctor who knows their patient and is always available has been shown to accomplish the triple aim of healthcare: better population health, enhanced patient experience and lower per capita cost.

Care Anywhere. Being free from the need to "bill for a visit" as is required to get paid in a fee-for-service setting, DPC practices are free to use the most efficient methods to reach and care for their patients. A 2020 Milliman study for the Society of Actuaries found that 99% of DPC practices allow access to care in any modality or setting the patient wants—that could be a traditional visit, when hands on treatment is needed, a virtual visit, a phone call or a secure text or just a web portal communication to refill a prescription or look at a lab result. This became a significant advantage for DPC practices during the pandemic, when other practices were all but shut down. DPC agreements are fundamentally agnostic to the setting of any "visit," leaving the decisions about modality of the care encounter entirely between the patient and their doctor.

DPC is NOT Insurance. It's important to note that DPC is NOT insurance or a replacement for health insurance. Indeed, to have a full, well-rounded health benefit, patients need insurance for expensive and unpredictable care including emergency department care, hospitalization, and specialty care. The data shows that when patients have access to a DPC physician who knows them and is always available, the overutilization of downstream emergency and specialty services is reduced significantly. So, to be clear, DPC practices take no insurance risk

and payments to DPC practices are for medical services, not insurance. Regulations promulgated for the Affordable Care Act (ACA) in Sec. 1301 (a) (3) on the Treatment of DPC Medical Home Plans point this out. There are now over 33 state laws and regulations that categorize DPC as primary care medical service outside of state insurance regulation. By paying for primary care directly and up front, outside of the cost of administering claims for routine primary care evaluation and management, a DPC practice can provide "well care" as insurance against using insurance coverage for "sick care." DPC is an increasingly important tool for patients to manage out of pocket costs outside of primary care which are skyrocketing with the rise in prevalence of HDHP health plans.

Affordable Primary Care. Fees for these services are very affordable and may be paid in full or in part by an employer, by a health plan, as a part of Medicare Advantage or by the patient directly. The Milliman study found that the average adult monthly DPC Fee is $73.92. For about the cost of a cell phone bill, patients receive unfettered access to their personal primary care doctor without any office visit charges, copayments, deductibles or any other fees for DPC physician services. DPC is not concierge medicine. First, DPC is much more affordable than concierge fees which tend to average somewhere between $1500-$3000 per year in advance, and can be as high as $10,000 per year. Second, the DPC fee is often paid for by an employer giving the employee first dollar primary care coverage. Employers, Medicare or Medicaid don't pay for concierge medicine. More importantly, concierge is still FFS medicine. Concierge practices tend to use a "fee-for-non-covered service" model, where a fee is charged for a service such as an executive physical, full genetic screening or some other service not typically covered by insurance. This concierge fee comes with increased access to the doctor and the promise of longer and more convenient visits. But then any charges for visits are paid for using fee for service insurance— claims are often filed by the patient. But there is no such double payment in DPC. The sole payment is for primary care medical services as outlined in a written agreement completely outside of FFS transactions. The value equation in DPC is completely changed. Instead of paying a physician to provide individual services, the periodic DPC fee ensures a lasting relationship with a primary care physician whose incentives are aligned with their patient, who knows their patient and is always available.

DPC in Medicaid? What if we could address these issues in Medicaid—traditionally our poorest and one of our sickest populations— by allowing Medicaid patients access to a personal physician of their choice with DPC? The possibilities for improved care and savings are immense. The Milliman study I referenced above found that when offered alongside a qualified employer health plan, enrollment in DPC lowered the cost of claims and is associated with a reduction in overall member demand for health care services outside primary care. Today many of the HDHP plans employers offer are "skinnier" plans than many Medicaid plans—but plans get paid a lot more for these arrangements than Medicaid pays. So, using the employer experience as a guide let's see what some of the results might be in Medicaid.

The Milliman study showed that:

- DPC members had 19.90% lower claim costs for employers on an unadjusted basis and 12.64% lower claim costs on a risk-adjusted basis during a two-year period.
- DPC members experienced approximately 40% fewer ER visits that those in traditional plans and a 53.6% reduction in ER claims cost.
- DPC members experienced 25.54% lower hospital admissions on an unadjusted basis.

I would ask members of the committee today to go back to their states and ask their Governors and Medicaid directors if they would like to consider an option that could reduce claims cost and hospitalization by upwards of 20 percent. States like Nebraska and New Jersey are already employing DPC programs as choices for state employees' health benefits programs. These DPC programs are universally supported by and have been initiated by state employees' unions. We think that passage of this bill could help bring that possibility to many state Medicaid programs.

CMS – Primary Care First, Direct Contracting and ACO Reach. CMS, through the Center for Medicare & Medicaid Innovation (CMMI) is aware of the progress DPC has made in the private sector and in Medicare Advantage. CMMI has worked closely with DPC Coalition on the rollout of a number of demonstrations. While none of these are true DPC models per se, some programs share attributes of DPC like a monthly fee based payment element and reduced reporting burdens. One fundamental problem DPC doctors have is that most physicians have opted out of the Medicare program altogether. It's not that DPC doctors will not or do not want to treat Medicare beneficiaries, they can and do. But current law requires that any Medicare

participating physician may only receive payment through the Medicare Physician Fee Schedule. Some states have similar requirements for Medicaid. As not to run afoul of the law, most DPC practices opt out of the Medicare program in case a Medicare patient wants to pay a DPC fee out of pocket—or does so without telling the physician that he or she is on Medicare. CMMI has the authority to waive this requirement as a part of any demonstration project like ACO Reach or the newly announced Making Care Primary Model program. The DPC Coalition has proposed several ideas about how to structure a value-based demonstration that would utilize this waiver authority, but to date CMS has chosen not to entertain the idea in this administration or the last one. In the interim, thousands of Medicare patients are paying for DPC services outside of their Medicare coverage, and very likely reducing their cost for Medicare by paying for this fee out of pocket. We would love to see CMS find a way to employ DPC appropriately in Medicare and Medicaid. But getting the details right is important and complicated. This legislation would start that process.

Reporting and Accountability. DPC physicians are directly accountable to our patients. A major reason we have more time to spend with our patients is the elimination of duplicative and often unnecessary reporting to health plans and CMS on measures that mean very little to the patient or the doctor providing the care. But DPC doctors are absolutely data driven and accountable for quality of care, service and cost. We understand that providing the right kind of data is critical to providing excellent primary care to our patients. It has also become crucial in order to demonstrate the value and cost-effectiveness of DPC to our patients and their employers (who often pay for the DPC benefit in an employee based DPC arrangement). We assume that any demonstration or contracting agreement with Medicaid will involve the reporting of data. It's important to understand that this is two-way street. Payers will want to understand that DPC is quality care as outlined in any agreement. But primary care doctors also need real time data on any care patients are getting outside of primary care. Furthermore, the best way to ensure accountability in primary care isn't to require primary care doctors to report CPT-code level data on individual procedures but to measure downstream utilization of medical services outside of the DPC practice. CMS knows that by measuring hospital and specialty care claims filed outside of primary care, they can effectively measure how the patient and the doctor are performing inside the primary care setting. DPC Coalition members who have provided care in programs like ACO Reach are happy to report that in these more recent CMMI

initiatives, those reporting burdens have been somewhat reduced, and that CMS has significantly improved the two-way flow of data. This is a major improvement that we hope will inform further positive changes in such value-based demonstrations. This transparent data sharing on the part of CMS, the states, the Medicaid contractor and the practice is a critical element that must be done correctly in any Medicaid program utilizing DPC.

Prescription Medication Dispensing. DPC practices often provide access to prescription drugs and a variety of ancillary medical services in the clinic as additional value to their patients. The most common services include prescription medications, immunizations, and routine laboratory testing. DPC practices may also negotiate significantly discounted prices for their members with imaging centers (x-rays, ultrasounds, CT scans, or MRIs), and to any needed specialists, physical therapists, dietitians, and other services. These arrangements are done on behalf of patients and usually provide them with significant savings particularly for members with HDHPs.

This is a critical element to good primary care. One of the biggest problems primary care doctors face today is medication adherence. The CDC says 20 to 30 percent of new prescriptions are never filled at the pharmacy and that medication is not taken as prescribed about 50 percent of the time. This is frequently due to increasingly high deductibles with large out of pocket costs. Patients simply cannot afford their share of the prescription cost. The Milliman Study showed in 2020 that about 57 percent of DPC practices dispensed medications on site in states that allow the practice. That number continues to grow. These practices allow their patients to get their meds in the primary care setting at the time of service and at heavily discounted prices —usually for less than the $10 copay that patient would have owed had they used their Pharmacy Benefit Manager (PBM) Prescription card. Patients can also receive initial doses or refills at home by mail order, and in states where dispensing is not allowed, a pharmacy cash discount card can be used so that patients may benefit from affordable prices without PBM reimbursement. Members of the DPC Coalition can participate in a program we call DPCRx to streamline this process, offering lower out of pocket costs for patients.

In Conclusion: Direct Primary Care is an important solution helping to fix primary care delivery across America. It promises affordable access to great primary care outside of the tangles of FFS insurance reimbursement. The data shows DPC delivers for patients with high quality care from a caring doctor of their choice, who knows them well and is almost always available. This value-based APM has been shown to improve health, enhance patient experience with care and decrease overall healthcare costs. I strongly support H.R. 3836, the Medicaid Primary Care Improvement Act. This legislation, along with the Primary Care Enhancement Act, will remove significant regulatory barriers and will pave the way for the Americans that are most in need to access the highest quality primary care available today.

Journal of the Endocrine Society, 2021, Vol. 5, No. 4, 1–16
doi:10.1210/jendso/bvab011
Meta-Analysis

Meta-Analysis

Hormone Therapy, Mental Health, and Quality of Life Among Transgender People: A Systematic Review

Kellan E. Baker,[1,3] Lisa M. Wilson,[1,3] Ritu Sharma,[1,3] Vadim Dukhanin,[1,3] Kristen McArthur,[1,3] and Karen A. Robinson[2,3]

[1]Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, Baltimore, MD 21205, USA; [2]Department of Medicine, Johns Hopkins University School of Medicine, Baltimore, MD, USA; and [3]Johns Hopkins Evidence-Based Practice Center, 615 North Wolfe Street, Baltimore, MD 21205, USA

ORCiD number: 0000-0002-9716-7936 (K. E. Baker).

Abbreviations: BDI, Beck Depression Inventory; ENIGI, European Network for the Investigation of Gender Incongruence; GnRH, gonadotropin-releasing hormone; HADS, Hospital Anxiety and Depression Scale; QOL, quality of life; RCT, randomized controlled trial; SF-36, Short Form-36 Health Survey; WPATH, World Professional Association for Transgender Health.

Received: 5 October 2020; Editorial Decision: 25 January 2021; First Published Online: 2 February 2021; Corrected and Typeset: 19 February 2021.

Abstract

We sought to systematically review the effect of gender-affirming hormone therapy on psychological outcomes among transgender people. We searched PubMed, Embase, and PsycINFO through June 10, 2020 for studies evaluating quality of life (QOL), depression, anxiety, and death by suicide in the context of gender-affirming hormone therapy among transgender people of any age. We excluded case studies and studies reporting on less than 3 months of follow-up. We included 20 studies reported in 22 publications. Fifteen were trials or prospective cohorts, one was a retrospective cohort, and 4 were cross-sectional. Seven assessed QOL, 12 assessed depression, 8 assessed anxiety, and 1 assessed death by suicide. Three studies included trans-feminine people only; 7 included trans-masculine people only, and 10 included both. Three studies focused on adolescents. Hormone therapy was associated with increased QOL, decreased depression, and decreased anxiety. Associations were similar across gender identity and age. Certainty in this conclusion is limited by high risk of bias in study designs, small sample sizes, and confounding with other interventions. We could not draw any conclusions about death by suicide. Future studies should investigate the psychological benefits of hormone therapy among larger and more diverse groups of transgender people using study designs that more effectively isolate the effects of hormone treatment.

Key Words: Transgender, hormone therapy, sex hormones, mental health, systematic review

ISSN 2472-1972

Transgender people are those whose gender identity is different from the sex they were assigned at birth. Estimates of the size of the transgender population vary depending on how the data are collected [1]. In studies that rely on clinical records, estimates range between 1 and 30 people per 100 000 (0.001% to 0.03%) [2]. Studies that focus instead on self-report among nonclinical populations find estimates that range between 0.1% and 2% [2].

Many transgender people seek medical services to affirm their gender identity. According to the *Standards of Care for Transsexual, Transgender, and Gender Non-Conforming People* maintained by the World Professional Association for Transgender Health (WPATH), gender-affirming medical care is different for each individual and may include a variety of services and procedures, such as psychological support, hormone therapy, and surgeries [3]. Hormone therapy, which typically involves estrogens and anti-androgens for transgender women and other trans-feminine people and testosterone for transgender men and other trans-masculine people, is a common component of medical gender affirmation [4]. Because hormone treatment can have a powerful effect on physical appearance, it is often a priority for transgender people seeking medical gender affirmation [5]. Gender-affirming hormone therapy can be managed for most patients by primary care providers, as it typically involves long-term maintenance on doses similar to those used for cisgender patients with conditions such as hypogonadism [6, 7]. Some clinicians require a minimum period of psychological counseling before hormone therapy can be initiated, while others provide hormone therapy on the basis of informed consent [8].

The need for gender-affirming care is often characterized using psychiatric diagnoses such as gender dysphoria, which replaced gender identity disorder in the fifth edition of the *Diagnostic and Statistical Manual of Mental Disorders* (DSM-5) [9]. The 11th International Classification of Diseases (ICD-11) replaces these terms with a diagnosis called gender incongruence (codes: HA60, HA61, HA6Z), which is located in a new chapter on sexual health. These changes clarify that the target of gender-affirming medical interventions is not the person's gender identity itself but rather the clinically significant distress that can accompany a misalignment between gender identity and sex assigned at birth [10]. Some countries have further underscored that transgender identity is not a pathology by recognizing gender affirmation as fundamental to the human right to self-definition and removing requirements that transgender people seeking gender-affirming medical care present with a diagnosis such as gender dysphoria [11].

Several previous reviews have indicated that gender-affirming hormone therapy is associated with psychological benefits that include reductions in depression and anxiety and improvements in quality of life (QOL) among transgender people [12-17]. Most of these reviews did not require a minimum duration of hormone therapy [14-17]. One review that did impose a minimum follow-up requirement is 10 years old [12]. The other that required a minimum of 3 months of therapy included only uncontrolled prospective cohorts, which resulted in a sample of only 3 studies [13]. A comprehensive review without a minimum follow-up period assessed gender-affirming hormone therapy and surgeries only in adolescents [17]. By requiring a minimum duration of hormone treatment but considering all ages and a variety of study designs, we sought to update and more completely summarize the growing evidence base regarding the relationship between gender-affirming hormone therapy and psychological outcomes in transgender people.

Search Strategy and Selection Criteria

This review is one of a series of systematic reviews on gender-affirming care conducted for WPATH to inform the eighth revision of the *Standards of Care*. The protocol is registered on PROSPERO (CRD42018115379) [18], and we followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines in reporting our findings [19].

We searched PubMed, Embase, and PyscINFO from inception to October 2018 and updated the search through June 10, 2020, for studies assessing QOL, depression, anxiety, and death by suicide among transgender participants of any age in the context of gender-affirming hormone therapy [20]. We also reviewed the reference lists of previous reviews and hand-searched the *International Journal of Transgenderism*. Using DistillerSR [21], 2 reviewers independently screened titles, abstracts, and full-text articles. Differences were resolved through consensus adjudication.

We included studies that evaluated the psychological effects of any testosterone, estrogen, or anti-androgen formulation used for gender affirmation. We also considered gonadotropin-releasing hormone (GnRH) analogues used as anti-androgens or for puberty delay. Study participants must have been on hormone therapy for at least 3 months in order to reflect a minimum time for expected onset of effects [3]. Health care provider supervision was not required. We excluded studies that did not state therapy type and duration, including the range for cross-sectional studies. We included studies regardless of language (the search terms were in English) and country of origin, and we accepted any study design except case reports.

We created standardized forms for data extraction using the Systematic Review Data Repository system. The data extracted included participant demographics; study design

and methods; hormone therapy type, dose, and duration; potential confounders such as gender-affirming surgery status; outcome scales [20]; and psychological outcomes. From studies that used the Short Form-36 Health Survey (SF-36) to measure QOL, we extracted scores in all domains [22]. For studies that used measures with depression or anxiety subscales, we extracted only the subscale scores corresponding to the psychological outcomes of interest (eg, the depression subscale of the Minnesota Multiphasic Personality Inventory [MMPI]). We extracted comparisons with cisgender controls or general population norms only when longitudinal findings in a transgender population or comparisons with an untreated transgender control group were not reported. We used WebPlotDigitizer to extract data reported only in figures [23].

Two reviewers independently assessed risk of bias [20]. For randomized controlled trials (RCTs), we used the revised Cochrane tool [24]. For non-randomized studies, we used the Cochrane Risk of Bias Assessment Tool for Non-Randomized Studies of Interventions (ROBINS-I) [25]. One reviewer graded strength of evidence for each outcome using the Agency for Healthcare Research and Quality Methods Guide for Conducting Comparative Effectiveness Reviews [26]. We considered the directionality and magnitude of effects reported in cross-sectional studies as additional context for our evaluation of evidence from trials and prospective and retrospective cohorts. Each strength of evidence assessment was confirmed by a second reviewer.

WPATH provided the research question and reviewed the protocol, evidence tables, and report. WPATH had no role in study design, data collection, analysis, interpretation, or drafting. The corresponding author had full access to all the data and had final responsibility for the decision to submit for publication. The authors are responsible for all content, and statements in this report do not necessarily reflect the official views of or imply endorsement by WPATH.

Results

We retrieved 1753 nonduplicate studies for the broader systematic review project of which this review was a part (Fig. 1). After screening and full-text review for the specific research question on the psychological effects of gender-affirming hormone therapy, 20 studies reported in 22 publications were included (Table 1): 1 RCT [27], 2 before-after trials [28, 29], 12 prospective cohorts reported in 13 publications [30-42], 1 retrospective cohort reported in 2 publications [43, 44], and 4 cross-sectional studies [45-48]. De Vries (2014) [35] reported on a subset of the participants in de Vries (2011) [34] who continued in care. We counted these publications as a single study but extracted and reported data separately because the characteristics of the study's adolescent population changed substantially in the period between the 2 publications. Similarly, Asscheman (2011) [44] reported on an extension of Asscheman (1989) [43]; we counted these as a single study but extracted data separately. In Table 1 and in the subsequent tables for each outcome, studies are ordered first by study design (RCTs, before-after trials, prospective cohorts, retrospective cohorts, and cross-sectional studies); within these categories, studies are presented in the following order according to how the study results were reported: adult transgender women only, adult transgender men only, adult transgender women and transgender men together, and transgender adolescents (no study reported separate results by gender identity for transgender youth). Where multiple studies shared the same study design and population, they are additionally ordered chronologically.

The time frame covered in the included studies began in 1972 [43], but most studies dated from post-2000. Eight studies were conducted in Italy [27-29, 31, 32, 36, 39, 41]; 2 each in Belgium [37, 48], the Netherlands [34, 35, 43, 44], the United States [30, 47], and Spain [38, 45]; and 1 in the United Kingdom [33], Turkey [42], and France [46]. One study recruited participants from Switzerland and Germany [40]. One study was part of the European Network for the Investigation of Gender Incongruence (ENIGI), which is a research collaborative between clinics providing gender-affirming care to transgender people in Ghent (Belgium), Amsterdam (Netherlands), Oslo (Norway), and Hamburg (Germany). The ENIGI study included in this review drew participants only from the Ghent clinic [37].

The study sizes ranged from 20 to 1331, although most had fewer than 60 participants. Fourteen studies reported on testosterone formulations in adult transgender men [27, 29, 31-33, 36, 39-46, 48]. These formulations were typically injectable testosterone cypionate or enanthate, although some studies used long-acting injectable testosterone undecanoate or daily transdermal gels. Ten studies reported on estrogen formulations in adult transgender women, usually in conjunction with an anti-androgen such as cyproterone acetate or spironolactone [28, 31, 33, 36, 37, 39, 43-47]. Estrogen formulations included transdermal, oral, or injectable estradiol (commonly estradiol valerate) or conjugated estrogens. Three studies reported on the psychological effects of GnRH therapy for puberty delay among mixed-gender groups of transgender adolescents [30, 34, 35, 38]. No study reported on hormone therapy among nonbinary people.

All studies that reported information about recruitment drew their participants largely or exclusively from specialized clinics dedicated to providing gender-affirming care for transgender people. These clinics were typically part of larger systems such as university hospitals. Clinic-based

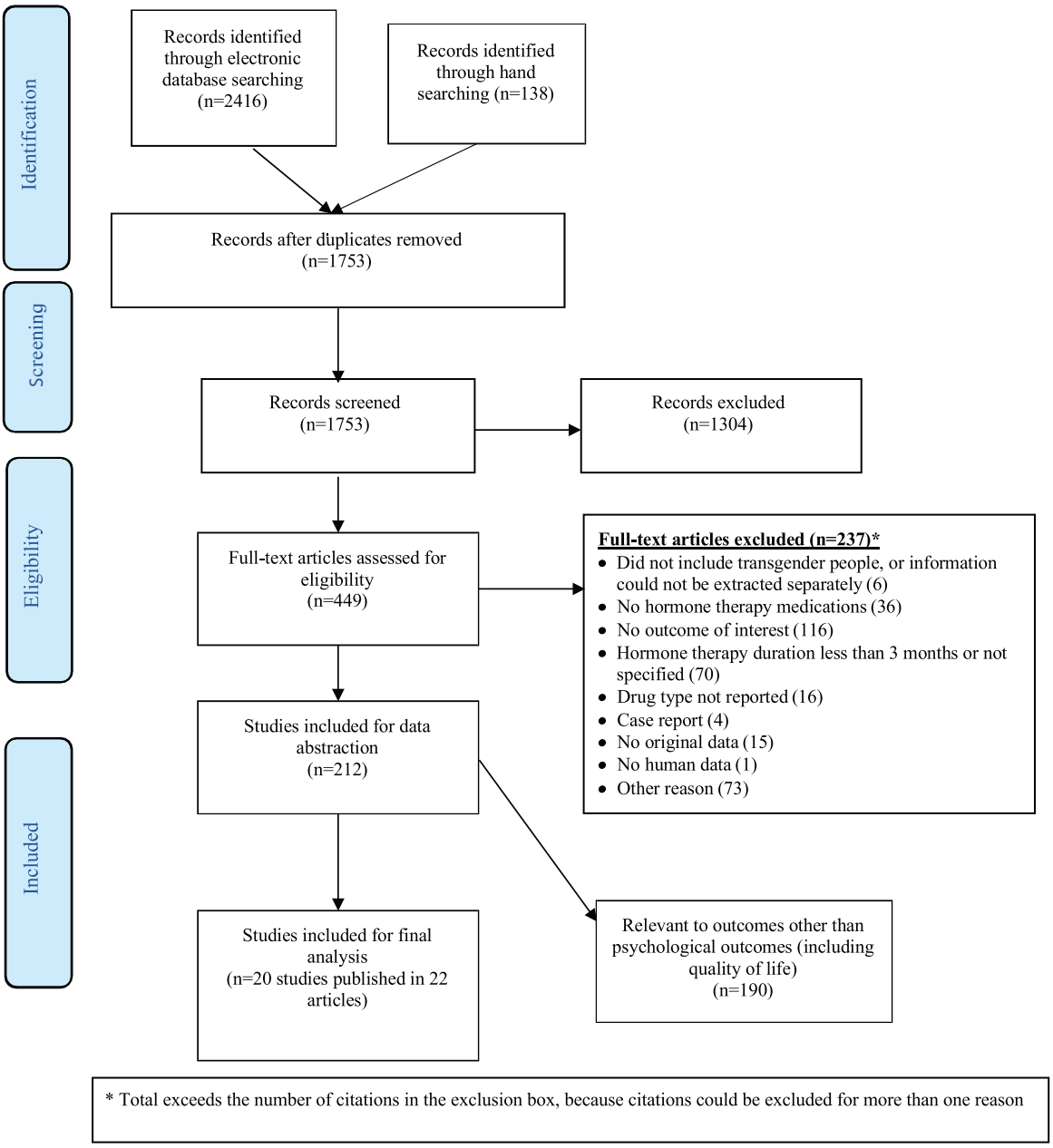


Figure 1. PRISMA flow diagram.

studies often applied strict eligibility criteria that included a period of psychiatric evaluation and a formal diagnosis of gender dysphoria before hormone therapy was initiated. Some studies also reported that psychological counseling was either available or required during the course of hormone therapy. In many cases, hormone therapy was considered a prerequisite for gender-affirming surgeries. The type and timing of gender-affirming surgeries and the proportion of participants for whom hormone therapy and surgeries were assessed simultaneously varied widely: some studies assessed only participants who had not had any type of gender-affirming surgery [27, 28, 30-32, 34, 36, 38-40, 42, 46, 47], while in others some or all participants underwent gender-affirming surgeries during the study period [29, 33, 35, 43-45, 48].

Quality of Life

Seven studies, including 1 RCT [27], 2 before-after trials [28, 29], 2 prospective cohorts [30, 39], and 2 cross-sectional studies [46, 48], assessed QOL (Table 2). An RCT found an improvement of approximately 5.5 points on a 10-point measure of life satisfaction across 3 groups of transgender men (n = 15 each) after 1 year of testosterone treatment ($P < 0.05$) [27]. A before-after trial similarly reported that life satisfaction scores almost

Table 1. Studies Reporting Effects of Gender-Affirming Hormone Therapy on Psychological Outcomes Among Transgender People

Author, year Location Study name	Study design	Start year	Transgender population	Overall N	Age in years	Baseline HT status	Outcomes	GAS status	Risk of bias
Pelusi, 2014 [27] Italy	Randomized controlled trial[a]	NR	Men	45	Mean: 29.5	No previous HT	QOL	No GAS before or during study	High
Gava, 2016 [28] Italy	Before-after trial	NR	Women	40	Mean: 3.2 (range, 19–55)	No previous HT	QOL, Depression	No GAS before or during study	Low
Gava, 2018 [29] Italy	Before-after trial[a]	NR	Men	50	Mean: 30.1 (range, 21–42)	No previous HT	QOL	72% (n = 36) had gonadectomy during study	Serious
Fuss, 2015 [37] Belgium ENIGI (NCT01072825)	Prospective cohort	2010	Women	20	Mean: 33.9 (range, 17–48)	No previous HT	Anxiety	NR	Serious
Costantino, 2013 [32] Italy	Prospective cohort	2001	Men	50	Mean: 29.8	No previous HT	Depression	No GAS before or during study	Serious
Motta, 2018 [41] Italy	Prospective cohort	2013	Men	52	Mean: 28.3	No previous HT	Anxiety	NR	Moderate
Turan, 2018 [42] Turkey	Prospective cohort[b]	NR	Men	37	Mean: 24.6	No previous HT	Depression, Anxiety	No GAS before or during study	Moderate
Metzger, 2019 [40] Switzerland, Germany	Prospective cohort[b]	2013	Men	23	Mean: 27.2 (range, 18–51)	No previous HT	Depression	No GAS before or during study	Moderate
Colizzi, 2014 [31] Italy	Prospective cohort	2008	Women and men	107	Mean: 29.2	No previous HT	Depression, Anxiety	No GAS before or during study	Low
Manieri, 2014 [39] Italy	Prospective cohort	NR	Women and men	83	Mean: 32.7 (women), 30.2 (men)	No previous HT	QOL	No GAS before or during study	Moderate
Fisher, 2016 [36] Italy	Prospective cohort	2012	Women and men	54	Mean: 32.5 (women), 26.3 (men)	No previous HT	Depression	No GAS before or during study	Low
Defreyne, 2018 [33] UK	Prospective cohort	2012	Women and men	155	Median: 27 (range, 18–52)	No previous HT	Depression, Anxiety	Some had GAS during study; % and type NR	Serious
Asscheman, 1989 [43] Netherlands	Retrospective cohort[b,d]	1972	Women and men	425	Median: 32 (women, range, 16–67); 25.4 (men, range, 16–54)	Previous HT for at least 6 months	Death by suicide	78% (n = 235) of transgender women had GAS during study; data NR for transgender men	Serious

Table 1. Continued

Author, year Location Study name	Study design	Start year	Transgender population	Overall N	Age in years	Baseline HT status	Outcomes	GAS status	Risk of bias
Asscheman, 2011 [44] Netherlands	Retrospective cohort[b,d]	1975	Women and men	1331	Mean: 31.4 (women, range, 16–76); 26.1 (men, range, 16–57)	Previous HT for at least 1 year	Death by suicide	87% (n = 834) of transgender women and 94% (n = 343) of transgender men had GAS during study	Serious
Leavitt, 1980 [47] US	Cross-sectional	1976	Women	41	Range, 18–35	54% (n = 22) on HT	Depression	No previous GAS	Serious
Wierckx, 2011 [48] Belgium	Cross-sectional[b]	2009	Men	47	Mean: 37 (range, 22–54)	100% on HT	QOL	100% had GAS, but not within previous year	Serious
Gómez-Gil, 2012 [45] Spain	Cross-sectional	NR	Women and men	187	Mean: 29.9 (range, 15–61)	64% (n = 120) on HT	Depression, Anxiety	42% (n = 79) of all participants and 64% (n = 77) of participants on HT had previous GAS	Serious
Gorin-Lazard, 2012 [46] France	Cross-sectional[b]	NR	Women and men	61	Mean: 34.7	72% (n = 44) on HT	QOL	No previous GAS	Serious
de Vries, 2011 [34] Netherlands	Prospective cohort	2000	Girls and boys	70	Mean: 14.8 (range, 11.3–18.6)	No previous HT	Depression, Anxiety	No GAS before or during study	Moderate
de Vries, 2014 [35] Netherlands	Prospective cohort[b,c]	2000	Girls and boys	55	Mean: 14.8 (range, 11.5–18.5)	No previous HT	Depression, Anxiety	100% had GAS during study	Serious
Achille, 2020 [30] US	Prospective cohort	2013	Girls and boys	50	Mean: 16.2	No previous HT	QOL, Depression	No GAS before or during study	Moderate
López de Lara, 2020 [38] Spain	Prospective cohort[b]	2018	Girls and boys	23	Mean: 16 (range, 14-18)	No previous HT	Depression, Anxiety	No GAS before or during study	Moderate

Abbreviations: ENIGI, European Network for the Investigation of Gender Incongruence; GAS, gender-affirming surgery; HT, hormone therapy; NR, not reported; QOL, quality of life.

[a]25 participants were included in both Pelusi [27] and Gava (2018) [29]

[b]Included a cisgender control group or a comparison to general population norms

[c]All participants were also included in de Vries (2011) [34]

[d]An unknown number of participants were included in both Asscheman (1989) [43] and Asscheman (2011) [44]

Table 2. Effects of Gender-Affirming Hormone Therapy on Quality of Life Among Transgender People

Author, year Study design	Transgender population	Treatment / comparison (n)	QOL measures	Length of treatment	Findings
Pelusi, 2014 [27] RCT[a]	Men	Testoviron depot (15) vs testosterone gel (15) vs testosterone undecanoate (15)	VAS (general life satisfaction)	54 weeks	Mean QOL scores increased from 2.8 to 8.5 ($P < 0.05$) in the testoviron depot arm, from 3.2 to 8.9 ($P < 0.05$) in the testosterone gel arm, and from 2.6 to 8.0 ($P < 0.05$) in the testosterone undecanoate arm.[d] There was no difference across arms.
Gava, 2016 [28] Before-after trial	Women	Cyproterone acetate + estradiol (20) vs leuprolide acetate + estradiol (20)	VAS (general life satisfaction) SF-36	12 months	Mean QOL scores did not change in either arm. No comparisons across arms were reported.
Gava, 2018 [29] Before-after trial[a]	Men	Testosterone undecanoate (25)[c] vs testosterone enanthate (25)[c]	VAS (general satisfaction)	5 years	Mean QOL scores increased from 4.3 ± 3.1 to 8.1 ± 1.8 ($P < 0.001$) in the testosterone undecanoate arm and from 4.3 ± 3.8 to 8.3 ± 1.7 ($P < 0.001$) in the testosterone enanthate arm. No comparisons across arms were reported.
Manieri, 2014 [39] Prospective cohort	Women	HT (56)	WHOQOL	12 months	Mean QOL scores increased from 62.5 to 72.2 ($P < 0.05$).[d]
Manieri, 2014 [39] Prospective cohort	Men	HT (27)	WHOQOL	12 months	Mean QOL scores did not change.
Wierckx, 2011 [48] Cross-sectional[b]	Men	HT (47)[c]	SF-36	At least 3 years	Mean QOL scores on the VT and MH subscales were lower for transgender men than cisgender men (VT subscale: 62.1 ± 20.7 vs 71.9 ± 18.3, $P = 0.002$; MH subscale: 72.6 ± 19.2 vs 79.3 ± 16.4, $P = 0.020$). There were no other differences between transgender men and either cisgender men or cisgender women.
Gorin-Lazard, 2012 [46] Cross-sectional[b]	Women and men	HT (44) vs no HT (17)	SF-36	Median: 20 months (range, 12–42 months)	Mean QOL scores were generally higher in the group receiving HT vs the group not receiving HT (MCS: 51.0 ± 7.7 vs 39.8 ± 12.7, $P = 0.003$; MH subscale: 76.4 ± 14.1 vs 59.1 ± 19.6, $P = 0.004$; RE subscale: 88.6 ± 22.7 vs 54.9 ± 40.7, $P = 0.001$; SF subscale: 83.2 ± 23.3 vs 69.9 ± 24.2, $P = 0.026$). There were no differences in the other subscales.
Achille, 2020 [30] Prospective cohort	Girls and boys	GnRH treatment + HT (47)	Q-LES-Q-SF	12 months	Mean QOL scores did not change.

Abbreviations: GnRH, gonadotropin-releasing hormone; HT, hormone therapy; MCS, Mental Component Summary; MH, mental health; QOL, quality of life; RCT, randomized controlled trial; RE, role functioning/emotional; SF, social functioning; SF-36, Short Form-36 Health Survey; VAS, visual analog scale; VT, vitality; WHOQOL, World Health Organization Quality of Life measure.

[a]10 participants on testosterone enanthate and 15 participants on testosterone undecanoate were included in both Pelusi [27] and Gava (2018) [29]

[b]Included a cisgender control group or a comparison to general population norms

[c]Included participants who had undergone gender-affirming surgery/surgeries, or surgery status not reported

[d]No standard deviations reported

doubled among transgender men (n = 50) over 5 years [29]. A prospective study found a 16% improvement in QOL scores among transgender women (n = 56) after 1 year of treatment ($P < 0.05$) but no change among transgender men (n = 27) [39]. Another before-after trial reported no difference in SF-36 scores among 2 groups of transgender women (n = 20 each) after 1 year [28]. Among adolescents, a mixed-gender prospective cohort (n = 50) showed no difference in QOL scores after a year of endocrine interventions, which included combinations of GnRH analogues and estrogen or testosterone formulations [30]. No study found that hormone therapy decreased QOL scores. We conclude that hormone therapy may improve QOL among transgender people. The strength of evidence for this conclusion is low due to concerns about bias in study designs, imprecision in measurement because of small sample sizes, and confounding by factors such as gender-affirming surgery status.

Depression

Twelve studies, including 1 before-after trial [28], 9 prospective cohorts [30-36, 38, 40, 42], and 2 cross-sectional studies [45, 47], assessed depression (Table 3). A prospective study found that the proportion of transgender men and transgender women (n = 107) showing symptoms of depression decreased from 42% to 22% over 12 months of treatment ($P < 0.001$) [31]. In 2 other prospective cohorts, Beck Depression Inventory (BDI-II) scores improved by more than half among both transgender men (n = 26) and transgender women (n = 28) after 24 months of therapy ($P < 0.001$) [36] and improved from 15.7 ± 12.3 to 8.1 ± 6.2 among transgender men (n = 23) after 6 months ($P < 0.001$) [40]. A fourth prospective study reported improvements of 1.05 points (95% CI: –1.87, –0.22) and 1.42 points (95% CI: –2.61, –0.24) on the 21-point Hospital Anxiety and Depression Scale (HADS) among 91 transgender women and 64 transgender men after 12 months ($P = 0.013$ and $P = 0.019$, respectively) [33]. A before-after trial, however, found no change in BDI-II scores among 2 groups of transgender women (n = 20 each) after 1 year [28]. Two prospective studies reported no difference among transgender men (n = 37) after 24 weeks [42] or among transgender men (n = 50) after 12 months [32], although in the latter study this outcome did not change from a baseline median of 0.0 ("not at all depressed") on an unvalidated 4-point scale. Among adolescents, 2 mixed-gender prospective cohorts (n = 50 and n = 23, respectively) showed improvements in depression scores after 1 year of treatment with GnRH analogues and estrogen or testosterone formulations (both $P < 0.001$) [30, 38]. Another prospective study reported that BDI scores improved almost by half among adolescents (n = 41) after a mean of 1.88 years of treatment with GnRH analogues to delay puberty ($P = 0.004$) [34]. The overall improvement after several subsequent years of testosterone or estrogen therapy in this cohort (n = 32) was smaller, however, resulting in no significant change from baseline [35]. No study found that hormone therapy increased depression. We conclude that hormone therapy may decrease depression among transgender people. The strength of evidence for this conclusion is low due to concerns about study designs, small sample sizes, and confounding.

Anxiety

Eight studies, including 7 prospective cohorts [31, 33-35, 37, 38, 41, 42] and 1 cross-sectional study [45], assessed anxiety (Table 4). One prospective study found that Symptom Checklist 90-Revised scores indicating a probable anxiety disorder among a mixed-gender group of adults (n = 107) improved from borderline to normal over 12 months ($P < 0.001$) [31]. Another prospective study, however, did not find a difference in HADS anxiety scores among either transgender men (n = 64) or transgender women (n = 91) after 1 year [33], and a third study reported no change in the number of transgender men (6/52, 12%) with a diagnosed anxiety disorder after 7 months [41]. Likewise, 2 other prospective studies found no difference in anxiety scores among transgender men (n = 37) after 24 weeks of treatment [42] or transgender women (n = 20) after 12 months [37], although this latter finding represented no change from a baseline median score of 0 (answering "no" to the question, "do you feel anxious?") on an unvalidated 3-point scale. Among adolescents, 1 prospective study saw mean anxiety scores in a mixed-gender group (n = 23) improve from 33.0 ± 7.2 to 18.5 ± 8.4 after 1 year ($P < 0.001$) [38], but another reported no changes in anxiety after approximately 2 years of puberty delay treatment with GnRH analogues and 4 years of hormone therapy (n = 32) [35]. No study found that hormone therapy increased anxiety. We conclude that hormone therapy may decrease anxiety among transgender people. The strength of evidence for this conclusion is low due to concerns about study designs, small sample sizes, and confounding.

Death by Suicide

One retrospective study reported in 2 publications assessed death by suicide (Table 5) [43, 44]. The first publication reported that 3 transgender women in the Amsterdam gender dysphoria study cohort (n = 303) died by suicide between 1972 and 1986 [43]. The authors calculated the number of suicide deaths expected in an age-matched stratum of

Table 3. Effects of Gender-Affirming Hormone Therapy on Depression Among Transgender People

Author, year Study design	Transgender population	Treatment / comparison (n)	Depression measures	Length of treatment	Findings
Gava, 2016 [28] Before-after trial	Women	Cyproterone acetate + estradiol (20) vs Leuprolide acetate + estradiol (20)	BDI-II	12 months	Mean depression scores did not change in either arm. No comparisons across arms were reported.
Fisher, 2016 [37] Prospective cohort	Women	HT (28)	BDI-II	24 months	Mean depression score decreased from 10.12 to 4.58 ($P < 0.001$).[d,e]
Defreyne, 2018 [33] Prospective cohort	Women	HT (91)[c]	HADS (depression subscale)	1 year	Median depression score decreased by 1.05 (95% CI: −1.87, −0.22) on a 21-point scale ($P = 0.013$).
Costantino, 2013 [32] Prospective cohort	Men	HT (50)	Ad hoc questionnaire	12 months	Depression score did not change from a median of 0.0 at baseline (IQR: 0.0, 1.0).
Fisher, 2016 [36] Prospective cohort	Men	HT (26)	BDI-II	24 months	Mean depression score decreased from 9.31 to 4.25 ($P < 0.001$).[d,e]
Defreyne, 2018 [33] Prospective cohort	Men	HT (64)[c]	HADS (depression subscale)	1 year	Median depression score decreased by 1.42 (95% CI: −2.61, −0.24) on a 21-point scale ($P = 0.019$).
Turan, 2018 [42] Prospective cohort[b]	Men	HT (37)	SCL-90-R (depression subscale)	24 weeks	Mean depression score did not change.
Metzger, 2019 [40] Prospective cohort[b]	Men	HT (23)	BDI-II	6 months	Mean depression score decreased from 15.7 ± 12.3 to 8.1 ± 6.2 ($P < 0.001$).
Colizzi, 2014 [31] Prospective cohort	Women and men	HT (107)	Zung SDS SCL-90-R (depression subscale)	12 months	Mean Zung SDS score improved from 48.40 ± 10.5 to 39.98 ± 10.79 ($P < 0.001$), and the proportion with Zung SDS scores indicating mild, moderate, or severe depression (vs no depression) decreased from 42% to 22% ($\chi^2 = 19.05$, $P < 0.001$). Mean SCL-90-R score decreased from 0.83 ± 0.74 to 0.51 ± 0.49 ($P < 0.001$), which represents an improvement from possible borderline depression to no depression.
Leavitt, 1980 [47] Cross-sectional	Women	HT (22) vs No HT (19)	MMPI (depression subscale)	At least 12 months	Mean depression score was lower in the group receiving HT vs the group not receiving HT (53.1 ± 14.7 vs 65.7 ± 11.2, $P = 0.004$).

Table 3. Continued

Author, year Study design	Transgender population	Treatment / comparison (n)	Depression measures	Length of treatment	Findings
Gómez-Gil, 2012 [45] Cross-sectional	Women and men	HT (120)[c] vs No HT (67)[c]	HADS (depression subscale)	Mean: 11.0 years (women, range, 1–46 years); 4.7 years (men, range, 1–22 years)	Mean depression score was lower in the group receiving HT vs the group not receiving HT (3.3 ± 3.2 vs 5.2 ± 4.2, $P = 0.002$).[f] The proportion with scores indicating depression (vs no depression) was larger in the group not receiving HT (31% vs 8%, $\chi^2 = 16.46$, $P = 0.001$).[f]
de Vries, 2011 [34] Prospective cohort	Girls and boys	GnRH treatment (41)	BDI	1.88 years	Mean depression score decreased from 8.31 ± 7.12 to 4.95 ± 6.72 ($P = 0.004$).
de Vries, 2014 [35] Prospective cohort[a,b]	Girls and boys	GnRH treatment + HT (32)[c]	BDI	5.9 years	Mean depression score did not change.
Achille, 2020 [30] Prospective cohort	Girls and boys	GnRH treatment + HT (47)	CESD-R, PHQ-9 (modified for adolescents)	12 months	Mean CESD-R score decreased from 21.4 to 13.9 ($P < 0.001$);[d] a score of <16 indicates no clinical depression. Mean PHQ-9 score decreased from 9.0 to 5.4 ($P < 0.001$).[d]
López de Lara, 2020 [38] Prospective cohort[b]	Girls and boys	GnRH treatment + HT (23)	BDI-II	1 year	Mean depression score decreased from 19.3 ± 5.5 to 9.7 ± 3.9 ($P < 0.001$).

Abbreviations: BDI/BDI-II, Beck Depression Inventory; GAS, gender-affirming surgery; GnRH, gonadotropin-releasing hormone; HADS, Hospital Anxiety and Depression Scale; HT, hormone therapy; IQR, interquartile range; MMPI, Minnesota Multiphasic Personality Inventory; NA, not applicable; SCL-90-R, Symptom Checklist 90-Revised; Zung SDS, Zung Self-Rating Depression Scale.

[a]All participants were also included in de Vries (2011) [34]

[b]Included a cisgender control group or a comparison to general population norms

[c]Included participants who had undergone gender-affirming surgery/surgeries, or surgery status not reported

[d]No standard deviations reported

[e]Adjusted for age, gender role, and surgery status

[f]Adjusted for age, gender, and education level

Table 4. Effects of Gender-Affirming Hormone Therapy on Anxiety Among Transgender People

Author, year	Transgender population	Treatment / comparison (n)	Anxiety measures	Length of treatment	Findings
Fuss, 2015 [37] Prospective cohort	Women	HT (20)[c]	Ad hoc questionnaire	12 months	Anxiety score did not change from a median of 0.0 at baseline.
Defreyne, 2018 [33] Prospective cohort	Women	HT (91)[c]	HADS (anxiety subscale)	1 year	Median anxiety score did not change.
Defreyne, 2018 [33] Prospective cohort	Men	HT (64)[c]	HADS (anxiety subscale)	1 year	Median anxiety score did not change.
Motta, 2018 [41] Prospective cohort	Men	HT (46)[c]	DSM	7 months	Proportion diagnosed with an anxiety disorder (6/46, 12%) did not change.
Turan, 2018 [42] Prospective cohort[b]	Men	HT (37)	SCL-90-R (anxiety subscale)	24 weeks	Mean anxiety score did not change.
Colizzi, 2014 [31] Prospective cohort	Women and men	HT (107)	SCL-90-R (anxiety subscale) Zung SAS	12 months	Mean SCL-90-R score decreased from 1.05 ± 0.95 to 0.54 ± 0.56 ($P < 0.001$), which represents an improvement from borderline anxiety disorder to no anxiety disorder. Mean Zung SAS score improved from 44.91 ± 9.59 to 37.90 ± 8.97 ($P < 0.001$), and the proportion with Zung SAS scores indicating mild, moderate, or severe anxiety (vs no anxiety) decreased from 50% to 17% ($\chi^2 = 33.03$, $P < 0.001$).
Gómez-Gil, 2012 [45] Cross-sectional	Women and men	HT (120)[c] vs No HT (67)[c]	HADS (anxiety subscale) SADS	Mean: 11.0 years (women, range, 1-46 years); 4.7 years (men, range, 1-22 years)	Mean HADS and SADS scores were lower in the group receiving HT vs the group not receiving HT (6.4 ± 3.7 vs 9.0 ± 4.0, $P = 0.001$; 8.5 ± 7.8 vs 11.0 ± 7.3, $P = 0.038$, respectively).[d] The proportion with scores indicating anxiety (vs no anxiety) was higher in the group not receiving HT ($\chi^2 = 14.46$, $P < 0.001$).[d]
de Vries, 2011 [34] Prospective cohort	Girls and boys	GnRH treatment (41)	STAI (trait subscale)	1.88 years	Mean anxiety score did not change.
de Vries, 2014 [35] Prospective cohort[a,b]	Girls and boys	GnRH treatment + HT (32)[c]	STAI (trait subscale)	5.9 years	Mean anxiety score did not change.
López de Lara, 2020 [38] Prospective cohort[b]	Girls and boys	GnRH treatment + HT (23)	STAI (trait subscale)	1 year	Mean anxiety score decreased from 33.0 ± 7.2 to 18.5 ± 8.4 ($P < 0.001$).

Abbreviations: BAI, Beck Anxiety Inventory; DSM, Diagnostic and Statistical Manual of Mental Disorders; GAS, gender-affirming surgery; GnRH, gonadotropin-releasing hormone; HADS, Hospital Anxiety and Depression Scale; HT, hormone therapy; IQR, interquartile range; SADS, Social Avoidance and Distress Scale; SCL-90-R, Symptom Checklist 90-Revised; STAI, State-Trait Anxiety Inventory; Zung SAS, Zung Self-Rating Anxiety Scale.

[a]All participants were also included in de Vries (2011) [34]

[b]Included a cisgender control group or a comparison to general population norms

[c]Included participants who have undergone gender-affirming surgery/surgeries, or surgery status not reported

[d]Adjusted for age, gender, and education level

the general male Dutch population over this period to be 0.208. No data were reported for transgender men (n = 122). An update to this study reported 17 deaths by suicide among transgender women (n = 966) and 1 among transgender men (n = 365) between 1975 and 2007 [44]. The age- and sex-stratified standardized mortality ratios were 5.70 (95% CI: 4.93, 6.54) and 2.22 (95% CI: 0.53, 6.18), respectively. The risk of bias for this study was serious due to the difficulty of identifying appropriate comparison groups and uncontrolled confounding by surgery

Table 5. Effects of Gender-Affirming Hormone Therapy on Death by Suicide Among Transgender People

Author, year	Transgender population	Treatment / comparison (n)	Measures	Length of treatment	Findings
Asscheman, 1989 [43] Retrospective cohort[a,b]	Women	HT (303)[c]	Death by suicide (confirmed by autopsy report)	Median: 4.4 years (range, 6 months to 13 years)	3 transgender women (1%) died by suicide between 1972 and 1986. The adjusted number of suicide deaths expected among the general Dutch male population was 0.208.
Asscheman, 2011 [44] Retrospective cohort[a,b]	Women	HT (966)[c]	Death by suicide (confirmed by medical report or physician information)	Median: 18.6 years (range, 0.7–44.5 years)	17 transgender women (2%) died by suicide between 1975 and 2007. The age-stratified SMR compared to the general Dutch male population was 5.70 (95% CI: 4.93, 6.54).
Asscheman, 1989 [43] Retrospective cohort[a,b]	Men	HT (122)[c]	Death by suicide (confirmation procedure NR)	Median: 3.6 years (range, 6 months to 13 years)	No deaths by suicide among transgender men were reported during the study period.
Asscheman, 2011 [44] Retrospective cohort[a,b]	Men	HT (365)[c]	Death by suicide (confirmed by medical report or physician information)	Median: 18.4 years (range, 4.7–42.6 years)	1 transgender man (0.3%) died by suicide between 1975 and 2007. The age-stratified SMR compared to the general Dutch female population was 2.22 (95% CI: 0.53, 6.18).

Abbreviations: HT, hormone therapy; NR, not reported; SMR, standardized mortality ratio.
[a]An unknown number of participants were included in both Asscheman (1989) [43] and Asscheman (2011) [44]
[b]Included a cisgender control group or a comparison to general population norms
[c]Includes participants who had undergone gender-affirming surgery/surgeries, or surgery status not reported

status and socioeconomic variables such as unemployment. We cannot draw any conclusions on the basis of this single study about whether hormone therapy affects death by suicide among transgender people.

Discussion

This systematic review of 20 studies found evidence that gender-affirming hormone therapy may be associated with improvements in QOL scores and decreases in depression and anxiety symptoms among transgender people. Associations were similar across gender identity and age. The strength of evidence for these conclusions is low due to methodological limitations (Table 6). It was impossible to draw conclusions about the effects of hormone therapy on death by suicide.

Uncontrolled confounding was a major limitation in this literature. Many studies simultaneously assessed different types of gender-affirming care and did not control for gender-affirming surgery status, making it difficult to isolate the effects of hormone therapy. Others failed to report complete information about surgery status. Additional factors that may influence both access to care and psychological outcomes, including extent of social or legal gender affirmation and exposure to determinants of health such as discrimination, were typically not considered. In addition, some evidence indicates that cyproterone acetate, a common anti-androgen assessed in many studies alongside estrogen therapy, may increase depression, which may be a source of confounding [49].

Another source of potential bias was recruitment of participants from specialized clinics that impose strict diagnostic criteria as a prerequisite for gender-affirming care. The dual role of clinicians and researchers as both gatekeepers and investigators may force transgender study participants to over- or understate aspects of their mental health in order to access gender-affirming care [8]. Similarly, transgender clinic patients may feel that they cannot opt out of research-related activities, which is a serious concern for the validity of psychological outcome measurements.

Clinic-based recruitment also overlooks transgender people who cannot access these clinics for financial or other reasons and misses those whose need for gender affirmation does not fit into current medical models. This is a particular concern for nonbinary and other gender-diverse people, for whom a model of gender affirmation as a linear transition from one binary gender to another is inaccurate [50].

Most studies used well-known scales for measuring psychological outcomes. None of these scales, however, have been specifically validated for use in transgender populations [51]. Furthermore, many scales are normed

Table 6. Strength of Evidence of Studies that Evaluate the Psychological Effects of Hormone Therapy Among Transgender People

Outcome	Number of studies (n)	Strength of evidence	Summary[a]
Quality of life	1 randomized controlled trial [27] (45)[b] 2 before-after trials [28, 29] (65)[b] 2 prospective cohorts [30, 39] (133) 2 cross-sectional studies [46, 48] (108)	Low[e]	Hormone therapy may improve quality of life among transgender people.[g]
Depression	1 before-after trial [28] (40) 9 prospective cohorts [30-36, 38, 40, 42] (569)[c] 2 cross-sectional [45, 47] (228)	Low[e]	Hormone therapy may alleviate depression among transgender people.[g]
Anxiety	7 prospective cohorts [31, 33-35, 37, 38, 41, 42] (464)[c] 1 cross-sectional [45] (187)	Low[e]	Hormone therapy may alleviate anxiety among transgender people.[g]
Death by suicide	1 retrospective cohort [43, 44] (1756)[d]	Insufficient[f]	There is insufficient evidence to draw a conclusion about the effect of hormone therapy on death by suicide among transgender people.

[a]Due to similarity of findings, the summary is the same for transgender men and transgender women and for adolescents and adults
[b]25 participants are included in both Pelusi [27] and Gava (2018) [29] and are counted once
[c]All 55 participants in de Vries (2014) [35] were also included among the 70 participants in de Vries (2011) [34] and are counted once
[d]An unknown number of participants were included in both Asscheman (1989) [43] and Asscheman (2011), [44] so the unique sample size is smaller than indicated here
[e]Evidence downgraded due to study limitations, including uncontrolled confounding, and imprecision because of small sample sizes
[f]Evidence downgraded due to study limitations, including confounding and a lack of meaningful comparison groups, and imprecision in measurement of a rare event
[g]The body of cross-sectional evidence tended to align with the conclusion

separately for (presumed cisgender) men and women [52]. Inconsistency in identification of appropriate general population norms hinders comparisons between transgender and cisgender groups, which is a major related research question that requires further investigation.

Beyond methodological concerns in the studies we assessed, our review has other limitations. First, it is likely subject to publication bias, as we may have missed studies not published in the peer-reviewed literature. Second, a number of potentially relevant studies could not be included because the authors did not report on a minimum of 3 months of treatment or did not clearly state the type and/or duration of therapy, including the range for cross-sectional studies [53-65]. Finally, even where outcome measurements were similar across studies, heterogeneity in study designs, study populations, intervention characteristics, and reporting of results (ie, some studies reported results separately by gender identity, while others did not), prevented us from quantitatively pooling results.

More research is needed to further explore the relationship between gender-affirming hormone therapy and QOL, death by suicide, and other psychological outcomes, especially among adolescents. Future studies should investigate these outcomes in larger groups of diverse participants recruited outside clinical settings. Studies assessing the relationship between gender-affirming hormone therapy and mental health outcomes in transgender populations should be prospective or use strong quasi-experimental designs; consistently report type, dose, and duration of hormone therapy; adjust for possible confounding by gender-affirming surgery status; control for other variables that may independently influence psychological outcomes; and report results separately by gender identity. Despite the limitations of the available evidence, however, our review indicates that gender-affirming hormone therapy is likely associated with improvements in QOL, depression, and anxiety. No studies showed that hormone therapy harms mental health or quality of life among transgender people. These benefits make hormone therapy an essential component of care that promotes the health and well-being of transgender people.

Acknowledgments

Financial Support: This review was partly funded by the World Professional Association for Transgender Health.

Author Contributions: R.S. developed and implemented the search strategy with input from K.B., L.W., and K.R. K.B., L.W., R.S., V.D., K.M., and K.R. screened and assessed studies, extracted data, and graded strength of evidence. K.B. wrote the report, which was reviewed by all co-authors.

Additional Information

Correspondence: Kellan E. Baker, MPH, MA, Department of Health Policy and Management, Johns Hopkins Bloomberg School of Public Health, 624 North Broadway, Baltimore, MD 21205, USA. Email: [redacted]

Disclosure Summary: This review was partially funded by the World Professional Association for Transgender Health (WPATH). The authors of this manuscript are responsible for its content. Statements in the manuscript do not necessarily reflect the official views of or imply endorsement by WPATH.

Data Availability: Some or all data generated or analyzed during this study are included in this published article or in the data repository listed in the References.

References

1. Collin L, Reisner SL, Tangpricha V, Goodman M. Prevalence of transgender depends on the "case" definition: a systematic review. *J Sex Med*. 2016;**13**(4):613-626.
2. Goodman M, Adams N, Corneil T, Kreukels B, Motmans J, Coleman E. Size and distribution of transgender and gender nonconforming populations: a narrative review. *Endocrinol Metab Clin North Am*. 2019;**48**(2):303-321.
3. Coleman E, Bockting W, Botzer M, et al. Standards of care for the health of transsexual, transgender, and gender-nonconforming people, version 7. *Int J Transgenderism*. 2012;**13**(4):165-232.
4. Hembree WC, Cohen-Kettenis PT, Gooren L, et al. Endocrine treatment of gender-dysphoric/gender-incongruent persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab*. 2017;**102**(11):3869-3903.
5. James SE, Herman JL, Rankin S, Keisling M, Mottet L, Anafi M. *The Report of the 2015 U.S. Transgender Survey*. National Center for Transgender Equality; 2016.
6. Deutsch MB, ed. Guidelines for the primary and gender-affirming care of transgender and gender nonbinary people. 2016. Accessed December 19, 2020. https://transcare.ucsf.edu/guidelines
7. Wylie K, Knudson G, Khan SI, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. *Lancet*. 2016;**388**(10042):401-411.
8. Schulz SL. The informed consent model of transgender care: an alternative to the diagnosis of gender dysphoria. *J Humanist Psychol*. 2018;**58**(1):72-92.
9. American Psychiatric Association. *Diagnostic and Statistical Manual of Mental Disorders*. 5th ed. American Psychiatric Association; 2013.
10. Robles R, Fresán A, Vega-Ramírez H, et al. Removing transgender identity from the classification of mental disorders: a Mexican field study for ICD-11. *Lancet Psychiatry*. 2016;**3**(9):850-859.
11. Arístegui I, Radusky PD, Zalazar V, Romero M, Schwartz J, Sued O. Impact of the Gender Identity Law in Argentinean transgender women. *Int J Transgenderism*. 2017;**18**(4):446-456.
12. Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010;**72**(2):214-231.
13. White Hughto JM, Reisner SL. A systematic review of the effects of hormone therapy on psychological functioning and quality of life in transgender individuals. *Transgend Health*. 2016;**1**(1):21-31.
14. Costa R, Colizzi M. The effect of cross-sex hormonal treatment on gender dysphoria individuals' mental health: a systematic review. *Neuropsychiatr Dis Treat*. 2016;**12**:1953-1966.
15. Nobili A, Glazebrook C, Arcelus J. Quality of life of treatment-seeking transgender adults: a systematic review and meta-analysis. *Rev Endocr Metab Disord*. 2018;**19**(3):199-220.
16. Rowniak S, Bolt L, Sharifi C. Effect of cross-sex hormones on the quality of life, depression and anxiety of transgender individuals: a quantitative systematic review. *JBI Database System Rev Implement Rep*. 2019;**17**(9):1826-1854.
17. Mahfouda S, Moore JK, Siafarikas A, et al. Gender-affirming hormones and surgery in transgender children and adolescents. *Lancet Diabetes Endocrinol*. 2019;**7**(6):484-498.
18. Sharma R, Robinson K, Wilson L, Baker KE. Effects of hormone therapy in transgender people. Accessed December 19, 2020. https://www.crd.york.ac.uk/prospero/display_record.php?RecordID=115379
19. Moher D, Liberati A, Tetzlaff J, Altman DG; PRISMA Group. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *BMJ*. 2009;**339**:b2535.
20. Baker KE, Wilson LM, Sharma R, Dukhanin V, McArthur K, Robinson KA. Data associated with the publication: Hormone therapy, mental health, and quality of life among transgender people: a systematic review. *Johns Hopkins Univ Data Arch*. **V1**. doi: 10.7281/T1/E70MXR.
21. *Evidence Partners*. DistillerSR [software]; 2020.
22. Ware JE Jr, Kosinski M, Bayliss MS, McHorney CA, Rogers WH, Raczek A. Comparison of methods for the scoring and statistical analysis of SF-36 health profile and summary measures: summary of results from the Medical Outcomes Study. *Med Care*. 1995;**33**(4 Suppl):AS264-AS279.
23. Rohatgi A. WebPlotDigitizer: an HTML5-based online tool for to extract numerical data from plot images. 2020. https://automeris.io/WebPlotDigitizer/index.html
24. Sterne JAC, Savović J, Page MJ, et al. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ*. 2019;**366**:l4898.
25. Sterne JA, Hernán MA, Reeves BC, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. *BMJ*. 2016;**355**:i4919.
26. Berkman ND, Lohr KN, Ansari MT, et al. Grading the strength of a body of evidence when assessing health care interventions: an EPC update. *J Clin Epidemiol*. 2015;**68**(11):1312-1324.
27. Pelusi C, Costantino A, Martelli V, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med*. 2014;**11**(12):3002-3011.
28. Gava G, Cerpolini S, Martelli V, Battista G, Seracchioli R, Meriggiola MC. Cyproterone acetate vs leuprolide acetate in combination with transdermal oestradiol in transwomen: a comparison of safety and effectiveness. *Clin Endocrinol (Oxf)*. 2016;**85**(2):239-246.
29. Gava G, Mancini I, Cerpolini S, Baldassarre M, Seracchioli R, Meriggiola MC. Testosterone undecanoate and testosterone

enanthate injections are both effective and safe in transmen over 5 years of administration. *Clin Endocrinol (Oxf)*. 2018;**89**(6):878-886.
30. Achille C, Taggart T, Eaton NR, et al. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. *Int J Pediatr Endocrinol*. 2020;**2020**:8.
31. Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology*. 2014;**39**:65-73.
32. Costantino A, Cerpolini S, Alvisi S, Morselli PG, Venturoli S, Meriggiola MC. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther*. 2013;**39**(4):321-335.
33. Defreyne J, T'Sjoen G, Bouman WP, Brewin N, Arcelus J. Prospective evaluation of self-reported aggression in transgender persons. *J Sex Med*. 2018;**15**(5):768-776.
34. de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. *J Sex Med*. 2011;**8**(8):2276-2283.
35. de Vries AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. *Pediatrics*. 2014;**134**(4):696-704.
36. Fisher AD, Castellini G, Ristori J, et al. Cross-sex hormone treatment and psychobiological changes in transsexual persons: two-year follow-up data. *J Clin Endocrinol Metab*. 2016;**101**(11):4260-4269.
37. Fuss J, Hellweg R, Van Caenegem E, et al. Cross-sex hormone treatment in male-to-female transsexual persons reduces serum brain-derived neurotrophic factor (BDNF). *Eur Neuropsychopharmacol*. 2015;**25**(1):95-99.
38. López de Lara D, Pérez Rodríguez O, Cuellar Flores I, et al. Evaluación psicosocial en adolescentes transgénero. *An Pediatría*. 2020;**93**(1):41-48.
39. Manieri C, Castellano E, Crespi C, et al. Medical treatment of subjects with gender identity disorder: the experience in an Italian Public Health Center. *Int J Transgenderism*. 2014;**15**(2):53-65.
40. Metzger NY, Boettger S. The effect of testosterone therapy on personality traits of trans men: a controlled prospective study in Germany and Switzerland. *Psychiatry Res*. 2019;**276**:31-38.
41. Motta G, Crespi C, Mineccia V, Brustio PR, Manieri C, Lanfranco F. Does testosterone treatment increase anger expression in a population of transgender men? *J Sex Med*. 2018;**15**(1):94-101.
42. Turan Ş, Aksoy Poyraz C, Usta Sağlam NG, et al. Alterations in body uneasiness, eating attitudes, and psychopathology before and after cross-sex hormonal treatment in patients with female-to-male gender dysphoria. *Arch Sex Behav*. 2018;**47**(8):2349-2361.
43. Asscheman H, Gooren LJ, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism*. 1989;**38**(9):869-873.
44. Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011;**164**(4):635-642.
45. Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, et al. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology*. 2012;**37**(5):662-670.
46. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med*. 2012;**9**(2):531-541.
47. Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis*. 1980;**168**(11):693-697.
48. Wierckx K, Van Caenegem E, Elaut E, et al. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011;**8**(12):3379-3388.
49. Heinemann LA, Will-Shahab L, van Kesteren P, Gooren LJ; Collaborating Centers. Safety of cyproterone acetate: report of active surveillance. *Pharmacoepidemiol Drug Saf*. 1997;**6**(3):169-178.
50. Reisner SL, Hughto JMW. Comparing the health of non-binary and binary transgender adults in a statewide non-probability sample. *Plos One*. 2019;**14**(8):e0221583.
51. Thompson HM, Reisner SL, VanKim N, Raymond HF. Quality-of-life measurement: assessing the WHOQOL-BREF scale in a sample of high-HIV-risk transgender women in San Francisco, California. *Int J Transgend*. 2015;**16**(1):36-48.
52. Webb A, Heyne G, Holmes J, Peta J. Assessment norms for gender and implications for transgender, nonbinary populations. *Division 44 Newsletter*. 2016. Accessed June 9, 2020. https://www.apadivisions.org/division-44/publications/newsletters/division/2016/04/nonbinary-populations
53. Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med*. 2014;**11**(1):119-126.
54. Gorin-Lazard A, Baumstarck K, Boyer L, et al. Hormonal therapy is associated with better self-esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis*. 2013;**201**(11):996-1000.
55. Gómez-Gil E, Vidal-Hagemeijer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *J Pers Assess*. 2008;**90**(4):368-374.
56. Oda H, Kinoshita T. Efficacy of hormonal and mental treatments with MMPI in FtM individuals: cross-sectional and longitudinal studies. *BMC Psychiatry*. 2017;**17**(1):256.
57. Elaut E, De Cuypere G, De Sutter P, et al. Hypoactive sexual desire in transsexual women: prevalence and association with testosterone levels. *Eur J Endocrinol*. 2008;**158**(3):393-399.
58. Warmuz-Stangierska I, Stangierski A, Ziemnicka K, et al. Emotional functions in transsexuals after the first step in physical transformation. *Endokrynol Pol*. 2015;**66**(1):47-52.
59. Colton Meier SL, Fitzgerald KM, Pardo ST, Babcock J. The effects of hormonal gender affirmation treatment on mental health in female-to-male transsexuals. *J Gay Lesbian Ment Health*. 2011;**15**(3):281-299.

60. Davis SA, Colton Meier S. Effects of testosterone treatment and chest reconstruction surgery on mental health and sexuality in female-to-male transgender people. *Int J Sex Health*. 2014;**26**(2):113-128.
61. Keo-Meier CL, Herman LI, Reisner SL, Pardo ST, Sharp C, Babcock JC. Testosterone treatment and MMPI-2 improvement in transgender men: a prospective controlled study. *J Consult Clin Psychol*. 2015;**83**(1):143-156.
62. Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res*. 2006;**15**(9):1447-1457.
63. Gooren LJ, Sungkaew T, Giltay EJ, Guadamuz TE. Cross-sex hormone use, functional health and mental well-being among transgender men (Toms) and Transgender Women (Kathoeys) in Thailand. *Cult Health Sex*. 2015;**17**(1):92-103.
64. van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf)*. 1997;**47**(3):337-342.
65. Wiepjes CM, den Heijer M, Bremmer MA, et al. Trends in suicide death risk in transgender people: results from the Amsterdam Cohort of Gender Dysphoria study (1972-2017). *Acta Psychiatr Scand*. 2020;**141**(6):486-491.

Flawed Medicaid Report in Florida

On June 17, 2022, the Florida Agency for Health Care Administration (AHCA) issued a proposed regulation that, if adopted, would deny Medicaid coverage for gender-affirming health care to Floridians of all ages. In response, our team submitted a public comment letter to the AHCA opposing the proposed regulation on the grounds that it is discriminatory in violation of the U.S. and Florida Constitutions and federal law. In addition, we submitted an in-depth report analyzing the purported scientific report offered by Florida in support of the proposed rule. Our analysis concludes that the Florida report blatantly violates the basic tenets of scientific inquiry. So repeated and fundamental are the errors in the Florida document that it seems clear that the report is not a serious scientific analysis but, rather, a document crafted to serve a political agenda. The letter and full report are available for review at the links below.

- Public comments on Florida proposed rule denying Medicaid coverage for gender-affirming medical care
- A Critical Review of the June 2022 Florida Medicaid Report on the Medical Treatment of Gender Dysphoria

April 28, 2022

Biased Science: The Texas and Alabama Measures Criminalizing Medical Treatment for Transgender Children and Adolescents Rely on Inaccurate and Misleading Scientific Claims

Susan D. Boulware, M.D., Associate Professor of Clinical Pediatrics (Endocrinology), Yale School of Medicine; Director Clinical Operations, Section of Pediatric Endocrinology; Medical Director, Yale Pediatric Gender Program

Rebecca Kamody, PhD (Clinical Psychology), Assistant Professor, Yale School of Medicine: Child Study Center, Pediatrics, and Psychiatry

Laura Kuper PhD (Psychology), ABPP, Assistant Professor in Psychiatry, University of Texas Southwestern; Child & Adolescent Psychologist, Children's Medical Center Dallas

Meredithe McNamara, M.D., M.S., FAAP, Assistant Professor of Pediatrics (Adolescent Medicine), Yale School of Medicine

Christy Olezeski, PhD (Clinical Psychology), Associate Professor of Psychiatry, Yale Child Study Center and Pediatrics, Yale School of Medicine; Director, Yale Pediatric Gender Program

Nathalie Szilagyi, M.D., Instructor, Yale Child Study Center, Yale Pediatric Gender Program; Director, Greenwich Child and Adolescent Psychiatry, Greenwich Center for Gender & Sexuality

Anne Alstott, J.D., Jacquin D. Bierman Professor, Yale Law School; Professor, Yale Child Study Center[*]

Introduction and Summary

On February 18, 2022, Texas Attorney General Ken Paxton issued an interpretation of Texas state law (the "AG Opinion"), taking the position that certain medical procedures constitute child abuse as defined in the Texas Family Code.[1] Texas Governor Greg Abbott cited the AG Opinion as authority for his February 22, 2022 directive requiring the Texas Department of Family and Protective Services to "conduct a prompt and thorough investigation of any reported instances of these abusive procedures" (the "Governor's Directive").[2]

[*] We would like to thank Dr. Sundes Kazmir, M.D., FAAP, who provided helpful information on medical research on child abuse investigations. Calleigh Higgins, Christina Lepore, and Henry Robinson provided excellent research assistance.

[1] Tex. Op. Att'y. Gen. No. KP-0401 (Feb. 18, 2022) (hereinafter, "AG Opinion").

[2] Letter from Greg Abbott, Governor of Texas, to Jaime Masters, Commissioner, Texas Department of Family and Protective Services, Feb. 22, 2022, at https://gov.texas.gov/uploads/files/press/O-MastersJaime202202221358.pdf

On April 7, 2022, Governor Kay Ivey of Alabama signed S.B. 184 (the "Alabama Law"), which imposes felony penalties on anyone providing certain medical care to any child, adolescent, or young adult under age 19.[3]

We are a group of six scientists and one law professor. Among the scientists, three of us are M.D.s., three are PhD's, and all treat transgender children and adolescents in daily clinical practice. We all hold academic appointments at major medical schools, including the University of Texas Southwestern and Yale University. In this report, we examine in depth the scientific claims made in the AG Opinion and the text of the Alabama Law about medical care for transgender children and adolescents. Note that, although we reject the AG's assertion that gender-affirming care constitutes child abuse and we oppose the Alabama Law's criminalization of such care, we do not address, in this report, the legal validity of either.[4] In accordance with our expertise, our focus is on the science.

After examining the AG Opinion and the findings of "fact" in the Alabama Law in detail, we conclude that their medical claims are not grounded in reputable science and are full of errors of omission and inclusion. These errors, taken together, thoroughly discredit the AG Opinion's claim that standard medical care for transgender children and adolescents constitutes child abuse. The Alabama Law contains similar assertions of scientific fact, and these too are riddled with errors, calling into question the scientific foundations of the law.

In this report, we focus closely on the AG Opinion, because it contains a full explanation of its reasoning, while the Alabama law presents a list of purported scientific findings without argument or citation. We note, throughout, when the purported findings in the Alabama law echo the claims made in the AG Opinion.

The Texas Attorney General either misunderstands or deliberately misstates medical protocols and scientific evidence. The AG Opinion and the Alabama Law make exaggerated and unsupported claims about the course of treatment for gender dysphoria, specifically claiming that standard medical care for pediatric patients includes surgery on genitals and reproductive organs. In fact, the authoritative protocols for medical care for transgender children and adolescents, which define what we term "gender-affirming care," specifically state that individuals must be over the age of majority before they can undergo such surgery. The AG Opinion and the Alabama Law also ignore the mainstream scientific evidence showing the significant benefits of gender-affirming care and exaggerate potential risks.

These are not close calls or areas of reasonable disagreement. The AG Opinion and the Alabama Law's findings ignore established medical authorities and repeat discredited, outdated, and poor-quality information. The AG Opinion also mischaracterizes reputable sources and repeatedly cites a fringe group whose listed advisors have limited (or no) scientific and medical credentials and include well-known anti-trans activists.

---

[3] Vulnerable Child Compassion and Protection Act, 2022 Ala. Laws 289 (hereinafter, "Alabama Law").
[4] For legal analysis, see Plaintiffs' Original Petition and Application for Temporary Restraining Order, Temporary Injunction, Permanent Injunction, and Request for Declaratory Relief, Doe v. Abbott, March 1, 2022, at https://www.aclu.org/legal-document/doe-v-abbott-petition.

The AG Opinion falsely implies that puberty blockers and hormones are administered to prepubertal children, when, in fact, the standard medical protocols recommend drug treatments only for adolescents (and not prepubertal children). For purposes of this report, we use the term "adolescent" to refer to a child under the age of majority in whom pubertal development has begun.

The AG Opinion also omits mention of the extensive safeguards established by the standard protocols to ensure that medication is needed and that adolescents and their parents give informed assent and consent, respectively, to treatment when it is determined to be essential care. There is no rush to treatment: the course of gender-affirming care is tailored to each individual, and standard protocols mandate a process of consultation involving an interdisciplinary team including mental health professionals, medical providers, and parents.

By omitting the evidence demonstrating the substantial benefits of treatment for gender dysphoria, and by focusing on invented and exaggerated harms, the AG Opinion and the Alabama Law portray a warped picture of the scientific evidence. Contrary to their claims, a solid body of reputable evidence shows that gender-affirming care can be lifesaving and significantly improves mental health and reduces suicide attempts. The standard medical protocols were crafted by bodies of international experts based on a solid scientific foundation and have been in use for decades. Thus, treating gender dysphoria is considered not only ethical but also the clinically and medically recommended standard of care. Indeed, it would be considered unethical to *withhold* medical care from patients with gender dysphoria, just as it would be unethical to withhold potentially lifesaving care for patients with any other serious medical condition.

The repeated errors and omissions in the AG Opinion are so consistent and so extensive that it is difficult to believe that the opinion represents a good-faith effort to draw legal conclusions based on the best scientific evidence. It seems apparent that the AG Opinion is, rather, motivated by bias and crafted to achieve a preordained goal: to deny gender-affirming care to transgender youth. The same is true of the scientific claims made in the Alabama Law.

Many reputable scientific and professional organizations have issued statements opposing the Texas action,[5] but to our knowledge, none have conducted the in-depth, point-by-point review that we provide here.

---

[5] See APA President Condemns Texas Governor's Directive to Report Parents of Transgender Minors [Internet]. Washington, D.C.: American Psychological Association; 2022 Feb 24 [cited 2022 Apr 15]. Available from: https://www.apa.org/news/press/releases/2022/02/report-parents-transgender-children; American Academy of Pediatrics, AAP, Texas Pediatric Society Oppose Actions in Texas Threatening Health of Transgender Youth [Internet]. Itasca (IL): American Academy of Pediatrics; 2022 Feb 24 [cited 2022 Apr 15]. Available from: https://www.aap.org/en/news-room/news-releases/aap/2022/aap-texas-pediatric-society-oppose-actions-in-texas-threatening-health-of-transgender-youth/; AACAP Statement Opposing Actions in Texas Threatening the Health, Mental Health and Well-Being of Transgender and Gender Diverse Youth and Their Families [Internet]. Washington, D.C.: American Academy of Child & Adolescent Psychiatry; 2022 March 1 [cited 2022 Apr 22]. Available from: https://www.aacap.org/AACAP/zLatest_News/AACAP_Statement_Opposing_Actions_in_Texas.aspx.
See also Letter from James L. Madara, CEO and Executive Vice President of the American Medical Association, to Bill McBride, Executive Director of the National Governors Association, April 26, 2021 (opposing legislation in

Throughout this report, we use the highest-quality scientific evidence available. In this context, large-scale, randomized controlled trials would be inappropriate for ethical reasons: when medical care has been shown (by other methods) to reduce gender dysphoria and improve mental health, as is the case for gender-affirming care for individuals with gender dysphoria, it would be unethical to deny that care to a control group of patients. This is true in many areas of medicine. In such cases, physicians instead rely on studies using other scientific methods, and they judge the relative quality of evidence based on several factors, including whether the study is peer-reviewed, published in a high-impact journal, up to date, and conducted by reputable investigators.

In this report, we cite studies that are peer-reviewed, up to date, conducted by respected investigators, and published in high-impact journals that are widely read. This represents the highest-quality evidence available to physicians making treatment decisions in this context. By contrast, the AG Opinion relies on very poor-quality evidence. Only two of its sources are peer-reviewed scientific studies. Of these, one is badly out-of-date, and the other is cited for a proposition that is irrelevant to the treatment of transgender children and adolescents.[6]

To summarize, we find that:

1. The AG Opinion and the Alabama Law falsely claim that current medical standards authorize the surgical sterilization of transgender children and adolescents. In fact, present medical standards state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs.

> Current medical protocols do not allow for either surgery or drug therapy for prepubertal children and specifically state that genital surgery should not be carried out before patients reach the legal age of majority. The standards of care do permit the careful use of drug therapies for adolescents (but not prepubertal children) and caution that drug therapies should be undertaken only after a careful, staged process of psychological and medical counseling. The AG Opinion's and Alabama Law's lists of "sex change procedures" and the claims that doctors are routinely sterilizing children and teenagers do not reflect current medical practice.

Arkansas and other states that would deny gender-affirming care), at https://www.ama-assn.org/press-center/press-releases/ama-states-stop-interfering-health-care-transgender-children; Clarke M, Farnan A, Barba A, Giovanni K, Brymer M, Julian J. Gender-Affirming Care Is Trauma-Informed Care [Internet]. Los Angeles (CA) and Durham (NC): National Child Traumatic Stress Network; 2022 [cited 2022 Apr 15]. Available from: https://www.nctsn.org/sites/default/files/resources/fact-sheet/gender-affirming-care-is-trauma-informed-care.pdf.

[6] One study is Dhejne C, Lichtenstein P, Boman M, Johansson AL, Langstrom N, Landen M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011 Feb 22;6(2):e16885. We discuss in Section 2 why Dhejne et al. is out of date and unsupportive of the AG's claims. The AG Opinion also cites one study for the proposition that "hysterectomy, oophorectomy, and orchiectomy result in permanent sterility." The cited study is Cheng PJ, Pastuszak AW, Myers JB, Goodwin IA, Hotaling JM. Fertility concerns of the transgender patient. Transl Androl Urol. 2019 Jun;8(3):209-218. As we explain in Section 1, current medical protocols do not authorize surgery on genitals or reproductive organs for anyone under the age of majority, and so the reference is irrelevant to the treatment of minors.

2. The AG Opinion and the Alabama Law ignore the substantial benefits of medical care for transgender children and adolescents, care which has consistently been shown to reduce gender dysphoria and improve mental health. The best scientific evidence shows that gender dysphoria is real, that untreated gender dysphoria leads predictably to serious, negative medical consequences, and that gender-affirming care significantly improves mental health outcomes, including reducing rates of suicide.

The AG Opinion and the Alabama Law omit any discussion of the demonstrated benefits of gender-affirming care as recognized by established medical science. The AG Opinion and the Alabama Law also greatly exaggerate the percentage of adolescents whose diagnosed gender dysphoria dissipates without gender-affirming care. And the AG Opinion repeats discredited evidence claiming that there is a wave of so-called "rapid-onset" gender dysphoria among U.S. adolescents.

3. The AG Opinion and the Alabama Law greatly exaggerate the risks of gender-affirming drug therapy.

The AG Opinion exhibits a poor understanding of medicine and consistently misstates medical protocols and scientific evidence. Contrary to the AG Opinion's statements, gender-affirming drug therapy (including puberty blockers and hormonal treatments) is safe and effective and has been approved by the major medical authorities. Puberty blockers are fully reversible; when discontinued, puberty begins, and fertility develops normally.

Gender-affirming hormone treatments can reduce fertility to some degree while ongoing, but the evidence suggests that these effects are reversible when hormone therapy is discontinued. Standard medical protocols manage these risks in the way any medical risks should be managed: by weighing the benefits of treatment against potential harms and by a careful and individualized process of consultation and consent. Indeed, the informed consent procedures for gender-affirming drug treatment are at least as rigorous as the consent required for any other drug treatment.

Table of Contents

Section 1. The AG Opinion and the Alabama Law falsely claim that current medical standards authorize the surgical sterilization of transgender children and adolescents. In fact, present medical standards state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs.

The AG Opinion asserts that the medical treatments for transgender children include a list of surgical procedures including "sterilization through castration, vasectomy, hysterectomy, oophorectomy, metoidioplasty, orchiectomy, penectomy, phalloplasty, and vaginoplasty."[7] The AG Opinion also claims that physicians dispense "drugs to children that induce transient or permanent infertility," including "(1) puberty-suppression or puberty-blocking drugs, (2) supraphysiologic doses of testosterone to females; and (3) supraphysiologic doses of estrogen to males."[8] The AG Opinion asserts that "[t] he novel trend of providing these elective sex changes to minors often has the effect of permanently sterilizing those minor children."[9] The Alabama Law contains similar statements.[10]

These statements are incorrect. Current medical protocols state that genital surgery should not be carried out before patients reach the legal age of majority. To make the distinction clear, we refer to the AG Opinion's list of procedures as the "AG Opinion claims." We refer to the standard medical protocols issued by the World Professional Association for Transgender Health ("WPATH") and the Endocrine Society as "gender-affirming care."[11]

The AG Opinion fails to engage with the WPATH and Endocrine Society guidelines (or any other recognized set of medical guidelines), even though these are well-known, widely viewed as authoritative, and readily available to the public.[12] These standards are explicitly

---

[7] AG Opinion, p. 1. The AG Opinion also includes "(2) mastectomies; and (3) removing from children otherwise healthy or non-diseased body part or tissue." These procedures do not affect fertility, which is the opinion's stated concern, and they are common among cisgender adolescents (e.g., rhinoplasty and breast reduction). We do not address these procedures in this report.

[8] AG Opinion, p. 1.

[9] AG Opinion, pp. 2-3.

[10] Alabama Law, Section 2(6).

[11] See Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfafflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. Standards of Care for the Health of Transsexual, Transgender, and Gender Nonconforming People, 7th version [Internet]. East Dundee (IL): World Professional Association for Transgender Health; 2012 [cited 2022 Apr 17]. Available from: https://www.wpath.org/publications/soc (hereinafter, "WPATH (2012)"); Hembree WC, Cohen-Kettenis PT, Gooren L, Hannema SE, Meyer WJ, Murad MH, Rosenthal SM, Safer JD, Tangpricha V, T'Sjoen GG. Endocrine Treatment of Gender-Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocrinol Metab. 2017 Sept 13;102(11):3869-3903 (hereinafter, "Endocrine Society (2017)").

[12] The AG Opinion quotes the WPATH standards once, but the opinion mischaracterizes the source material and persists in its repeated claims that gender-affirming care involves genital surgery on children. At page 4, the AG Opinion quotes WPATH (2012) to the effect that genital surgery should not be carried out before patients reach the age of majority. See AG Opinion, p. 4. The AG Opinion misleadingly uses the WPATH quotation as evidence that there is no benefit from gender-affirming care; in fact, WPATH (2012), pp. 10-21, acknowledges the benefits of psychotherapy and, in the case of adolescents, puberty blockers and hormone therapy. Apart from the isolated and misleading citation to WPATH (2012) at p. 4, the AG Opinion does not otherwise discuss the WPATH standards or correct its repeated assertion that children and adolescents are undergoing "sex change" procedures.

followed by major gender clinics in the United States.[13] We address the AG Opinion's misstatements in turn.

a. The medical standards of care for transgender children specifically state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs.

Gender dysphoria is a recognized medical condition[14] that merits medical treatment, and the evidence shows that treatment improves mental health outcomes, including reducing rates of suicidal ideation and suicide attempts. (See Section 2 of this report.)

Individuals with gender dysphoria seek care at a wide variety of ages, which depends on sociocultural and environmental factors, including parental support, socioeconomic status, and access to care. In the early phases of treatment, gender-affirming care consists of using the individual's preferred pronouns, psychosocial support, and education about the next stages of transition if desired. Medical professionals draw an important distinction between hormonal treatment and gender-affirming surgery. Hormonal transition is an established practice in older adolescents experiencing gender dysphoria, but current standards for gender-affirming care set the age of majority as the threshold for considering surgery on genitals and reproductive organs.

Two of the leading guidelines for the medical treatment of transgender children and adolescents are those published by WPATH and by the Endocrine Society. WPATH is a leading international organization of scientists, which has issued standards of care for transgender adults and children since 1979.[15] Several revisions have been made as scientific evidence drives changes in standards. The current version, WPATH Standards of Care, version 7, is viewed as authoritative in the medical community and is widely consulted by physicians and other clinicians. The WPATH standards explicitly state that genital surgery should not be carried out until the patient reaches the age of majority. Further, WPATH advises that "the age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention."[16]

The Endocrine Society is the leading international organization of endocrinologists, i.e., physicians specializing in the study and treatment of the human endocrine system, including hormonal treatment.[17] In 2017, the Endocrine Society issued clinical practice guidelines for the

[13] See Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics 2020 Apr;145(4):e20193006. doi: 10.1542/peds.2019-3006 (stating that Endocrine Society guidelines are followed). The same is true of the Greenwich Center for Gender & Sexuality. The Yale Pediatric Gender Clinic generally follows WPATH standards.

[14] American Psychiatric Association, Diagnostic and Statistical Manual of Mental Disorders (DSM-5), Fifth edition. 2013.

[15] The current version is WPATH (2012). According to WPATH, the first six versions were published in 1979, 1980, 1981, 1990, 1998, and 2001.

[16] WPATH (2012), at p. 21: "Genital surgery should not be carried out until (i) patients reach the legal age of majority to give consent for medical procedures in a given country, and (ii) patients have lived continuously for at least 12 months in the gender role that is congruent with their gender identity. The age threshold should be seen as a minimum criterion and not an indication in and of itself for active intervention."

[17] Who We Are [Internet]. Washington, D.C.: The Endocrine Society; c2022 [cited 2022 Apr 15]. Available from: https://www.endocrine.org/about-us.

treatment of gender dysphoria.[18] Like WPATH, the Endocrine Society does not authorize surgery on the genitals or reproductive organs of transgender children or adolescents.[19]

Both WPATH and Endocrine Society guidelines are based on reviews of the best available science conducted by panels of experts across medical disciplines. These guidelines are updated periodically to ensure that they reflect a current understanding of scientific knowledge and clinical practice. The statements in this report refer to current WPATH and Endocrine Society standards, i.e., those in force as of the date of publication of this report.

b. The standards of care do not recommend drug treatments (puberty blockers or hormones) for prepubertal children.

The AG Opinion wrongly conflates treatments available to adolescents with those offered to children.[20] In fact, current medical protocols for gender-affirming care do not recommend either surgery or drug treatments (puberty blockers and hormones) for prepubertal children.

The WPATH standards state clearly that physical interventions, including drug therapy, are recommended only for adolescents and only after an in-depth process of mental health and medical counseling, described below. The WPATH standards state that social transition, which is entirely reversible, may be considered by the parents of prepubertal children.[21] (Social transition consists of, e.g., wearing clothes and using a name that are consistent with the child's gender identity.) The Endocrine Society also "recommend[s] against puberty blocking and gender-affirming hormone treatment in prepubertal children."[22] (There is, of course, no need for such medication in children who have not reached puberty.)

c. Present standards of care recommend drug treatments for adolescents (youth who have developed pubertal changes) only for those with puberty-induced worsening gender dysphoria and only after a careful protocol that begins with psychological and medical counseling to ensure valid consent.

The AG Opinion claims that "[c]hildren and adolescents are promised relief and asked to 'consent' to life-altering, irreversible treatment—and to do so in the midst of reported psychological distress, when they cannot weigh long-term risks the way adults do."[23] The Alabama Law contains a similar statement.[24]

This statement misdescribes both medical practice and the consent procedures used for the treatment of adolescents. Legally, a parent or guardian must consent to the medical treatment of a minor, and so the AG Opinion is incorrect in implying that medical treatment depends on a

[18] Endocrine Society (2017).
[19] Id. (Guideline 5.5).
[20] AG Opinion, p. 2 (claiming that there is a "novel trend of providing these elective sex changes to minors," with "sex changes" previously defined to include surgery and drug therapies).
[21] WPATH (2012), p. 17.
[22] Endocrine Society (2017) (Guideline 1.4).
[23] AG Opinion, p. 4.
[24] Alabama Law, Section 2(15).

child or teenager's consent alone. [25] As noted above, medical protocols do not recommend drug therapy for prepubertal children, and so consent by young children is never an issue. For adolescents, the standard medical protocols provide for gender-affirming drug therapy only when medically necessary and after a comprehensive process that includes specialist medical consultation and assessment, parent consent and youth assent, and mental health evaluation.

A key feature of both the WPATH Standards of Care and the Endocrine Society Clinical Practice Guidelines is the central role of mental health professionals in assessing gender dysphoria and appropriate modes of medical treatment. The Endocrine Society notes, for example, that, "because of the psychological vulnerability of many individuals with [gender dysphoria], it is important that mental health care is available before, during, and sometimes also after transitioning."[26] Both WPATH and the Endocrine Society provide extensive guidance on how to provide psychosocial support to youth experiencing gender dysphoria, as well as a definition of what constitutes a properly trained mental health professional.

Contrary to the AG Opinion's implication, there is no medical rush to prescribe drug treatments to transgender adolescents. The current WPATH and Endocrine Society standards recommend a staged process for physical interventions, one that takes into account the presentation of gender dysphoria in each individual, along with their medical history and psychological functioning. Social transition, puberty blockers, and hormonal treatment may be used in stages, but not all adolescents with gender dysphoria undergo each treatment.[27] As always in medicine, the priority is to treat the patient as an individual and to address their physical and mental health needs holistically. WPATH, for example, expressly states that, "[b]efore any physical interventions are considered for adolescents, extensive exploration of psychological, family, and social issues should be undertaken …. The duration of this exploration may vary considerably depending on the complexity of the situation."[28]

WPATH and Endocrine Society standards recommend puberty-suppressing medications (GnRH agonist treatment), only for adolescents and only with guardrails to ensure that medication is medically necessary and that adolescents and their parents give informed consent to treatment. These safeguards are worth summarizing in some detail, because they contradict the AG Opinion's claim that gender-affirming care, including drug therapy, is being casually administered.[29]

For puberty-suppressing medications, the standards require the participation of a qualified mental health practitioner, who confirms that the adolescent has demonstrated a long-lasting and intense pattern of gender dysphoria, that gender dysphoria worsened with the onset of

[25] While the law usually grants parents the final decision, bioethicists have found that adolescents can be meaningful participants in the consent process. Clark BA, Virani A. "This Wasn't a Split-Second Decision": An Empirical Ethical Analysis of Transgender Youth Capacity, Rights, and Authority to Consent to Hormone Therapy. J Bioeth Inq. 2021 Mar;18(1):151-64; Vrouenraets LJJJ, de Vries ALC, de Vries MC, van der Miesen AIR, Hein IM. Assessing Medical Decision-Making Competence in Transgender Youth. Pediatrics 2021 Dec 1;148(6):e2020049643.
[26] Endocrine Society (2017).
[27] WPATH (2012), p. 18; Endocrine Society (2017) (Guidelines 2.1 and 2.2).
[28] WPATH (2012), p. 16.
[29] We quote the Endocrine Society phrasing, but the two protocols are substantively the same.

puberty, and that any coexisting psychological, medical, or social problems that could interfere with treatment have been addressed, so that the adolescent's situation and functioning are stable enough to start treatment. The guidelines also require informed assent by adolescents and (if under the age of majority) informed consent by their parents, and they require the involvement of a pediatric endocrinologist (or another physician versed in gender-affirming treatment) to ensure that puberty-blocking medication is warranted, that puberty has begun in the adolescent patient, and that there are no medical contraindications to puberty-blocking medication. [30]

For those adolescents for whom progression to hormone therapy is medically indicated, WPATH and the Endocrine Society require additional counseling regarding the possible fertility effects of hormone therapy. In addition to parental consent, the guidelines require that a mental health practitioner confirm that the adolescent has "sufficient mental capacity (which most adolescents have by age 16 years)" to evaluate the benefits and risks of treatment.[31]

Section 2. The AG Opinion and the Alabama Law ignore the substantial benefits of medical care for transgender children and adolescents, care which has consistently been shown to reduce gender dysphoria and improve mental health. The best scientific evidence shows that gender dysphoria is real, that untreated gender dysphoria leads predictably to serious, negative medical consequences, and that gender-affirming care significantly improves mental health outcomes, including reducing rates of suicide.

The AG Opinion omits any discussion of the documented benefits of gender-affirming care and vastly overstates potential risks by relying on misrepresented or unreliable studies. The AG Opinion also misstates scientific evidence on the percentage of children and adolescents whose gender dysphoria resolves without treatment (sometimes termed "desistance"), and the opinion repeats discredited evidence on a purported novel trend of so-called rapid-onset gender dysphoria. The Alabama Law contains similar errors.[32]

The AG Opinion falsely states that "The medical evidence does not demonstrate that children and adolescents benefit from engaging in these irreversible sterilization procedures."[33] Contrary to the AG Opinion's statements, scientific studies have demonstrated that gender dysphoria is a well-documented condition for which medical care is essential treatment. The established scientific evidence shows that treatment improves mental health outcomes, including reducing rates of suicidal ideation and suicide attempts.

In this Section, we review the scientific evidence on gender dysphoria and the benefits of gender-affirming treatment, and we correct the AG Opinion's and Alabama Law's erroneous claims.

a. Gender dysphoria is real, and untreated gender dysphoria is harmful.

The American Psychiatric Association explains that

[30] Endocrine Society (2017) (Table 5), citing WPATH (2012), p. 16.
[31] Endocrine Society (2017) (Table 5).
[32] Alabama Law, Section 2 and Section 2(4).
[33] AG Opinion, at 3.

> [T]he term "transgender" refers to a person whose sex assigned at birth (i.e., the sex assigned by a physician at birth, usually based on external genitalia) does not match their gender identity (i.e., one's psychological sense of their gender). Some people who are transgender will experience "gender dysphoria," which refers to psychological distress that results from an incongruence between one's sex assigned at birth and one's gender identity. Though gender dysphoria often begins in childhood, some people may not experience it until after puberty or much later.[34]

In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, the standard reference for the diagnosis of mental health conditions. The DSM-5 recognizes gender dysphoria and sets forth criteria for diagnosis. These criteria include "a marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics" and "a strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's assigned gender)." To meet diagnostic criteria, an individual must exhibit "clinically significant distress or impairment in social, occupational, or other important areas of functioning."[35]

In other words, individuals who live in a manner that is physically and socially incongruent to their gender identity can experience gender dysphoria – a clinically significant psychological distress that can lead to depressed mood.[36] Suicidal ideation and attempts have been found to be significantly higher among transgender adolescents who cannot obtain or do not receive gender-affirming care than among their cisgender peers. The harm of not providing gender-affirming care is well documented: 40% of trans individuals who do not receive hormones will attempt or complete suicide in their lifetime.[37] Untreated gender dysphoria can also lead to disordered eating. Patients may engage in unsafe eating behaviors (e.g., food restriction or purging) as a body-affirming tool and an effort to align their bodies with their gender identity. These behaviors can impair physical health and development.[38]

---

[34] What is Gender Dysphoria? [Internet]. Washington, D.C.: American Psychiatric Association; 2020 Nov [cited 2022 Apr 15]. Available from: https://www.psychiatry.org/patients-families/gender-dysphoria/what-is-gender-dysphoria.

[35] American Psychiatric Association. Diagnostic and Statistical Manual of Mental Disorders. 5th ed. Washington, D.C.: American Psychiatric Association; 2013.

[36] Sorbara JC, Chiniara LN, Thompson S, Palmert MR. Mental health and timing of gender-affirming care. Pediatrics 2020 Oct 1;146(4):e20193600 (hereinafter, "Sorbara et al. 2020").

[37] Herman JL, Brown TNT, Haas AP. Suicide Thoughts and Attempts Among Transgender Adults [Internet]. Los Angeles (CA): The Williams Institute, UCLA School of Law; 2019 Sept [cited 2022 Apr 1]. Available from: https://williamsinstitute.law.ucla.edu/publications/suicidality-transgender-adults/. So-called "conversion" therapy (an extreme form of denying gender-affirming care, which attempts to change a person's gender identity to match the sex assigned at birth) has been shown to create psychological distress and prompt suicide. Turban JL, Beckwith N, Reisner SL, Keuroghlian AS. Association Between Recalled Exposure to Gender Identity Conversion Efforts and Psychological Distress and Suicide Attempts Among Transgender Adults. JAMA Psychiatry 2019 Sept 11;77(1):68-76.

[38] Coelho JS, Suen J, Clark BA, Marshall SK, Geller J, Lam PY. Eating Disorder Diagnoses and Symptom Presentation in Transgender Youth: a Scoping Review. Curr Psychiatry Rep. 2019 Oct 15;21(11):107; Kamody RC, Yonkers K, Pluhar EI, Olezeski CL. Disordered Eating Among Trans-Masculine Youth: Considerations Through a Developmental Lens. LGBT Health. 2020 May/Jun;7(4):170-73; Legroux I, Cortet B. Factors influencing bone loss in anorexia nervosa: assessment and therapeutic options. RMD Open. 2019 Nov 13;5(2):e001009.

For all these reasons, the American Academy of Pediatrics, the American Psychological Association, and the American Academy of Child and Adolescent Psychiatry – the three major professional associations of pediatricians, psychologists, and child and adolescent psychiatrists – have endorsed gender-affirming care and condemned efforts to deny medical care to transgender people, as have the Texas Medical Society and the Alabama Psychological Association.[39] These organizations have also condemned so-called "conversion therapy" as ineffective, unethical, and dangerous.[40]

The scientific consensus is clear: denying gender-affirming care harms transgender people and puts their lives at risk.[41]

b. Gender-affirming care has measurable and significant benefits.

The AG Opinion incorrectly states that "There is no evidence that long-term mental health outcomes are improved or that rates of suicide are reduced by hormonal or surgical intervention."[42] The AG's statement that gender-affirming care is not beneficial is contradicted by a significant body of recent scientific evidence.[43]

---

[39] Rafferty J, Committee on Psychosocial Aspects of Child and Family Health; Committee on Adolescence; Section on Lesbian, Gay, Bisexual, and Transgender Health and Wellness, Ensuring Comprehensive Care and Support for Transgender and Gender-Diverse Children and Adolescents. Pediatrics. 2018 Oct;142(4):e20182162; American Psychological Association. Guidelines for psychological practice with transgender and gender nonconforming people. American Psychologist 2015 Dec;70(9):832-64 (hereinafter, "American Psychological Association (2015)"); AAP Continues to Support Care of Transgender Youth as More States Push Restrictions [Internet]. Itasca (IL): American Academy of Pediatrics; 2022 Jan 6 [cited 2022 Mar 31]. Available from: https://publications.aap.org/aapnews/news/19021/AAP-continues-to-support-care-of-transgender; Criminalizing Gender Affirmative Care with Minors [Internet]. Washington, D.C.: American Psychological Association; [cited 2022 Mar 30]. Available from: https://www.apa.org/pi/lgbt/resources/policy/issues/gender-affirmative-care; AACAP Statement Opposing Actions in Texas Threatening the Health, Mental Health and Well-Being of Transgender and Gender Diverse Youth and Their Families, Washington, D.C.: American Academy of Child & Adolescent Psychiatry; 2022 March 1 [cited 2022 Apr 22=]. Available from: https://www.aacap.org/AACAP/zLatest_News/AACAP_Statement_Opposing_Actions_in_Texas.aspx; Statement of the Alabama Psychological Association (aPA) Supporting Gender-Affirming Care for Transgender Youth and Urging Opposition to Alabama SB184/HB266 [internet]. Alabama Psychological Association 2022. Available at https://cdn.ymaws.com/www.alapsych.org/resource/resmgr/2022/sb184-hb266_apa_statement_3-.pdf; Sorrel AL, TMA Supports Evidence-Based Gender-Affirming Care in Lawsuit [internet]. Texas Medical Association. March 14, 2022. Available from https://www.texmed.org/TexasMedicineDetail.aspx?id=59040.

[40] APA Resolution on Gender Identity Change Efforts [Internet]. Washington, D.C.: American Psychological Association; 2021 Feb [cited 2022 Mar 31]. Available from: https://www.apa.org/about/policy/resolution-gender-identity-change-efforts.pdf.

[41] Abreu RL, Sostre JP, Gonzalez KA, Lockett GM, Matsuno E. "I am afraid for those kids who might find death preferable": Parental figures' reactions and coping strategies to bans on gender-affirming care for transgender and gender diverse youth. Psychology of Sexual Orientation and Gender Diversity [Internet]. 2021 Jul 29 [cited 2022 Mar 31]; advance online publication. Available from: https://psycnet.apa.org/record/2021-67997-001; Hughes LD, Kidd KM, Gamarel KE, Operario D, Dowshen N. (2021). "These Laws Will Be Devastating": Provider Perspectives on Legislation Banning Gender-Affirming Care for Transgender Adolescents. Journal of Adolescent Health 2021 Dec;69(6):976-82; Kidd KM, Sequeira GM, Paglisotti T, Katz-Wise SL, Kazmerski TM, Hillier A, Miller E, Dowshen N. "This could mean death for my child": Parent perspectives on laws banning gender-affirming care for transgender adolescents. Journal of Adolescent Health 2021 Jun;68(6):1082-88.

[42] AG Opinion, p. 4.

[43] De Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: A prospective follow-up study. The Journal of Sexual Medicine 2011 Aug;8(8):2276-83; De Vries

As explained in Section 1 of this report, social transition is an important first step for adolescents (and is the only medically accepted form of gender-affirming care for prepubertal children). The scientific evidence shows that social transition, including using a child or adolescent's chosen name, reduces depression and suicide risk.[44]

A solid body of reliable research has shown that the potential next steps in gender-affirming care for adolescents with gender dysphoria – puberty-blocking medications and hormone therapy – have major mental-health benefits, including higher levels of general well-being and significantly decreased levels of suicidality.[45] Puberty blockers have been shown to

---

AL, McGuire JK, Steensma TD, Wagenaar EC, Doreleijers TA, Cohen-Kettenis PT. Young adult psychological outcome after puberty suppression and gender reassignment. Pediatrics 2014 Oct;134(4):696-704; Costa R, Dunsford M, Skagerberg E, Holt V, Carmichael P, Colizzi M. Psychological Support, Puberty Suppression, and Psychosocial Functioning in Adolescents with Gender Dysphoria. The Journal of Sexual Medicine 2015 Nov;12(11):2206-14 (hereinafter, "Costa et al. 2015"); Allen LR, Watson LB, Egan AM, Moser CN. Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology 2019 Sept;7(3):302-11 (hereinafter, ("Allen et al 2019"); Kaltiala R, Heino E, Tyolajarvi M, Suomalainen L. Adolescent development and psychosocial functioning after starting cross-sex hormones for gender dysphoria. Nordic Journal of Psychiatry 2020 Apr;74(3):213-19; de Lara DL, Rodriguez OP, Flores IC, Masa JLP, Campos-Munoz L, Hernandez MC, Amador JTR. Psychosocial assessment in transgender adolescents. Anales de Pediatria (English Edition) 2020 Jul;93(1):41-48; van der Miesen AI, Steensma TD, de Vries AL, Bos H, Popma A. Psychological Functioning in Transgender Adolescents Before and After Gender-Affirmative Care Compared with Cisgender General Population Peers. Journal of Adolescent Health 2020 Jun;66(6):699-704; Achille C, Taggart T, Eaton NR, Osipoff J, Tafuri K, Lane A, Wilson TA. Longitudinal impact of gender-affirming endocrine intervention on the mental health and well-being of transgender youths: preliminary results. International Journal of Pediatric Endocrinology 2020;2020:8; Kuper LE, Stewart S, Preston S, Lau M, Lopez X. Body Dissatisfaction and Mental Health Outcomes of Youth on Gender-Affirming Hormone Therapy. Pediatrics 2020 Apr;145(4):e20193006; Turban JL, King D, Carswell JM, Keuroghlian AS. Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. Pediatrics 2020 Feb;145(2):e20191725; Carmichael P, Butler G, Masic U, Cole TJ, De Stavola BL, Davidson S, Skageberg EM, Khadr S, Viner RM. 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. PLoS One 2021 Feb 2;16(2):e0243894; Grannis C, Leibowitz SF, Gahn S, Nahata L, Morningstar M, Mattson WI, Chen D, Strang JF, Nelson EE. Testosterone treatment, internalizing symptoms, and body image dissatisfaction in transgender boys. Psychoneuroendocrinology 2021 Oct;132:105358; Hisle-Gorman E, Schvey NA, Adirim TA, Rayne AK, Susi A, Roberts TA, Klein DA. Mental Healthcare Utilization of Transgender Youth Before and After Affirming Treatment. The Journal of Sexual Medicine 2021 Aug;18(8):1444-54; Green AE, DeChants JP, Price MN, Davis CK. Association of Gender-Affirming Hormone Therapy with Depression, Thoughts of Suicide, and Attempted Suicide Among Transgender and Nonbinary Youth. Journal of Adolescent Health 2022 Apr;70(4):643-49 (hereinafter, "Green et al. 2022"); Turban JL, King D, Kobe J, Reisner SL, Keuroghlian AS. Access to gender-affirming hormones during adolescence and mental health outcomes among transgender adults. PLoS One 2022 Jan 12;17(1):e0261039 (hereinafter, "Turban et al. 2022"); Tordoff DM, Wanta JW, Collin A, Stephney C, Inwards-Breland DJ, Ahrens K. Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. JAMA Network Open 2022 Feb 1;5(2):e220978 (hereinafter, "Tordoff et al. (2022)").

[44] Russell ST, Pollitt AM, Li G, Grossman AH. Chosen name use is linked to reduced depressive symptoms, suicidal ideation, and suicidal behavior among transgender youth. Journal of Adolescent Health 2018 Oct;63(4):503-05; Durwood L, McLaughlin KA, Olson KR. Mental health and self-worth in socially transitioned transgender youth. Journal of the American Academy of Child & Adolescent Psychiatry 2017 Feb;56(2):116-23.

[45] Allen et al. 2019, cited in note 43; Green et al. (2022), cited in note 43; Connolly MD, Zervos MJ, Barone II CJ, Johnson CC, Joseph CL. The Mental Health of Transgender Youth: Advances in Understanding. Journal of Adolescent Health 2016 Nov;59(5):489-95; Turban et al. 2022, cited in note 43; Costa et al. (2015), cited in note 43; See also Witcomb GL, Bouman WP, Claes L, Brewin N, Crawford JR, Arcelus J. Levels of depression in transgender people and its predictors: Results of a large matched control study with transgender people accessing clinical services. Journal of Affective Disorders 2018 Aug 1; 235:308-15.

decrease suicidality in adulthood and to improve affect and psychosocial functioning as well as social life.[46] Hormone therapy has been shown to reduce suicidality in transgender adolescents when compared to peers with gender dysphoria who did not receive it.[47] Notably, none of the studies has found a worsening of these mental health measures among recipients of gender-affirming care.

Among children and adolescents, patients who present for gender-affirming care at later pubertal stages are more likely to require psychoactive medications and are more likely to have considered or attempted suicide than patients who received gender-affirming care at earlier stages of pubertal development.[48]

As evidence for the proposition that "[t]here is no evidence that long-term mental health outcomes are improved or that rates of suicide are reduced by hormonal or surgical intervention," the AG Opinion cites a 2011 Swedish study by Dhejne et al. that, the AG Opinion claims, "monitored transitioned individuals for 30 years [and] found high rates of post-transition suicide and significantly elevated all-cause mortality, including increased death rates from cardiovascular disease and cancer, although causality could not be established."[49] In fact, the 2011 study by Dhejne is badly out-of-date and does not support the AG Opinion's claim.

The Dhejne study compared post-gender-affirmation transgender individuals with cisgender individuals from the general population, as opposed to transgender individuals who did not receive gender-affirming care. Therefore, as the study's author explicitly cautions in the body of the text, *it is impossible to conclude from this data* that gender-affirming procedures were a causative factor in suicidality among transgender individuals.[50] Rather, the study shows only that transgender adults were more likely to experience suicidal ideation/attempts and risky behavior when compared to the general population in Sweden between 1973 and 2003. Further, the Dhejne study is not generalizable to a modern American population or to adolescents. During the study period, Swedish law required that individuals seeking gender-affirming surgery be

---

[46] Rew L, Young CC, Monge M, Bogucka R. Review: Puberty blockers for transgender and gender diverse youth – a critical review of the literature. Child and Adolescent Mental Health 2021 Feb;26(1):3-14; de Vries AL, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study. J Sex Med. 2011 Aug;8(8):2276-83. Epub 2010 Jul 14 (hereinafter, "de Vries et al. (2011)").

[47] Tordoff et al (2022), cited in note 43; Sorbara et. al. (2020), cited in note 36.

[48] Sorbara JC et. al. (2020), cited in note 36. Studies of adults confirm that gender-affirming treatment has been associated with marked improvement in mental health outcomes in transgender patients. See Almazan AN, Keuroghlian AS. Association Between Gender-Affirming Surgeries and Mental Health Outcomes. JAMA Surgery 2021 Jul 1;156(7):611-18; Marano AA, Louis MR, Coon D. Gender-Affirming Surgeries and Improved Psychosocial Health Outcomes. JAMA Surgery 2021 Jul 1;156(7):685-87; Swan J, Phillips TM, Sanders T, Mullens AB, Debattista J and Bromdal A. Mental health and quality of life outcomes of gender-affirming surgery: A systematic literature review, Journal of Gay & Lesbian Mental Health, 2022.

[49] AG Opinion, at 4, citing Dhejne C, Lichtenstein P, Boman M, Johansson AL, Langstrom N, Landen M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One 2011 Feb 22;6(2):e16885 (hereinafter, "Dhejne (2011)").

[50] "It is therefore important to note that the current study is only informative with respect to [transgender] persons' health after sex reassignment; *no inferences can be drawn as to the effectiveness of sex reassignment as a treatment for transsexualism*. In other words, the results should not be interpreted such as sex reassignment per se increases morbidity and mortality. Things might have been even worse without sex reassignment." Dhejne (2011) at 7 (emphasis added).

sterilized. The presence of this law alone might account for the higher risk of suicide attempts and risky behavior in the transgender population compared to the cisgender population at the time.[51]

The AG Opinion also mischaracterizes an important governmental decision, claiming incorrectly that the Centers for Medicare and Medicaid Services ("CMS") found that gender-affirming care has no benefits. The AG Opinion claims that "there is no scientific consensus that [medical care] even serve[s] to benefit minor children dealing with gender dysphoria," and that "[t]he lack of evidence in this field is why the CMS rejected a nationwide coverage mandate for adult gender transition surgeries during the Obama Administration."[52] Although the CMS did issue a 2016 Decision Memo denying blanket, automatic coverage for gender-affirming surgery, the decision specifically *authorizes* Medicare and Medicaid providers to cover such surgery on a case-by-case basis.[53] Thus, contrary to AG Opinion's claim, the CMS decision memo expressly *permits* state and local decision-makers to authorize coverage for gender-affirming surgery.[54] The federal directive simply declines to authorize automatic coverage in every case. And, in fact, the 2016 CMS decision marks an expansion of the permissibility of gender-affirming treatment: the Decision Memo followed the 2014 revocation of the CMS's 1989 decision to deny nationwide coverage.[55]

Further, the CMS did not reach any negative conclusion on the benefits of gender-affirming care for children and adolescents. The CMS reviewed only studies on the outcomes of surgery (not hormone treatment) for an adult population that is overwhelmingly elderly (over age 65) and has a high prevalence of preexisting medical conditions that can make surgery risky, regardless of its purpose.[56]

---

[51] Nelson R. Transgender People in Sweden No Longer Face Forced Sterilization. Time [Internet]. 2013 Jan 14 [cited 2022 Apr 1]; Available from: https://newsfeed/time.com/2013/01/14/transgender-people-in-sweden-no-longer-face-forced-sterilization/. The presence of this law alone might account for the higher risk of suicide attempts and risky behavior in the transgender population at the time.

[52] AG Opinion, at 3-4, citing Jensen TS, Chin J, Rollins J, Koller E, Gousis L. Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N). Baltimore (MD): Centers for Medicare and Medicaid Services; 2016 Aug 30 [cited 2022 Feb 18]. Available from: https://www.cms.gov/medicare-coverage-database/view/ncacal-decision-memo.aspx?proposed=N&NCAId=282.

[53] Id.

[54] Id. ("We acknowledge that [gender reassignment surgery] may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a [national coverage decision] that identifies the precise patient population for whom the service would be reasonable and necessary.")

[55] Id.

[56] The CMS Decision Memo notes that "the Medicare population is different from the general population in age (65 years and older) and/or disability as defined by the Social Security Administration. Due to the biology of aging, older adults may respond to health care treatments differently than younger adults. These differences can be due to, for example, multiple health conditions or co-morbidities, longer duration needed for healing, metabolic variances, and impact of reduced mobility. All of these factors can impact health outcomes. The disabled Medicare population, who are younger than age 65, is different from the general population and typical study populations due to the presence of the causes of disability such as psychiatric disorders, musculoskeletal health issues, and cardiovascular issues." Id.

c. The AG Opinion repeats discredited and unreliable evidence on "desistance" and "rapid-onset gender dysphoria."

The AG Opinion greatly exaggerates the extent to which adolescent gender dysphoria abates without treatment, and it repeats discredited claims that there is a novel wave of rapid-onset dysphoria among today's teens.

"Desistance." The AG Opinion asserts that "[c]hildhood-onset gender dysphoria has been shown to have a high rate of natural resolution, with 61-98% of children reidentifying with their biological sex during puberty."[57] The Alabama law makes a parallel statement.[58] The assertion is incorrect.

As authority for the claimed 61-98% figure, the AG Opinion does not cite reputable scientific evidence. Instead, it cites a biased source – the website of the so-called Society for Evidence-Based Gender Medicine ("SEGM"). SEGM is not a recognized scientific organization, and in Appendix A we document the bias that infuses its medical claims. The SEGM website badly mischaracterizes the underlying source that it cites for the 61-98% figure.

The study SEGM cites is Steensma et al. (2013).[59] But the Steensma study was not designed to (and the lead author has acknowledged) does not provide a basis for calculating what percentage of prepubertal children diagnosed with gender dysphoria persist with that diagnosis into adolescence. Rather, the Steensma study was designed only to study the characteristics of those who persisted. [60] Among other limitations, in Steensma (2013), former patients who opted to not participate in the study (either refused to participate or did not respond to an offer to participate) were categorized as "desisters," i.e., patients whose gender dysphoria resolved without transition or treatment. Patients can fail to respond to a study request for many reasons, including having moved away, receiving treatment elsewhere, or being uninterested in participating in a study. Thus, SEGM misuses the Steensma data by counting nonresponding patients as having "desisted" in experiencing gender dysphoria.[61] Indeed, in published correspondence, Steensma emphasizes that the 2013 study should *not* be used to calculate the percentages of "persisters" and "desisters."[62] The misrepresentation of Steensma on the SEGM website constitutes a major violation of the scientific method and the accepted conventions of research.

---

[57] AG Opinion, at 4.
[58] Alabama Law, Section 2(4).
[59] Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry. 2013 Jun;52(6):582-90.
[60] Steensma TD, Cohen-Kettenis PT. A critical commentary on follow-up studies and "desistence" theories about transgender and gender non-conforming children. Int J Transgend. 2018 May; 19(2):225-30.
[61] See American Psychological Association (2015), p. 842 (noting that several studies categorized youth who did not return to the clinic after initial assessment as "desisters" who no longer identified with a gender different than sex assigned at birth; "As a result, this research runs a strong risk of inflating estimates of the number of youth who do not persist with a TGNC identity").
[62] Id.

Actual scientific evidence on the course of gender dysphoria emphasizes the importance of distinguishing between prepubertal children and adolescents. The evidence suggests that the course of dysphoria is more diverse for prepubertal children, and so it is critical to recognize them as a distinct population from adolescents. By referring to "children," the AG Opinion creates the misimpression that most or all children *and* teens diagnosed with dysphoria will cease identifying with the gender not assigned at birth. This is false.

The evidence suggests that the vast majority of adolescents who are diagnosed with gender dysphoria will persist in their gender identity and will benefit from gender-affirming medical care.[63] In a Dutch study, among 70 adolescents diagnosed with gender dysphoria and treated with puberty-suppressing hormones, 100% opted to continue with gender-affirming treatment.[64] A recent U.S. study found a consistent pattern. Following a large cohort of U.S. young people who reported some evidence of gender dysphoria but had not yet been formally diagnosed, the study found that adolescents were far more likely than prepubertal children to go on to a formal diagnosis of gender dysphoria and to receive gender-affirming treatment.[65]

The course of gender dysphoria is different in pre-pubertal children. For this group, the percentage of those whose dysphoria resolves without treatment is higher than for adolescents but likely lower than the AG Opinion's claimed 61-98% figure. When prepubertal children experience gender dysphoria, some will find that their dysphoria resolves before adolescence. That is, many of these children will not, as adolescents, identify as transgender or proceed with gender-affirming medical care. Importantly, as we have emphasized, standard medical protocols do not treat prepubertal children with drug therapy or genital surgery, and so there is zero risk that a prepubertal child with dysphoria will have received physical interventions.

Further, the AG Opinion's claim of 98% "desistance" is overstated even for prepubertal children. The Endocrine Society reports that, "[c]ombining all outcome studies to date, the [gender dysphoria]/gender incongruence of a minority of prepubertal children appears to persist

---

[63] American Psychological Association (2015), p. 843; WPATH (2012), p. 11; Endocrine Society (2017). See also Turban JL, DeVries ALC, Zucker K. Gender Incongruence & Gender Dysphoria. In Martin A, Bloch MH, Volkmar FR (editors): Lewis's Child and Adolescent Psychiatry: A Comprehensive Textbook, Fifth Edition. Philadelphia: Wolters Kluwer 2018, pp. 20-21 ("we must recognize that [the existing studies of persistence] have been quite limited in power and generalizability and should not be misused to create barriers for TGD youth seeking gender-affirming care. The most relevant conclusions from these studies are that insistent cross-gender identification in adolescence most often correlates with persistent TGD identities in adulthood").

[64] de Vries et al. 2011, cited in note 43 ("None of the gender dysphoric adolescents in this study renounced their wish for [gender reassignment] during puberty suppression. This finding supports earlier studies showing that young adolescents who had been carefully diagnosed show persisting gender dysphoria into late adolescence or young adulthood").

[65] Wagner S, Panagiotakopoulos L, Nash R, Bradlyn A, Getahun D, Lash TL, Roblin D, Silverberg MJ, Tangpricha V, Vupputuri S, Goodman M. Progression of Gender Dysphoria in Children and Adolescents: A Longitudinal Study. Pediatrics. 2021 Jul;148(1):e2020027722. doi: 10.1542/peds.2020-027722. Epub 2021 Jun 7. PMID: 34099504; PMCID: PMC8276590. Wagner et. al (2021) studied this cohort for only (on average) 3.5 years; by the end of the study period, roughly 35% of teens but only about 15-18% of prepubertal children received a formal diagnosis of gender dysphoria. Note that these data do *not* establish that only 35% of teens *with gender dysphoria* persist in their diagnosis. This was not a population already diagnosed with dysphoria, and so the persistence rate cannot be calculated. Rather, Wagner et al. (2021) shows that, among a population with some evidence of dysphoria, adolescents are far more likely than young children to continue to a formal diagnosis.

in adolescence."[66] A reasonable summary of the literature would be that around 50% of prepubertal children diagnosed with gender dysphoria (using older, less stringent diagnostic criteria) will not persist in identifying as transgender into adolescence and adulthood.[67]

Recent evidence suggests that the spontaneous resolution of true gender dysphoria among prepubertal children is likely even lower. Earlier studies likely overstate the spontaneous resolution of gender dysphoria among children diagnosed before puberty, because their data incorporated broader diagnostic criteria.[68] That is, the studies likely included prepubertal children with gender variant behavior (e.g., boys with feminine interests or "tomboy" girls) alongside children who would meet today's diagnostic criteria for gender dysphoria – a deeply felt and lasting transgender identity with clinically significant distress and impaired functioning.[69] Consistent with this hypothesis is the recent finding that "the intensity of early dysphoria appears to be an important predictor" of the persistence of dysphoria into adolescence.[70] The evidence thus implies that, had the earlier studies focused on prepubertal children with intense gender dysphoria, the rates of spontaneous resolution of dysphoria would be lower.

To summarize, then, the key to the question of whether gender dysphoria persists over time is whether the patient is diagnosed with gender dysphoria in adolescence. (This might be a new diagnosis or it might be a persistent diagnosis from childhood.) Put plainly: *adolescents with gender dysphoria rarely find that their dysphoria resolves without treatment.*

"Rapid-onset" gender dysphoria. The AG Opinion also asserts that there has been a recent spike in gender dysphoria diagnosis and gender-affirming treatment among U.S. adolescents.[71] The AG insists that this is a "novel cohort" of youth and implies that their gender dysphoria is transient.[72]

As evidence, the AG Opinion again fails to consult reputable science and instead cites the SEGM website, which features a graph showing an increase from 2010 to 2020 in referrals of British adolescents to a specialized gender clinic.[73] The graph is calibrated to look as if the

---

[66] Endocrine Society (2017). See Wallien MS, Cohen-Kettenis PT. Psychosexual outcome of gender-dysphoric children. J Am Acad Child Adolesc Psychiatry. 2008 Dec;47(12):1413-23. doi: 10.1097/CHI.0b013e31818956b9. PMID: 18981931.

[67] American Psychological Association (2015), pp. 841-2 ("existing research suggests that between 12% and 50% of children diagnosed with gender dysphoria may persist in their identification with a gender different than sex assigned at birth into late adolescence and young adulthood").

[68] See Temple Newhook J, Pyne J, Winters K, Feder S, Holmes C, Tosh J, Sinnott ML, Jamieson A, and Pickett S, A critical commentary on follow-up studies and "desistance" theories about transgender and gender-nonconforming children, International Journal of Transgenderism, vol. 19(2), pp. 212-224 (2018) doi: 10.1080/15532739.2018.1456390.

[69] Endocrine Society (2017).

[70] Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. J Am Acad Child Adolesc Psychiatry. 2013 Jun;52(6):582-90 (finding that "children with persistent GID are characterized by more extreme gender dysphoria in childhood than children with desisting gender dysphoria").

[71] AG Opinion, at 3 (stating that "the spike in [surgical and drug] procedures is a relatively recent development").

[72] AG Opinion, at 4.

[73] The AG Opinion cites to the website of the Society for Evidence-Based Gender Medicine (SEGM). SEGM's homepage provides an uncredited and unverifiable graph, which claims to depict referrals to an undefined term,

increase is very large, but in fact, the absolute numbers are small. The information depicted cannot be verified, because SEGM provides no citation. But taking the data at face value, in 2020 about 2600 children and teens sought treatment at the U.K. gender clinic. That is a very small percentage of Britain's child population. Further, the data appear to show only the number of children and adolescents referred for consultation; only a subset of these will ultimately be diagnosed with gender dysphoria and will continue with medical treatment.[74] The claimed "spike" in referrals certainly reflects the reduction in social stigma over the past decade and the expansion of care options.

By contrast, reliable recent data shows that, among high-school students, the percentage who identify as transgender is under 2% (1.8%).[75] These data come from the Centers for Disease Control's Youth Risk Behavior Surveillance System, which is the largest repository of data on self-reported behaviors in the United States. Because not all transgender people seek medical treatment, the percentage seeking medical care would be smaller.

The AG Opinion also repeats a discredited claim that a novel wave of "adolescent-onset gender dysphoria" is sweeping the U.S.[76] This statement echoes (without citing or quoting) a poor-quality study by Lisa Littman.[77] Littman's 2018 article contended that a novel pathology, "rapid-onset gender dysphoria" was leading teenagers to claim a transgender identity because of peer influence. WPATH, among other authorities, has taken a skeptical view of Littman's claim,[78] and the study has been criticized for serious methodological errors, including the use of parent reports instead of clinical data and the recruitment of its sample of parents from anti-transgender websites.[79] The journal of publication required an extensive correction of the

---

"GIDS." SEGM [Internet]. c2020 [cited 2022 Apr 1]. Available from: https://segm.org/. Although GIDS is not defined on the SEGM site, it appears to refer to the Gender Identity Development Service, a specialized UK gender clinic for children and adolescents. GIDS [Internet]. c2022 [cited 2022 Apt 1]. Available from: https://gids.nhs.uk/about-us#main-content.

[74] A referral means that a medical provider (or, possibly, the patient) has suggested an appointment with GIDS. A referral does not equate to the receipt of gender-affirming care. See GIDS [internet]. Available from https://gids.nhs.uk/about-us#main-content.

[75] Johns MM, Lowry R, Andrzejewski J, Barrios LC, Demissie Z, McManus T, Rasberry CN, Robin L, Underwood JM. Transgender Identity and Experiences of Violence Victimization, Substance Use, Suicide Risk, and Sexual Risk Behaviors Among High School Students – 19 States and Large Urban School Districts, 2017. MMWR Morb Mortal Wkly Rep. 2019 Jan 25;68(3):67-71.

[76] AG Opinion, at 4.

[77] Littman L. Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One. 2018 Aug 16;13(8):1-44; Littman L. Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One. 2019 Mar 19;14(3):1-7.

[78] WPATH Global Board of Directors. WPATH Position on "Rapid-Onset Gender Dysphoria" [Internet]. 2018 Sep 4 [cited 2022 Apr 1]. Available from: https://www.wpath.org/media/cms/Documents/Public%20Policies/2018/9_Sept/WPATH%20Position%20on%20Rapid-Onset%20Gender%20Dysphoria_9-4-2018.pdf (stating that ROGD "constitutes nothing more than an acronym created to describe a proposed clinical phenomenon that may or may not warrant further peer-reviewed scientific investigation").

[79] Restar AJ. Methodological Critique of Littman's (2018) Parental-Respondents Accounts of "Rapid-Onset Gender Dysphoria". Arch Sex Behav. 2020 Jan;49(1):61-66. doi: 10.1007/s10508-019-1453-2 (hereinafter, "Restar 2020"); Temple Newhook, J, Pyne, J, Winters, K, Feder, S, Holmes, C, Tosh, J, and Pickett, S. A critical commentary on follow-up studies and "desistance" theories about transgender and gender-nonconforming children. *International Journal of Transgenderism*, *19*(2), 212-224. (2018).

original Littman article because of its misstatements.[80] Such a correction in reputable, peer-reviewed academic journals is taken only when a panel of experts, in retrospect, came to recognize the methodological flaws of the original study and concluded that it would be unscientific to allow the originally published findings to stand.

Littman's hypothesis that rapid-onset gender dysphoria exists as a distinct condition has not been supported by studies of clinical data.[81] Neither the American Psychiatric Association nor any other reputable professional organization has recognized rapid-onset gender dysphoria as a distinct clinical condition or diagnosis.[82]

Section 3. The AG Opinion and the Alabama Law greatly exaggerate the risks of gender-affirming drug therapy.

The AG Opinion claims that "sex change procedures," including surgery and drug therapies "often ha[ve] the effect of permanently sterilizing those minor children."[83] The Alabama Law makes similar claims.[84] Section 1 of this report has established that the AG Opinion's claim with respect to surgery is false: current medical protocols state that individuals must be the age of majority or older before undergoing surgery on genitals or reproductive organs. In this Section, we focus on the AG Opinion's (and Alabama Law's) claims regarding the medical effects of drug treatment for transgender adolescents.

a. The AG Opinion and the Alabama Law greatly overstate the risks of puberty-blocking medication and incorrectly state that it results in sterilization.

The Texas Attorney General claims that "[t]here is insufficient medical evidence available to demonstrate that discontinuing [puberty-blocking] medication resumes a normal puberty process."[85] The Alabama Law contains similar statements.[86] The claim is false: puberty-blocking medication has been shown to be safe, effective, and fully reversible.

As noted in Section 1 of this report, puberty-blocking medication (gonadotropin-releasing hormone agonists, or GnRHa's) can be part of a staged approach to gender-affirming care for

[80] Littman L. Correction: Parent reports of adolescents and young adults perceived to show signs of a rapid onset of gender dysphoria. PLoS One. 2019 Mar 19;14(3):1-7 (altering the original article to, inter alia, clarify that the article collected no data from adolescents or clinicians and generates only a hypothesis for further exploration).
[81] Bauer GR, Lawson ML, Metzger DL; Trans Youth CAN! Research Team. Do Clinical Data from Transgender Adolescents Support the Phenomenon of "Rapid Onset Gender Dysphoria"? J Pediatr. 2022 Apr; 243:224-227. See also Arnoldussen M, Steensma TD, Popma A, van der Miesen AIR, Twisk JWR, de Vries ALC. Re-evaluation of the Dutch approach: are recently referred transgender youth different compared to earlier referrals? Eur Child Adolesc Psychiatry. 2020 Jun;29(6):803-811. Erratum in: Eur Child Adolesc Psychiatry. 2020 Dec 16 (concluding that there has been no marked change in the characteristics of the population of adolescents referred for gender dysphoria from 2000 to 2016; the authors hypothesize that the increase in number of referrals reflects the increasing social acceptability of seeking treatment).
[82] Restar (2018), cited in note 79.
[83] AG Opinion, at 2-3. The AG Opinion repeats its claim about sterilization. Id. at 5 ("The surgical and chemical procedures you ask about can and do cause sterilization.")
[84] Alabama Law, Sections 2(9), 2(11), 2(12), 2(13) and 2(14).
[85] AG Opinion, at 5.
[86] Alabama Law, Sections 2(7), (11), (12) and (13).

adolescents. By stalling pubertal maturation, the medication relieves adolescents of the intense gender dysphoria that can accompany pubertal development along the pathway of their assigned sex. During this pause, the adolescent is given time to confirm their gender identity and to consider the need for appropriate gender-affirming hormone therapy without having had their body mature along pubertal path incongruent with their gender identity. Adolescents who continue to identify as transgender will be able to proceed with gender-affirming hormone therapy when they, their parents, and their providers determine that treatment is medically appropriate. Puberty blockers not only alleviate gender dysphoria in adolescence but have beneficial lifelong effects on dysphoria and can minimize the need for subsequent treatments, including surgery in adulthood. In the unlikely event that a teen realizes that they identify as cisgender, they can discontinue the blocker and spontaneous pubertal maturation will resume.

The scientific evidence clearly shows that treatment with puberty blockers is fully reversible. GnRHa therapy has been used since the 1980's in children with precocious puberty, and a solid body of evidence documents that pubertal progression stops with drug therapy and that spontaneous pubertal development occurs after discontinuation of the medication.[87]

Recent studies suggest that puberty-blocking medication has negligible or small effects on bone development in adolescents, and any negative effects are temporary and reversible. The most recent studies show that puberty-blocking drug therapy either has no effect on bone mineral density (BMD), a proxy measure of bone strength, or is associated with a very small decrease.[88]

---

[87] Manasco PK, Pescovitz OH, Feuillan PP, Hench KD, Barnes KM, Jones J, Hill SC, Loriaux DL, Cutler Jr GB. Resumption of puberty after long term luteinizing hormone-releasing hormone agonist treatment of central precocious puberty. J Clin Endocrinol Metab. 1988 Aug 1;67(2):368-72; Heger S, Muller M, Ranke M, Schwarz H, Waldhauser F, Partsch C, Sippell WG. Long-term GnRH agonist treatment for female central precocious puberty does not impair reproductive function. Mol Cell Endocrinol. 2006 Jul 25;254-255:217-220; Feuillan PP, Jones JV, Barnes K, Oerter-Klein K, Cutler Jr GB. Reproductive Axis after Discontinuation of Gonadotropin-Releasing Hormone Analog Treatment of Girls with Precocious Puberty: Long Term Follow-Up Comparing Girls with Hypothalamic Hamartoma to Those with Idiopathic Precocious Puberty. J Clin Endocrinol Metab. 1999 Jan;84(1):44-49; Bertelloni S, Baroncelli GI, Ferdeghini M, Menchini-Fabris F, Saggese G. Final height, gonadal function and bone mineral density of adolescent males with central precocious puberty after therapy with gonadotropin-releasing hormone analogues. Eur J Pediatr. 2000 May;159(5):369-74 (hereinafter, "Bertelloni et al (2000)"); Bertelloni S, Mul D. Treatment of central precocious puberty by GnRH analogs: long-term outcome in men. Asian J Androl. 2008 Jul;10(4):525-34; Luo X, Liang Y, Hou L, Wu W, Ying Y, Ye F. Long-term efficacy and safety of gonadotropin-releasing hormone analog treatment in children with idiopathic central precocious puberty: A systematic review and meta-analysis. Clin Endocrinol. 2021 May; 94(5):786-96.

[88] Klink D, Caris M, Heijboer A, van Trotsenburg M, Rotteveel J. Bone mass in young adulthood following gonadotropin-releasing hormone analog treatment and cross-sex hormone treatment in adolescents with gender dysphoria. J Clin Endocrinol Metab. 2015 Feb;100(2):E270-75 (hereinafter, "Klink et al. 2015"); Schagen SEE, Wouters FM, Cohen-Kettenis PT, Gooren LJ, Hannema SE. Bone Development in Transgender Adolescents Treated With GnRH Analogues and Subsequent Gender-Affirming Hormones. J Clin Endocrinol Metab. 2020 Dec 1;105(12): e4252-e4263 (hereinafter, Schagen et al. 2020"); Delemarre-van de Waal HA, Cohen-Kettenis PT. Clinical management of gender identity disorder in adolescents: a protocol on psychological and paediatric endocrinology aspects. Eur J Endocrinol. 2006;155:S131-S137. Studies of children treated for precocious puberty found that BMD was normal at final height attainment. Alessandri SB, Pereira F de A, Villela RA, Antonini SRR, Elias PCL, Martinelli Jr CE, de Castro M, Moreira AC, de Paula FJA. Bone mineral density and body composition in girls with idiopathic central precocious puberty before and after treatment with a gonadotropin-releasing hormone agonist. Clinics (Sao Paulo). 2012;67(6):591-96; Antoniazzi F, Zamboni G, Bertoldo F, Lauriola S, Mengarda F, Pietrobelli A, Tato L. Bone mass at final height in precocious puberty after gonadotropin-releasing hormone agonist with and without calcium supplementation. J Clin Endocrinol Metab. 2003 Mar;88(3):1096-1101 (hereinafter,

Calcium supplementation has been shown to protect patients from bone loss.[89] Critically, any reduction in BMD is recovered when adolescents cease taking puberty-blocking medication, whether or not they continue to gender-affirming hormone therapy.[90]

Tellingly, the AG Opinion does not cite scientific evidence for its claim regarding "insufficient medical evidence"[91] Instead, it cites two legal cases, neither of which contains sound scientific evidence on this subject.[92] One of the cited cases is irrelevant, because it involves legal claims about surgery, not puberty blockers.[93] The other cited case, Bell v. Tavistock and Portman NHS Foundation Trust (2020), was reversed on appeal in the U.K. in 2021 because the decision relied on biased and inexpert scientific testimony.[94]

The AG Opinion also attacks puberty blockers by claiming that their use "is not approved by the federal Food and Drug Administration and is considered an 'off-label' use of the medications."[95] The Alabama Law makes a similar claim.[96] The implication is that off-label use of medication is harmful, but this claim is unfounded.

"Antoniazzi et al. (2003)"); Heger S, Partsch CJ, Sippell WG. Long-term outcome after depot gonadotropin-releasing hormone agonist treatment of central precocious puberty: final height, body proportions, body composition, bone mineral density, and reproductive function. J Clin Endocrinol Metab. 1999 Dec;84(12):4583-90; Neely EK, Bachrach LK, Hintz RL, Habiby RL, Slemenda CW, Feezle L, Pescovitz OH. Bone mineral density during treatment of central precocious puberty. J Pediatr. 1995 Nov;127(5):819-22.

[89] Antoniazzi et al. (2003), cited in note 88.

[90] Klink et al. (2015), cited in note 88; Schagen et al. (2020), cited in note 88. Bertelloni et al. (2000), cited in note 87; Pasquino AM, Pucarelli I, Accardo F, Demiraj V, Segni M, Di Nardo R. Long-term observation of 87 girls with idiopathic central precocious puberty treated with gonadotropin-releasing hormone analogs: impact on adult height, body mass index, bone mineral content, and reproductive function. J Clin Endocrinol Metab. 2008 Jan;93(1):190-195; Magiakou MA, Manousaki D, Papadaki M, Hadjidakis D, Levidou G, Vakaki M, Papaefstathiou A, Lalioti N, Kanaka- Gantenbein C, Piaditis G, Chrousos GP, Dacou-Voutetakis C. The efficacy and safety of gonadotropin-releasing hormone analog treatment in childhood and adolescence: a single center, long-term follow-up study. J Clin Endocrinol Metab. 2010 Jan;95(1):109-17; Bertelloni S, Baroncelli GI, Sorrentino MC, Perri G, Saggese G. Effect of central precocious puberty and gonadotropin-releasing hormone analogue treatment on peak bone mass and final height in females. Eur J Pediatr. 1998 May;157(5):363-67.

[91] AG Opinion, at 5.

[92] The AG Opinion's citation is "see generally Hennessy-Waller v. Snyder, 529 F. Supp. 3d 1031, 1042 (D. Ariz. 2021), citing Bell v. Tavistock and Portman NHS Foundation Trust, 2020 EWHC 3274, para. 134 (Dec. 1, 2020) (referring to Bell's conclusion that a clinic's practice of prescribing puberty-suppressing medication to individuals under age 18 with gender dysphoria and determining such treatment was experimental)." Id. at 5-6.

[93] Hennessy-Waller is a decision that denies a motion for preliminary injunction against an insurance company for failure to cover gender-affirming surgery. The decision involves surgery, not puberty blockers, and it is not a fully-adjudicated factual determination about either surgery or puberty blockers. Hennessy-Waller v. Snyder, 529 F. Supp. 3d 1031 (D. Ariz. 2021).

[94] Bell v. The Tavistock and Portman NHS Foundation Trust [2021] EWCA (Civ) 1363 [38] (Eng.) (noting that the claimant's (plaintiff's) expert evidence was faulty: "None of it complied with the rules regarding expert evidence and a good deal of it is argumentative and adversarial."). For a scientific review of the evidence in the lower court decision, see de Vries ALC, Richards C, Tishelman AC, Motmans J, Hannema SE, Green J, Rosenthal SM. Bell v Tavistock and Portman NHS Foundation Trust [2020] EWHC 3274: Weighing current knowledge and uncertainties in decisions about gender-related treatment for transgender adolescents. Int J Transgend Health. 2021 Apr 5;22(3):217-24.

[95] AG Opinion, at 5.

[96] Alabama Law, Section 2(7).

"Off label" means only that the FDA has not specifically approved a particular medication for a particular use. The off-label use of medications for children is quite common and often necessary, because an "overwhelming number of drugs" have no FDA-approved instructions for use in pediatric patients.[97] This is in part because pharmaceutical companies often lack financial incentives to support research required for FDA approval for specific use in children.[98] Indeed, the American Academy of Pediatrics specifically approves the off-label use of drugs:

> The purpose of off-label use is to benefit the individual patient. Practitioners use their professional judgment to determine these uses. As such, *the term "off-label" does not imply an improper, illegal, contraindicated, or investigational use*. Therapeutic decision-making must always rely on the best available evidence and the importance of the benefit for the individual patient.[99]

Many common medications, including hormones, are used off-label in adults and minors. In fact, pediatricians prescribe off-label drugs in 20% of patient visits.[100] Estrogen and testosterone are often used off-label to treat adolescents with intersex conditions. Common hormonal medications used off-label include norethindrone, a progesterone analogue used off-label for the treatment of heavy menstrual bleeding in those with polycystic ovarian syndrome, bleeding disorder, and anovulatory bleeding of early puberty. It is also used to treat endometriosis, which is a painful inflammatory condition. Many forms of combined hormonal contraception, as well as a testosterone-blocking medication (spironolactone), are used off-label to treat acne. Other examples include clonidine, a blood pressure medication used off-label for the treatment of ADHD, migraine headaches, disorders of behavioral regulation, and insomnia; and propranolol, a blood pressure medication used off-label for the treatment of performance anxiety.

> <u>b. The AG Opinion and the Alabama Law exaggerate the fertility risks of gender-affirming hormonal treatment.</u>

[97] The quote is from the American Academy of Pediatrics Committee on Drugs. See Frattarelli DA, Galinkin JL, Green TP, Johnson TD, Neville KA, Paul IM, Van Den Anker JN; American Academy of Pediatrics Committee on Drugs. Off-label use of drugs in children. Pediatrics. 2014 Mar;133(3):563-7 (hereinafter, "AAP Committee on Drugs (2014)"); see also Allen HC, Garbe MC, Lees J, Aziz N, Chaaban H, Miller JL, Johnson P, DeLeon S. Off-Label Medication use in Children, More Common than We Think: A Systematic Review of the Literature. J Okla State Med Assoc. 2018 Oct;111(8):776-783.

[98] AAP Committee on Drugs (2014), cited in note 97.

[99] AAP Committee on Drugs (2014), cited in note 97 (emphasis added). See also Schrier L, Hadjipanayis A, Stiris T, Ross-Russell RI, Valiulis A, Turner MA, Zhao W, De Cock P, de Wildt SN, Allegaert K, van den Anker J. Off-label use of medicines in neonates, infants, children, and adolescents: a joint policy statement by the European Academy of Paediatrics and the European society for Developmental Perinatal and Pediatric Pharmacology. Eur J Pediatr. 2020 May;179(5):839-847.

[100] Hoon D, Taylor MT, Kapadia P, Gerhard T, Strom BL, Horton DB. Trends in Off-Label Drug Use in Ambulatory Settings: 2006-2015. Pediatrics. 2019 Oct;144(4):1-10 (emphasis added).

The AG Opinion claims that gender-affirming hormone treatments cause infertility.[101] The Alabama Law contains a similar statement.[102] These are unwarranted exaggerations, which ignore the substantial evidence of reversibility of the fertility effects of hormone therapy.

Treatment with gender-affirming sex hormones impacts fertility while drug therapy is ongoing, but the effect is anticipated to be reversible if medication is discontinued. Importantly, hormone therapy is always individualized, and some transgender and non-binary teens remain on puberty blockers up to the age of majority without proceeding to hormone treatment.

For transgender men (persons assigned female sex at birth who retain ovaries), testosterone treatment can affect ovarian function, inhibiting menses in the majority of those on therapy. The evidence shows that most transgender men who had regular menses before starting testosterone therapy are reported to resume menses if testosterone is discontinued.[103] Some transgender men may retain fertility during hormone treatment: spontaneous pregnancies have occurred in testosterone-treated transgender men, some while still amenorrheic.[104] Further, a number of transgender men have discontinued testosterone therapy prior to undergoing assisted reproductive technology and have carried pregnancies to term with delivery of normal infants.[105]

The effects of gender-affirming estrogen treatment on testicular histology vary among individuals. Reduced spermatogenesis is common while patients remain on estrogen, but fully normal spermatogenic activity has been documented.[106] Importantly, return of spermatogenesis occurred quickly in patients who discontinued hormone treatment.[107] Patients who were treated with puberty blockers (GnRHa's) starting at the onset of pubertal development and estrogen at

[101] AG Opinion, at 3.
[102] Alabama Law, Section 2(13).
[103] Endocrine Society (2017). Light AD, Obedin-Maliver J, Sevelius JM, Kerns JL. Transgender men who experienced pregnancy after female-to-male gender transitioning. *Obstet Gynecol.* 2014;124(6):1120–1127 (hereinafter, "Light et al. 2014"); Pelusi C, Costantino A, Martelli V, et al. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med.* 2014;11(12):3002–3011.; Smith KP, Madison CM, Milne NM. Gonadal suppressive and cross-sex hormone therapy for gender dysphoria in adolescents and adults. *Pharmacotherapy.* 2014;34(12):1282–1297.
[104] Light et al. (2014), cited in note 103; Light A, Wang LF, Zeymo A, Gomez-Lobo V. Family planning and contraception use in transgender men. Contraception. 2018 Oct;98(4):266-69.
[105] Leung A, Sakkas D, Pang S, Thornton K, Resetkova N. Assisted reproductive technology outcomes in female-to-male transgender patients compared with cisgender patients: a new frontier in reproductive medicine. Fertil Steril. 2019 Nov;112(5):858-65; Wallace SA, Blough KL, Kondapalli LA. Fertility preservation in the transgender patient: expanding oncofertility care beyond cancer. Gynecol Endocrinol. 2014;30(12):868-71; Maxwell S, Noyes N, Keefe D, Berkeley AS, Goldman KN. Pregnancy outcomes after fertility preservation in transgender men. Obstet Gynecol. 2017 Jun;129(6):1031-34.; Gale J, Magee B, Forsyth-Greig A, Visram H, Jackson A. Oocyte cryopreservation in a transgender man on long-term testosterone therapy: a case report. F S Rep. 2021 Feb 20;2(2):249-51.
[106] Schneider F, Kliesch S, Schlatt S, Neuhaus N. Andrology of male -to-female transsexuals: influence of cross-sex hormone therapy on testicular function. Andrology. 2017 Sept;5(5):873-80.
[107] Schneider F, Neuhaus N, Wistuba J, Zitzmann M, Heß J, Mahler D, van Ahlen H, Schlatt S, Kliesch S. Testicular functions and clinical characterization of patients with gender dysphoria (GD) undergoing sex reassignment surgery (SRS). J Sex Med. 2015 Nov;12(11):2190-2200.

16 years of age were shown to have normal-appearing, immature sperm-producing cells in the testes, suggesting those individuals retained fertility potential.[108]

As with any other medical decision, parents and providers carefully weigh the risks of treating the individual adolescent against the risks of not treating them, including the mental health impact and potential suicide risk of not beginning gender-affirming care.

As the standard protocols summarized in Section 1 of this report demonstrate, there is no push by physicians to proceed to hormone therapy. On the contrary, the decision to proceed with drug therapy and the choice of therapy are determined after assessing each adolescent's medical history as well as their past and ongoing mental health concerns. The standard of care specifically states that any existing mental health issues must be stable prior to moving forward with gender-affirming medical interventions. When counseling transgender adolescents who are considering gender-affirming drug therapy, physicians can also offer sperm or oocyte (egg) cryopreservation.

In addition to its claims about fertility, the AG Opinion offers a list of asserted medical harms without citation to any existing medical authority. The cited source is a healthcare website, and the underlying document has been removed from the site and is not otherwise available on the Internet.[109] The opinion offers no scientific foundation for its claims but seems to conflate long-outdated practice with the current standard of care.[110]

A more accurate perspective begins with an understanding of the role of hormones in the body. Hormones play a role in determining the medical profile of cisgender people. Generally speaking, cisgender women have relatively higher levels of estrogen and lower levels of testosterone, and cisgender men have the reverse. Each hormonal profile carries with it medical benefits and risks. Cisgender women, for example, have lower rates of cardiovascular disease than cisgender men but higher risks of venous thromboembolism. When a transgender individual receives gender-affirming hormone treatment, they take doses of exogenous sex hormones that approximate the physiologic state of their identified gender. Put simply, a transgender female is supplied an amount of estrogen similar to the estrogen that a cisgender woman's ovaries typically produce. Similarly, a transgender male receives a dose of testosterone that approximates what a cisgender male's testicles typically produce. Protocols provide explicit dosage guidelines to approximate the physiology of the patient's identified gender rather than to develop desired physical characteristics.

The medical result is that transgender individuals move toward the typical medical profile of their identified gender. And so transgender women, like cisgender women, have lower risks of

---

[108] de Nie I, Mulder CL, Meißner A, Schut Y, Holleman EM, van der Sluis WB, Hannema SE, den Heijer M, Huirne J, van Pelt AMM, van Mello NM. Histological study on the influence of puberty suppression and hormonal treatment on developing germ cells in transgender women. Hum Reprod. 2022 Jan 28;37(1):297-308.

[109] The AG Opinion cites to Timothy Cavanaugh, M.D., Cross-Sex Hormone Therapy, FENWAY HEALTH (2015), https://www.lgbtqiahealtheducation.org/wp-content/uploads/Cross-Sex-Hormone-Therapy1.pdf. A search conducted in March 2022 found that the link was broken and the document could not be found on the Fenway Health website or elsewhere on the Internet.

[110] The iatrogenic (drug-induced) risks of hepatotoxicity, meningioma, and prolactinoma are now zero, because the medication associated with those risks (cyproterone) is no longer in use in the United States. WPATH (2012), p. 48.

cardiovascular disease than cisgender men.[111] Transgender women, like cisgender women, have a slightly higher risk of venous thromboembolism than cisgender men. In fact, transgender women have a *lower* risk of venous thromboembolism than cisgender women, and the overall risk is extremely low (less than 1%) for all transgender individuals, both women and men.[112] The risk of venous thromboembolism in transgender women and non-pregnant cisgender women is less than the risk in pregnancy, which is the highest estrogenic physiologic state known.

It is also critical to note that the medical impact of gender-affirming treatment is generally the same in transgender people as in cisgender people who take the same hormone medications. For example, physicians commonly prescribe hormonal contraceptives containing ethinyl estradiol (a synthetic estrogen) to adolescents for reasons including birth control, management of irregular or painful menstrual periods, and acne. In other words, similar doses of exogenous sex hormones are commonly administered to cisgender individuals for a host of reasons and are well tolerated.

[111] Connelly PJ, Marie Freel E, Perry C, Ewan J, Touyz RM, Currie G, Delles C. Gender-Affirming Hormone Therapy, Vascular Health and Cardiovascular Disease in Transgender Adults. Hypertension. 2019 Dec;74(6):1266-1274. doi: 10.1161/HYPERTENSIONAHA.119.13080. Epub 2019 Oct 28. Erratum in: Hypertension. 2020 Apr;75(4):e10. PMID: 31656099; PMCID: PMC6887638.

[112] Oral estradiol, the preferred estrogen formulation that is given to transgender women in the United States, carries a VTE risk of <1%. T'Sjoen G, Arcelus J, Gooren L, Klink DT, Tangpricha V. Endocrinology of Transgender Medicine. Endocr Rev. 2019 Feb 1;40(1):97-117. In transgender men, the overall risk of VTE ranges from 0% to 0.34%. Maraka S, Singh Ospina N, Rodriguez-Gutierrez R, Davidge-Pitts CJ, Nippoldt TB, Prokop LJ, Murad MH. Sex Steroids and Cardiovascular Outcomes in Transgender Individuals: A Systematic Review and Meta-Analysis. J Clin Endocrinol Metab. 2017 Nov 1;102(11):3914-23.

Appendix A: Additional Information on Biased Sources of Information in the AG Opinion

Here, we address two sources of information mischaracterized by the AG Opinion as authorities on, respectively, science and medical ethics.

a. The Society for Evidence-Based Gender Medicine

The AG Opinion twice cites the Society for Evidence-Based Gender Medicine ("SEGM"). SEGM claims to be "an international group of over 100 clinicians and researchers concerned about the lack of quality evidence for the use of hormonal and surgical interventions as first-line treatment for young people with gender dysphoria."[113]

Despite SEGM's statement, the group appears to be nothing more than a website; it does not appear to hold meetings, screen its members, or publish a journal. The original content on the website includes statements unsupported by any citations. When the content does provide citations, they are often unreliable or misleading. The SEGM website includes a list of citations to more than 100 articles as evidence for the medical risks of gender-affirming care, but we reviewed each article and found the vast majority to be of low quality. The site's content omits mention of the standards of care published by mainstream scientific organizations, and it falsely claims that the standard protocols permit gender-affirming surgery before the age of majority. The long list of citations omits mainstream scientific articles that do not support the SEGM agenda, and the list includes a large number of letters to the editor, which are not peer-reviewed or fact-checked,[114] as well as other sources of little scientific value, including opinion pieces and case studies.

Although the SEGM site claims "over 100 clinicians and researchers" as members, it lists as "clinical and academic advisors" a group of only 14 people, many of whom have limited (or no) scientific qualifications related to the study of medical treatment for transgender people. Of the 14, only eight claim academic credentials above the master's degree level (and, of these, two of the PhD's are in sociology and evolutionary biology). None have academic appointments in pediatric medicine or child psychology; none have published original empirical research on the medical treatment of transgender people in a peer-reviewed publication; and none currently treat patients in a recognized gender clinic.[115]

A contextual examination reveals that SEGM is an ideological organization without apparent ties to mainstream scientific or professional organizations. Its 14 core members are a small group of repeat players in anti-trans activities – a fact that the SEGM website does not disclose. These 14 often write letters to the editor of mainstream scientific publications; these letters appear in the list of publications on the website (even though letters to the editor typically are not peer-reviewed or fact-checked). (Our review shows that the group of 14 has a total of 39 relevant publications and that 75% of these are letters to the editor.)

---

[113] All SEGM.org website citations reflect visits to the site in March 2022.
[114] Of the 123 listed papers (some are listed more than once), 49 (or 40%) are letters to the editor or opinion pieces.
[115] These findings are based on the biographical data posted on the SEGM.org website, supplemented with searches of Google (to determine academic appointments and listed publications) and the database PubMed (to determine medical publication records).

The core members of SEGM frequently serve together on the boards of other organizations that oppose gender-affirming treatment and, like SEGM, feature biased and unscientific content. These include Genspect, Gender Identity Challenge (GENID), Gender Health Query, Rethink Identity Medicine Ethics, Sex Matters, Gender Exploratory Therapy Team, Gender Dysphoria Working Group, and the Institute for Comprehensive Gender Dysphoria Research.

b. Purported bioethics experts

The AG Opinion cites two purported ethics experts for the proposition that "it is particularly unethical to radically intervene in the normal physical development of a child to 'affirm' a 'gender identity' that is at odds with bodily sex."[116]

This is an unreliable citation for two reasons. First, the cited item is not published in a peer-reviewed or mainstream legal or ethics journal. It appears, instead, in *Public Discourse*, an online journal on the website of an organization with no clear academic or professional affiliation.[117] Second, the two authors have strong ties to anti-trans activism. The first author, Ryan T. Anderson, is the president of a right-wing, Catholic-identified think tank. [118] (Anderson is also the founder of the publishing journal, *Public Discourse*, further undermining the credibility of the citation.) The second author, Robert George, is a professor at Princeton who has long been engaged in anti-trans political activism. George is the founder of The American Principles Project, which states: "We want to impose a political cost on the Left's anti-family extremism. If they want to attack parental rights [or] confuse young children about their gender…they are going to be punished at the polls."[119]

By contrast, academic experts in bioethics consider gender-affirming treatment to be ethical.[120] They emphasize "the importance of balanced decision making when counseling and

---

[116] AG Opinion, at 4 (citing Anderson RT, George RP. Physical Interventions on the Bodies of Children to "Affirm" their "Gender Identity" Violate Sound Medical Ethics and Should Be Prohibited [Internet]. Public Discourse: The Journal of the Witherspoon Institute; 2019 Dec 8 [cited 2022 Mar]. Available from: https://www.thepublicdiscourse.com/2019/12/58839/.

[117] "*Public Discourse* is the online journal of the Witherspoon Institute, a 501(c)3 research center located in Princeton, New Jersey". Our Mission. Public Discourse: The Journal of the Witherspoon Institute; c2022 [cited 2022 Mar]. Available from: https://www.thepublicdiscourse.com/our-mission/.

[118] "Founded in 1976, the Ethics and Public Policy Center" works "to apply the riches of the Judeo-Christian tradition to contemporary questions of law, culture, and politics, in pursuit of America's continued civic and cultural renewal." About. Ethics & Public Policy Center; c2022 [cited 2022 Mar]. Available from: https://eppc.org/about/. The EPPC's programs include "Catholic Studies" and the "Catholic Women's Forum. Programs. Ethics & Public Policy Center; c2022 [cited 2022 Mar]. Available from: https://eppc.org/program/. Anderson is listed as the president. Ryan T. Anderson. Ethics & Public Policy Center; c2022 [cited 2022 Mar]. Available from: https://eppc.org/author/ryan_anderson/.

[119] About. American Principles Project; c2020 [cited 2022 Mar]. Available from: https://americanprinciplesproject.org/about/. On another page, the website states that the American Principles Project was founded in 2009 by George and "veteran political strategist Frank Cannon." History. American Principles Project; c2020 [cited 2022 Mar]. Available from: https://americanprinciplesproject.org/about/history-story/.

[120] For examples, see Kimberly LL, Folkers KM, Friesen P, Sultan D, Quinn GP, Bateman-House A, Parent B, Konnoth C, Janssen A, Shah LD, Bluebond-Langner R, Salas-Humara C. Ethical Issues in Gender-Affirming Care for Youth. Pediatrics. 2018 Dec;142(6):e20181537; Bizic MR, Jeftovic M, Pusica S, Stojanovic B, Duisin D,

treating adolescents with nonconforming gender identities,"[121] and they have evaluated decision-making procedures that can ensure that adolescents and their parents give fully-informed consent to treatment.[122] These considerations align with the consent processes prescribed by standard medical protocols, which we discuss in Section 1.

Vujovic S, Rakic V, Djordjevic ML. Gender Dysphoria: Bioethical Aspects of Medical Treatment. BioMed Res Int. 2018 Jun 13;2018:9652305; Strang JF, Powers MD, Knauss M, Sibarium E, Leibowitz SF, Kenworthy L, Sadikova E, Wyss S, Willing L, Caplan R, Pervez N, Nowak J, Gohari D, Gomez-Lobo V, Call D, Anthony LG. "They Thought It Was an Obsession": Trajectories and Perspectives of Autistic Transgender and Gender-Diverse Adolescents. J Autism Dev Disord. 2018 Dec;48(12):4039-55.

[121] Steensma TD, Wensing-Kruger SA, Klink DT. How Should Physicians Help Gender-Transitioning Adolescents Consider Potential Iatrogenic Harms of Hormone Therapy? AMA J Ethics. 2017 Aug 1;19(8):762-70.

[122] Vrouenraets LJJJ, Hartman LA, Hein IM, de Vries ALC, de Vries MC, Molewijk BAC. Dealing with Moral Challenges in Treatment of Transgender Children and Adolescents: Evaluating the Role of Moral Case Deliberation. Arch Sex Behav. 2020 Oct;49(7):2619-34.

gillette CHILDREN'S

The Honorable Brett Guthrie, Chair
The Honorable Anna Eshoo, Ranking Member
House Energy and Commerce Committee, Subcommittee on Health
2125 Rayburn House Office Building
Washington, DC 20515

June 14, 2023

Dear Chair Guthrie, Ranking Member Eshoo, and Members of the House Energy and Commerce Committee Subcommittee on Health:

Thank you for the opportunity to share feedback on the Children's Hospital Graduate Medical Education (CHGME) program. As a pediatric specialty care healthcare system, Gillette Children's Specialty Healthcare can provide a unique perspective on the importance of this program.

Gillette Children's was founded over 125 years ago and was our country's first hospital dedicated to providing clinical care to children living with a disability. We care for children who have some of the most complex, traumatic, and rare conditions. Our patients typically require intense, lifelong care and medical intervention due to conditions such as cerebral palsy, Duchenne muscular dystrophy, spina bifida, and epilepsy, as well as spinal cord and brain injury and skeletal deformities. Most of our patients have multiple overlaying and disabling conditions and are Medicaid beneficiaries due to their disability or income level.

Our care model is team-based and combines the expertise of specialists from a variety of disciplines. For example, patients that need a spasticity evaluation see a physical therapist, physiatrist, neurosurgeon, and orthopedic surgeon. We believe this highly specialized and closely coordinated care model helps our patients achieve the best possible outcomes.

Gillette Children's is one of approximately 50 US children's hospitals that receives CHGME funding. As a specialty hospital, we provide exceptional training opportunities for medical students, residents and fellows. In academic year 2022 alone, over 100 residents, fellows, and medical students were trained across various specialties including pediatric orthopedic surgery, complex care pediatrics, craniofacial surgery, dentistry, endocrinology, and physical medicine and rehabilitation.

The CHGME program is distinct from the Medicare Graduate Medical Education (GME) program, which is distributed using a formula that is linked to Medicare patient volume. Freestanding children's hospitals do not qualify for Medicare GME, as they do not provide care for the Medicare population. Adult-based teaching hospitals that receive Medicare GME funding may offer some pediatric training, but children are not the majority of the patients seen in these facilities, so training options are limited. In 1999, Congress recognized the need for a dedicated source of federal funding to support the training of pediatricians and pediatric specialists and subspecialists and created the CHGME program.

Pediatrics is a clinically distinct field and demands specialized expertise. For children living with a disability, the need for thoughtfully trained providers who specialize in caring for this population becomes even more pronounced. The difference in the orthopedic surgical needs of adults and children

illustrates how training for these providers differs, though there are many examples. A pediatric trained orthopedic surgeon has specialized training in treating musculoskeletal problems of infants, children, and adolescents. This includes conditions related to growth and development, such as scoliosis, hip dysplasia, and limb length discrepancies, as well as a variety of sports-related injuries and traumas, both accidental and non-accidental.

An adult orthopedic surgeon typically focuses on treating conditions that primarily affect adults, such as arthritis and degenerative joint diseases. While they may also have training and experience in treating children, they usually do not have the same level of expertise or specialized knowledge as a pediatric trained orthopedic surgeon based on training as well as experience in the field. Pediatric trained orthopedic surgeons are better trained to diagnose and treat orthopedic problems that are unique to children and have the skills to provide appropriate and effective treatment for younger patients.

People living with a disability already face significant barriers in accessing care, particularly finding providers who are trained to address their unique, complex medical needs. The training opportunities provided by Gillette and supported by CHGME funding play a pivotal role in ensuring that the next generation of providers is equipped to care for children living with a disability. We urge the Subcommittee to support a clean, bipartisan reauthorization of the CHGME program, as has been the norm since the program's creation.

Thank you for the opportunity to share our comments regarding the importance of the CHGME program. Also included is an article and video demonstrating how CHGME funding is used in our hospital. Please contact Andrea Stoesz, Director of External Affairs, (andreaestoesz@gillettechildrens.com) with any questions or for additional information.

Sincerely,

Barbara Joers
President and CEO
Gillette Children's Specialty Healthcare

Micah Niermann, MD
Executive Vice President of Clinical Affairs and Chief Medical Officer
Gillette Children's Specialty Healthcare

June 9, 2023

The Honorable Rep. Michael Burgess
U.S. House of Representatives
2161 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
U.S. House of Representatives
272 Cannon House Office Building
Washington, DC 20515

The Honorable Mariannette Miller-Meeks
U.S. House of Representatives
1034 Longworth House Office
Washington, DC 20515

The Honorable Robin Kelly
U.S. House of Representatives
2329 Rayburn House Office Building
Washington, DC 20515

The Honorable Jen Kiggans
U.S. House of Representatives
1037 Longworth House Office
Washington, DC 20515

The Honorable Lisa Blunt Rochester
U.S. House of Representatives
1724 Longworth House Office Building
Washington, DC 20515

Dear Representatives Burgess, Eshoo, Miller-Meeks, Kelly, Kiggans and Blunt Rochester:

On behalf of the undersigned 79 organizations, we write to join you in expressing our strong support for the PREEMIE Reauthorization Act of 2023 (S.1573/H.R.3226), vital legislation to reauthorize and expand research, education and intervention activities related to preterm birth. It was introduced on May 11, 2023 by Sen. Michael Bennet (D-CO), Sen. John Boozman (R-AR), Rep. Michael Burgess (R-TX), Rep. Anna Eshoo (D-CA), Rep. Mariannette Miller-Meeks (R-IA), Rep. Robin Kelly (D-IL), Rep. Lisa Blunt Rochester (D-DE) and Rep. Jen Kiggans (R-VA).

U.S. preterm birth rate has steadily increased since 2014 to 10.5% in 2021, with a significant 4% increase in just one year and the highest recorded rate since 2007. This represents an increase to 383,082 preterm births. Black and Native American women are 62% more likely to have a preterm birth and their babies are twice as likely to die as compared to White women. Preterm birth also accounts for 35.8% of infant deaths in the U.S. and the annual societal economic cost (medical, education, and lost productivity) is an estimated $25.2 billion.

Although there are some clinical predictors of preterm birth, all pregnant individuals are at risk for preterm birth. Infants born prematurely have increased risks of morbidity and death throughout childhood, especially during the first year of life. Long-term health impacts include intellectual and developmental delays, behavioral problems, neurological disorders, visual and hearing impairments, cerebral palsy, and respiratory insufficiency or intestinal insufficiency.[1]

While many risk factors associated with preterm birth have been identified, the "biological basis for many of these risk factors and the underlying mechanisms remain poorly understood.[2]" This is particularly true for social and structural disparities. The PREEMIE Act will help reduce preterm birth,

[1] Prediction and prevention of spontaneous preterm birth. ACOG Practice Bulletin No. 234. American College of Obstetricians and Gynecologists. Obstet Gynecol 2021;138:e65–90.
[2] Rubens C, Sadovsky Y, LMuglia L, et al. Prevention of preterm birth: Harnessing science to address the global epidemic. Science Translational Medicine. 2014; 6(262):262sr5. doi: 10.1126/scitranslmed.3009871.

prevent newborn death and disability caused by preterm birth, expand research into the causes of preterm birth, and promote the development, availability, and uses of evidence-based standards of care for pregnant women.

Among the programs authorized by the PREEMIE Act is CDC's highly successful Pregnancy Risk Assessment Monitoring System (PRAMS). PRAMS collects site-specific, population-based data tracking maternal attitudes and experiences before, during, and shortly after pregnancy on 81% of births and is used by researchers and state, territory, and local governments to plan and review programs and policies aimed at reducing health problems among mothers and infants. This legislation will also provide for a new study on the costs, impact of non-medical factors, gaps in public health programs that lead to prematurity, and calls for recommendations to prevent preterm birth.

We look forward to working with you this year to advance this critical legislation. For more information, please contact Andrew Fullerton, Deputy Director of Federal Affairs, at [redacted].

Sincerely,

AIDS Action Baltimore
AIDS Foundation Chicago
American Academy of Ophthalmology
American Academy of Pediatrics
American Association for Pediatric Ophthalmology & Strabismus
American Association of Colleges of Pharmacy
American Association on Health and Disability
American College of Nurse-Midwives
American College of Obstetricians and Gynecologists
American Public Health Association
American Society for Reproductive Medicine
Arnold Solutions 53, Incorporated
Association of Black Cardiologists
Association of Maternal & Child Health Programs
Blue Cross Blue Shield Association
Blue Skies Consultation
Calming Nature Doula Service & Center
CARES Foundation Inc.
CDH International
Cerebral Palsy Foundation
Child Neurology Foundation
Children's Hospital Association
dsm firmenich North America
Educare Learning Network
Endocrine Society
Erie Niagara Area Health Education Center
Etana Tax and Accounting LLC
Families USA
Family Voices
Family Voices NJ

First Focus Campaign for Children
Futures Without Violence
Galactosemia Foundation
Genetic Alliance
Global Down Syndrome Foundation
Hadassah, The Women's Zionist Organization of America
Health Equity Solutions
Healthy Birth Day, Inc.
Impetus - Let's Get Started LLC
Ipas
Jericho Road Community Health Center
John Burton Advocates for Youth
Kaleida Health Family Planning
Lakeshore Foundation
March for Moms
March of Dimes
Michigan Council for Maternal and Child Health
MTS Sickle Cell Foundation, Inc.
National Association of Pediatric Nurse Practitioners
National CMV Foundation
National Health Law Program
National League for Nursing
National Partnership for Women & Families
National WIC Association
National Women's Health Network
Necrotizing Enterocolitis (NEC) Society
Nemours Children's Health
North American Society for Pediatric Gastroenterology, Hepatology and Nutrition
Preeclampsia Foundation
Prevent Blindness
Public Advocacy for Kids (PAK)
PUSH for Empowered Pregnancy
RESOLVE: The National Infertility Association
Rhia Ventures
Sigma Gamma Rho Sorority Inc.
Sigma Gamma Rho Sorority, Inc.- Lambda Epsilon Chapter
Sigma Gamma Rho, Alpha Phi Sigma Chapter Pretty Poodles
Society for Birth Defects Research and Prevention
Society for Maternal-Fetal Medicine
SPAN Parent Advocacy Network
Spina Bifida Association
STChealth
SWCyril Holdings Inc
Tennessee Health Care Campaign
The Collaborative
The Fibroid Foundation
U.S. Breastfeeding Committee
Unite for Reproductive & Gender Equity (URGE)

United Way of Buffalo & Erie County

CC:
Rep. Troy Balderson
Rep. Nanette Barragan
Rep. Buddy Carter
Rep. Kathy Castor
Rep. Angie Craig
Rep. Brian Fitzpatrick
Rep. Barry Moore
Rep. Lauren Underwood

JOURNAL OF JPOSNA®

Volume 4, Number S1, August 2022

JPOSNA® Special Edition
Advances in Pediatric Orthopaedic Education and Technical Training

A Surgical Simulation Module on Pediatric Femoral Osteotomies for Orthopaedic Surgery Residents

Zachary A. Quanbeck, MD[1]; Walter H. Truong, MD[1,2]; Michael T. Healy, MD[1,2]; Deborah S. Quanbeck, MD[1,2]; Emmalynn J. Sigrist, DO[2]

[1]Department of Orthopedic Surgery, University of Minnesota, Minneapolis, MN; [2]Gillette Children's Specialty Healthcare, St. Paul, MN

Correspondence: Emmalynn J. Sigrist, DO, 200 East University Ave., St. Paul, MN 55101. E-mail: [redacted]

Received: April 12, 2022; Accepted: April 17, 2022; Published: August 15, 2022

DOI: 10.55275/JPOSNA-2022-0062

Introduction

Based on the descriptions of the utility of surgical simulation in resident training by multiple authors[1-5] we developed a six-module pediatric orthopaedic surgical simulation program in November of 2012. Our goals were to enhance orthopaedic resident education through active learning, address essential requirements by the Accreditation Council for Graduate Medical Education (ACGME), and prepare for anticipated mandates by the American Board of Orthopaedic Surgery. We strove to diminish the patient's burden in the achievement of surgical competence and to reduce the level of trainee stress in learning complex skills.

The content for each of the six modules was established based on appropriate subject matter for second-year residents on their first pediatric orthopaedic rotation. Specific topics were chosen with respect to frequency, complexity, or a combination of these. For example, closed reduction with percutaneous pin fixation of supracondylar humerus fractures was selected because it is a frequent childhood injury with a moderate technical skill requirement for competency. By contrast, fixation of femur fractures in children was elected because, although the occurrence of this fracture is infrequent, its treatment is more demanding from a technical standpoint. In addition to these two simulations, our modules also included femoral osteotomies, external fixation of the femur and tibia, percutaneous pinning of slipped capital femoral epiphysis, and pelvic osteotomies.

The simulations typically occur once a month in our dedicated simulation center over 2-3 hours. A one-hour lecture on the topic is provided at a morning didactic session prior to the event. Residents are emailed a required reading list. Some of the modules have a pretest to aid in focused preparation. The session is attended

by three second-year residents, one or two mid-level residents who act as assistant instructors, a rotating medical student, and one or two orthopaedic staff surgeons. In addition, the support staff includes a surgery simulation center employee, radiology technologists, and an operating room assistant. Residents are relieved of their clinical duties during these sessions.

Following the model developed by Van Heest et al.,[1] we incorporate two evaluation tools: an Objective Structured Assessment of Technical Skills (OSATS) Checklist (Appendix Table A1) and a Global Rating Scale of Performance (Appendix Table A2) during and after the session to assess the trainees' level of medical knowledge, judgment, capabilities, and technical skills. The tools were adapted from the work of other authors[2,6-8] and tailored for each of our specific modules. Currently, we have the trainees complete the tools as a self-assessment.

These opportunities are possible because our institution has provided a budget and resources including a dedicated simulation center (Figure 1), surgical equipment, employed staff members, and synthetic bone models.

The staff manage the budget, order and modify the models, set up the room, and actualize the experience. The pediatric orthopaedic site director develops the curriculum for the sessions including creation of the modified OSATS Check Lists and Global Rating Scales. Surgeons volunteer their time to present a 1-hour lecture as well as create and supervise the simulation module. In some cases, we have enlisted vendor support for necessary specialized instruments. As an underlying principle, we have tried to keep the simulations low fidelity to manage cost while still providing a sufficiently realistic experience.

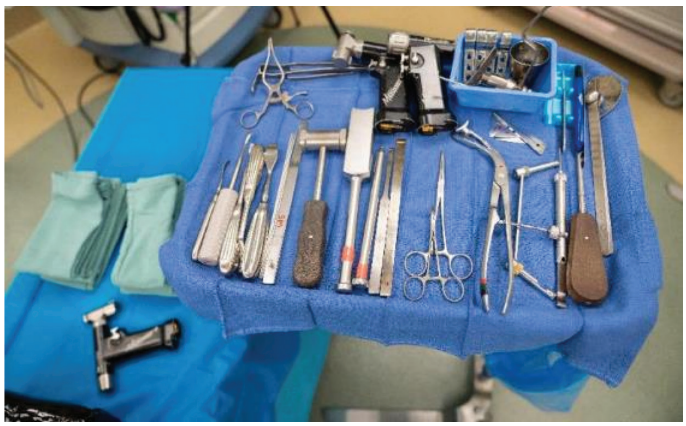
Figure 1. *The simulation center.*

Description of Simulation Exercise: Setup

At the beginning of our surgery simulation curriculum, the pediatric orthopaedic site director, the surgeons instructing each of the six topic-focused individual modules, and the simulation center staff met to discuss the plans for each module including model creation, room setup, and equipment needs. After completion of the first session for each module these meetings were brief and served to accomplish modifications to enhance the experience based on global feedback from all participants.

The laboratory is set up by the simulation center staff prior to the arrival of the trainees. The center can accommodate three stations. The number of stations is determined based on the anticipated attendance by trainees. Usually, two trainees work at one station with a bilateral lower extremity model affording each to act as surgeon and assistant. If the number of trainees exceeds six, then occasionally more than two trainees will be positioned at one spot. There are equipment stands and implant specific trays at each station and a back table for additional tools (Figures 2 and 3). The C-arm is shared amongst the stations with appropriate safety precautions utilized.

The trainees have already participated in a didactic session regarding the specific procedure and its indications. They have been given several articles and links to videos on our hospital's website or the internet. Sometimes, if an instructor prefers, they are given a multiple-choice, task-specific pretest and then the results are discussed at the didactic session. When the trainees arrive, the plan for the session is reviewed and they are then either assigned to a station or allowed to self-select their partners. If senior-level trainees are present, they



Figures 2 and 3. *Mayo stand and back table.*

may play an assistant instructor role while also having the opportunity to do the procedure themselves. In this proximal femoral osteotomy module, the models have been altered to create non-anatomic alignment with alteration of the neck shaft angle or the degree of anteversion. The trainees are warned that this is the case. At least one of the models has usually been placed in significant retroversion to challenge the learner. They are given a specific assignment such as, "The goal for this patient is for you to achieve a neck shaft angle of 110 degrees and residual anteversion of 10 degrees." The task assigned to any given resident can be individualized to make it more straightforward or complex based on that resident's level of learning.

At each of the stations, the session starts with a review of the previously instructed methods of measuring alignment. At our institution, these osteotomies are often performed in the prone position, so the simulation is also done with the model prone. The models are built to include synthetic bony legs and feet to afford practice at rotational profile measurement by using the tibial shaft as a surrogate for the distal femoral condylar axis (Figure 4).

The residents are handed the OSATS Checklist and the Global Rating Scale. These guide their task and prepare them to self-evaluate at completion of the session.

The trainees then proceed with the proximal femoral osteotomies. We use blade plates as they are a basic, affordable implant. Explanted plates and decommissioned surgical tools assist with cost reduction. Other systems could certainly be used.

Once all learners have had the chance to perform an osteotomy, a debriefing is performed, and residents complete the self-assessment forms (Figure 5).

In this module, if time permits, the instructor performs a distal femoral osteotomy. This allows the learner to see an experienced surgeon perform a similar procedure with the same instruments in a more skilled manner. While doing this, the instructor reinforces the learning that occurred earlier by asking and soliciting questions.

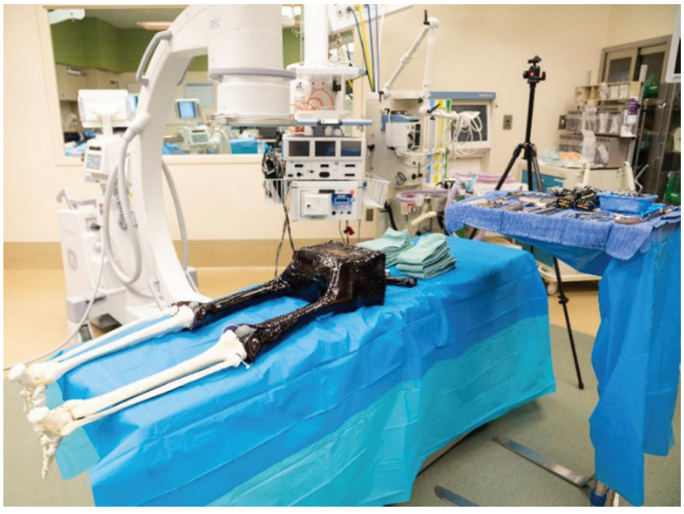


Figure 4. *Prone model.*

Figure 5. *A resident completing evaluation tools.*

This is the same overall format for each of the surgical modules. We chose to have the individual instructors create the plans for the specific sessions and encouraged them to teach in a manner with which they are comfortable while still utilizing the overall principles of active learning. It is helpful to have more than one surgeon connected to each module so that the scheduled session happens even if a particular surgeon becomes unavailable.

Description of Simulation Exercise: Training Technique

Principles of active learning, including those for resident education as described by Luc and Antonoff[9] and by faculty at the AAOS Course for Orthopaedic Educators,[10] guide this curriculum. For example, we adapt the knowledge content and procedural complexity for the sessions to the individual student's zone of development. As most of the trainees are second-year residents, this module was chosen and developed to review basic anatomy concepts, emphasize preoperative planning, increase exposure to equipment and implants, provide repeatable opportunities for performing specific skills, and improve self-awareness of surgical technical ability. For higher-level residents, participation provides the ability to learn by teaching. It is hoped that this learning is transferable to other procedures for all learners.

Figure 6. *A simulation crew.*

Other goals of all sessions are to foster communication and teamwork. Furthermore, surgeons have the opportunity to share and inspire passion for their art. We believe these enjoyable, interactive sessions lead to enhanced relationships between staff and learners. This interaction is presumed to translate in the future to a better operating room experience for all and most importantly, for the patient (Figure 6).

Active Learning Tips for Teachers for All Modules:

- Avoid over-instruction. Let the learner struggle with concepts and skills but balance this with real-time, constructive feedback for specific skills rather than allowing repetitive practice of poor technique.
- Keep the event learner-centered.
- Provide clear expectations.
- Encourage curiosity.
- Ask thought-provoking questions.
- Stick to the schedule.
- Make the experience fun.
- Apply the sandwich method of coaching, "You did that part well, you could do this differently, oh, and you performed that skill well."
- Capitalize on trainees' learning preferences.
- Solicit and apply improvements to the sessions.

Modifications to the curriculum and modules are made as needed. Simulation models evolve. For example, the original models were painted with radiopaque zinc-based paint. Now, they are purchased in this state to save time. Ponseti treatment of clubfeet and spine instrumentation have been added to the original modules. We added closed reduction of forearm fractures to the supracondylar humerus fracture session, as we found there was enough available time. Maintaining a consistent schedule requires attention to detail with effective communication across the residency program, some flexibility by all, and a strong commitment to the curriculum.

Summary

There have been several important components to the success of our surgical simulation program. As Karam et al.[11] found in their survey, the most substantial obstacle to the adoption of skills laboratories and a surgical skills curriculum is lack of funding. Funding provided by our institution was and continues to be essential. With the vision of our chief medical officer, the support of hospital administration, and the monetary contributions of donors the surgical simulation center was planned and created as a part of a renovation project of our entire operating room floor.

Hospital staff participate as a part of their work roles. The annual budget and designated donor gifts contribute to the expendable supplies. In some instances, vendors provide specialized equipment. Orthopaedic staff surgeons share their time, energy, and talents (Figure 7).

Engagement of the residency program director, the site director, and the site coordinator has been crucial. The trainees' enthusiasm, commitment to their education, and honest feedback have enhanced the ongoing experience.

A number of plans are in place to improve our program. First, we hope to re-establish the repeatable schedule of monthly sessions that occurred regularly prior to the pandemic. Reduced financial and personnel resources as well as our hospital's policy for social distancing decreased the frequency of these opportunities. As we learned at the outset of the program, development of a well-communicated calendar 6 months prior to the group of sessions is important so that instructors, trainees, staff, and other resources are all available.

Figure 7. *Orthopaedic staff instructors and residents.*

Second, we plan to optimize implementation of evaluation tools. Technologies, including motion capture and real-time video, are future considerations. Currently, the OSAT Checklist and the Global Rating scale are used to guide the actual performance of each simulation. The residents complete them as a self-assessment. This provides an opportunity for review and self-reflection, but the tools might be better used for formal evaluation. In order to do this, our tools must be modified.

Although similar to others' validated versions, our OSAT Checklists and Global Rating Scales have not yet been validated. Therefore, the outcome of our program cannot be scientifically demonstrated. Gratifyingly, the benefits of these sessions and the motivation to continue holding them have been realized based on trainee feedback. Annually, our orthopaedic residency program evaluates all scheduled learning sessions. In all years except one, from 2014 to 2019, our group of simulation modules ranked first out of 30. Residents' comments provide

further endorsement: "I really enjoy the simulations and felt these were the most helpful," and "The sim labs are excellent—probably the best-protected education time we have in residency."

Validation of our tools may allow achievement of objectives beyond that of resident satisfaction. As outlined by Kalun et al.,[12] matching surgical simulation tools to validated intraoperative assessment tools might determine whether skills are transferred from the simulation laboratory to the operating room. Better tools have the potential to assist with documentation of ABOS competency-based verification. Despite efforts to minimize costs, including use of recycled equipment, low-fidelity experiences, and efficient use of resources, these training sessions are expensive. To justify them, we need to be able to prove their worth.

From a broad perspective, research on evidence-based teaching using active learning in simulation settings has the potential to address the heightened challenges of surgical education.[9] Development of a standardized curriculum of pediatric orthopaedic simulations across multiple institutions may optimize patient outcomes, enhance learner development, and allow us to be better stewards of available resources.

Acknowledgements

Special thanks to Steven E. Koop, MD; Lily Wood, MD; John Wulfing; Amanda Handt; Jamie Price; Amy Schall; the radiologic technologists; and Ben Brewer. This article is dedicated to Debra Berny who served as pediatric orthopaedic site coordinator for 20 years and made this simulation program a success!

Disclaimer

Funding provided by the generous donors of Gillette Children's Specialty Healthcare. The authors have no conflicts of interest to report.

References

1 Van Heest A, Putnam M, Agel J, et al. Assessment of technical skills of orthopaedic surgery residents performing open carpal tunnel release surgery. *J Bone Joint Surg Am*. 2009;91(12):2811-2817.
2 Sonnadara RR, Van Vliet A, Safir O, et al. Orthopedic boot camp: examining the effectiveness of an intensive surgical skills course. *Surgery*. 2011;149(6):745-749.
3 Seymour NE, Gallagher AG, Roman SA, et al. Virtual reality training improves operating room performance: results of a randomized, double-blinded study. *Ann Surg*. 2002;236(4):458-463; discussion 63-4.
4 Atesok K, Mabrey JD, Jazrawi LM, et al. Surgical simulation in orthopaedic skills training. *J Am Acad Orthop Surg*. 2012;20(7):410-422.
5 Howells NR, Auplish S, Hand GC, et al. Retention of arthroscopic shoulder skills learned with use of a simulator. Demonstration of a learning curve and loss of performance level after a time delay. *J Bone Joint Surg Am*. 2009;91(5):1207-1213.
6 Lentz GM, Mandel LS, Goff BA. A six-year study of surgical teaching and skills evaluation for obstetric/gynecologic residents in porcine and inanimate surgical models. *Am J Obstet Gynecol*. 2005;193(6):2056-2061.
7 Doyle JD, Webber EM, Sidhu RS. A universal global rating scale for the evaluation of technical skills in the operating room. *Am J Surg*. 2007;193(5):551-555; discussion 5.
8 Reznick R, Regehr G, MacRae H, et al. Testing technical skill via an innovative "bench station" examination. *Am J Surg*. 1997;173(3):226-230.
9 Luc JGY, Antonoff MB. Active learning in medical education: application to the training of surgeons. *J Med Educ Curric Dev*. 2016;3.
10 Kern KRK. The final cut: An educational call to arms: Recovering from the impact of Covid-19. AAOSNow; 2021 March 2, 2022. Available at: https://aaos.org/aaosnow/2021/dec/commentary/commentary02/.
11 Karam MD, Pedowitz RA, Natividad H, et al. Current and future use of surgical skills training laboratories in orthopaedic resident education: a national survey. *J Bone Joint Surg Am*. 2013;95(1):e4.
12 Kalun P, Wagner N, Yan J, et al. Surgical simulation training in orthopedics: current insights. *Adv Med Educ Pract*. 2018;9:125-131.

Appendix

Appendix Table A1. Objective Structured Assessment of Technical Skills (OSATS) Checklist

(Modified with permission of Ranil Sonnadara, PhD, University of Toronto, Surgical Skills Centre, Toronto, ON, Canada)

Proximal Femoral Osteotomies

	Incomplete, Incorrect	Complete, Correct
Preoperative Elements		
1. Prone for proximal	0	1
2. C-arm from bottom for small patient. Angled from side (avoiding pedestal) for larger patient	0	1
3. Safe site sign, time out, antibiotic	0	1
Assessment of Deformity		
4. Describe torsional measurement methods	0	1
5. Able to define anatomy (anteversion, tibial torsion) and normal values (Describes exposure including length of incision and location)	0	1
Placement of Steinman Pin		
6. Correct size pin	0	1
7. Correct entry site	0	1
8. Less than 4 passes	0	1
9. Acceptable final position	0	1
10. Understands how to achieve AP/lateral views	0	1
Insertion of Chisel		
11. Knows which chisel (based on plate size)	0	1
12. Correct placement (location, depth, angle, rotation)	0	1
13. Disimpacts/reimpacts	0	1
Osteotomy		
14. Understands number and location of cuts	0	1
15. Performs cuts safely	0	1
Fixation/Correction		
16. Removes chisel in controlled manner	0	1
17. Places/impacts correct plate	0	1

18. Applies Verbrugge	0	1
19. Achieves correct alignment (derotation +/- other e.g., shortening, varus, flex/ext, etc.	0	1
20. Drills without plunging	0	1
21. Measures screw length	0	1
22. Places screws (one in compression)	0	1
23. Documents final result in 2 radiographic views	0	1
Maximum Total Score		23

Trainee Name:

Trainee Signature:

Trainee Comments:

Appendix Table A2. Global Rating Scale of Performance

(Modified with permission of Ranil Sonnadara, PhD)

Preoperative Planning				
1	2	3	4	5
Unclear about indications/ goals for procedure		Good understanding about indications/ goals but room for additional knowledge acquisition		Excellent familiarity with indications/goals for procedure
Time and Motion				
1	2	3	4	5
Many unnecessary movements Did not use time efficiently		Efficient but some unnecessary moves		All steps performed with economy of motion
Knowledge of Instruments				
1	2	3	4	5
Does not know names/ sizes of instruments or their purpose		Knows names of most instruments and how to use them		Knows all instruments and selects proper sizes

Instrument Handling				
1	2	3	4	5
Unable to use instruments in an appropriate manner		Competent use of instruments but requires significant additional thought or appears awkward		Skilled movements In control of instruments at all times
Flow of Procedure				
1	2	3	4	5
Stops frequently or is frantic Unsure of next steps Disorganized		A little too slow or rushed but makes progress		Confident about correct sequence, plans ahead
Knowledge of Specific Procedure				
1	2	3	4	5
Requires frequent instruction about instruments, alignment, steps of procedure. Appears anxious, unsure		Knows all of the important steps, missing few details		Excellent knowledge of osteotomies and how to achieve goal
Understanding of Safety Issues				
1	2	3	4	5
Too concerned with getting through procedure to exercise safety measures		Aware of risks to patient and care providers and caution evident (e.g., x-ray exposure, sharps)		Appropriate regard for risks (radiation exposure, sharps), avoids damage to soft tissues by using instruments properly
Overall Performance				
1	2	3	4	5
Novice		Competent		Advanced

Trainee Name:

Trainee Signature:

Trainee Comments:

Supplies for Femoral Osteotomy Simulation Session

General

Simulation room, which is a replica of a standard operating room
Radiolucent tables with protective drape. We do not drape the models but this could be incorporated.
C arm fluoroscope
C arm monitors
Lower extremity models
X-ray gowns
Gloves
Eye protection
Face masks (especially since the start of the pandemic)
We are unable to use biologic materials, as the simulation center is in proximity to the operating room suite and we do not have appropriate cleaning equipment.

Standard Orthopaedic Surgical Instruments Available in a Simulation Center Dedicated Pan

Arm/Navy
Chandler
Cobb elevator
Coker
Crego elevators
Drill bit set
Drills
Forceps
Freer
Goniometer
Homan
Joker
Kirschner wires
Mallet
Marking pen
Mayo
Osteotomes
Ruler
Saw blades
Scalpel
Self-retainers
Spinal needle
Spring retractors
Steinmann pins
Syringe with saline
Triangles

Implant Instrument Tray

Chisel
Tuning fork
Plate handle
Alignment guide
Verbrugge clamp
Screwdriver

Decommissioned Reusable Implants

Variety of sizes of blade plates
Variety of screw sizes and types

Involved Personnel

Orthopaedic site coordinator
Trainees
Orthopaedic staff surgeons
Simulation center staff
Operating room nurse
Radiology technologists
Housekeeping staff

Femoral Osteotomy Lower Extremity Model

Supplies for one model for this module

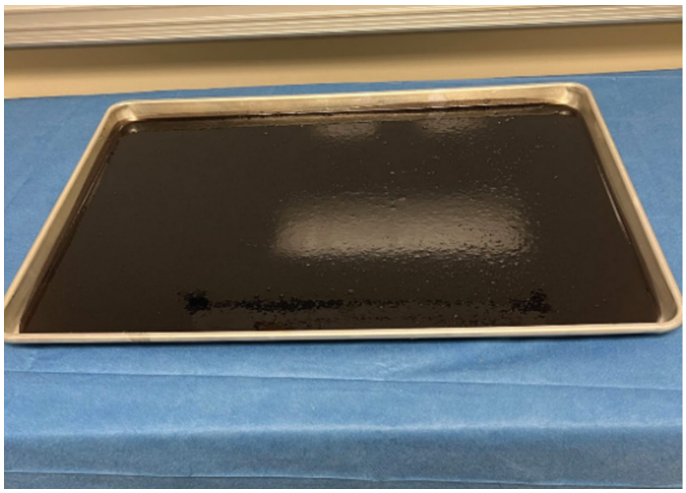
1. Pelvis
2. 2 Femurs (Left & Right)
3. 2 Tibias and Fibulas & Feet (Left & Right)
4. Zinc based gray spray paint
5. Power drill/bit
6. Scissors
7. Oven or hot air gun
8. Elastic
9. Plastic washers
10. Zip ties
11. 1 Gel base for pelvis
12. 2 18” x 26” sheets of gel. One for each femur

Supplies needed for one 18" x 26" model gel covering or base for pelvis

1. 1 16 oz can unflavored gelatin
2. 3 cups glycerin (food grade)
3. 3 cups water
4. Food coloring
5. 8 cup glass measuring bowl
6. 4 cup glass measuring bowl
7. Large container/mold
8. 18" x 26" baking sheet
9. Microwave

Instructions for Making the Model

Add 3 cups glycerin to an 8 cup measuring bowl. Add 1 (16 oz) can unflavored gelatin to glycerin, gently mix until dissolved, then add 3 cups water. Heat in microwave, stirring frequently. Once thoroughly mixed, add food coloring. Pour into a large container or mold and let dry overnight. This will help reduce the amount of air bubbles in the final mold. After completely cooled, mold can be covered and stored until needed. Cut into pieces, place in an 8 cup bowl, and melt in microwave. Pour into 18" x 26" baking sheet. (Appendix Figure A1). Let dry.



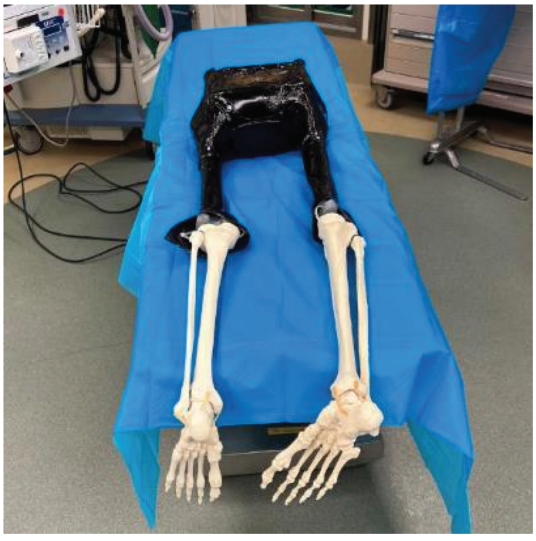
Appendix Figure A1. *Gel in baking sheet.*

Drill small hole through acetabulum, femur head, distal femur, and proximal tib/fib. Paint pelvis and femurs with zinc-based paint. To mount and stabilize pelvis, place pelvis in container, and pour gel mixture into container. Let dry overnight. Heat femurs in oven or with a hot air gun. Once heated, bone can be twisted to desired degree.

Cut 18" x 26" gel sheet into 3 equal parts. Using small amount of gel melted in small bowl as "glue," paint one small gel sheet and femur with gel. Wrap femur in small gel sheet and let dry (Appendix Figure A2). Repeat using 2nd gel sheet and 2nd femur. Using melted gel, glue 3rd gel sheet to center of pelvis.

Appendix Figure A2. *Gel sheet wrap of femur.*

Attach femurs to acetabulum using elastic and plastic washers. Cover pelvis (with attached femurs) using full 18" x 26" gel sheet. Use melted gel as glue to hold in place. Allow to dry. Attach leg using zip ties (Appendix Figure A3).



Appendix Figure A3. *Completed model.*

Cost of Supplies

Lower Extremity Model Sawbones® Parts

Part	Cost of Radiopaque in $	SKU	Cost of nonradiopaque in $	SKU
Pelvis, full male	172.50	130-96	54	1301
Femur, right, med.	30.25	1121-20-5	17.50	113-100
Femur, left, med	31.25	1121-69	17.50	1130
Foot + ankle, left			73.50	1132-3
Foot + ankle, right			73.50	1132-65

Bony parts purchased from Sawbones.com®, 10221 SW 188th St., Vashon Island, WA 98070.

Following the session, the pelvis and tibias are reclaimed and reused. Approximately 50% of the gel on the femurs can be reclaimed and reused. The gelatin materials for one model cost approximately $46. If zinc-based paint is used, the content for the zinc must be >93%. The pre-painted models are better quality but more costly.

Recipe for modification of models created by John Wulfing, Simulations Operations, Gillette Children's Specialty Healthcare. For further information, contact [redacted]

June 14, 2023

The Honorable Brett Guthrie
Chairman
Energy and Commerce Committee
Subcommittee on Health
Washington, D.C. 20515

The Honorable Anna Eshoo
Ranking Member
Energy and Commerce Committee
Subcommittee on Health
Washington, D.C. 20515

Dear Chairman Guthrie and Ranking Member Eshoo:

The Healthcare Leadership Council (HLC) appreciates the opportunity to provide comments in advance of your hearing, "Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases."

HLC is a coalition of chief executives from all disciplines within American healthcare. It is the exclusive forum for the nation's healthcare leaders to jointly develop policies, plans, and programs to achieve their vision of a 21st century healthcare system that makes affordable high-quality care accessible to all Americans. Members of HLC – hospitals, academic health centers, health plans, pharmaceutical companies, medical device manufacturers, laboratories, biotech firms, health product distributors, post-acute care providers, homecare providers, group purchasing organizations, and information technology companies – advocate for measures to increase the quality and efficiency of healthcare through a patient-centered approach. We are uniquely positioned to address innovation comprehensively from all perspectives in the healthcare industry.

HLC enthusiastically supports your goal to expand treatment innovation and access for the estimated 30,000 Americans living with a rare disease. Since Congress enacted the Orphan Drug Act forty years ago with the goal of stimulating the development of drugs for rare diseases, the US Food and Drug Administration (FDA) has approved more than 650 orphan drugs. With over 7,000 rare diseases identified, much more needs to be done.[1] If this progress is to be accelerated, Congress must unequivocally reprioritize innovation. Unfortunately, Congress has instead reversed course. Price setting provisions in the Inflation Reduction Act (IRA) will hinder innovation, including desperately needed treatments for rare diseases.

Specifically, the IRA's drug pricing provisions, once fully implemented, are likely to result in fewer small-molecule products developed and less continued research on already-approved drugs.

Small-molecule targeted therapies that patients can take orally are a promising recent innovation for treating a variety of rare diseases, particularly rare cancers.[2] Although the effective patent life for these small-molecule medicines has been found to be 13 to 14 years, when the IRA is fully implemented, small-molecule drugs will be eligible for possible government price setting only seven years after their FDA approval, with actual price ceilings applied at the

[1] Rare Diseases at FDA, U.S. Food and Drug Administration, (June 9, 2023), https://www.fda.gov/patients/rare-diseases-fda.

[2] Small Molecules in Targeted Cancer Therapy: Advances, Challenges, and Future Perspectives, Signal Transduction and Targeted Therapy, (May 31, 2021), https://doi.org/10.1038/s41392-021-00572-w.

nine-year mark.[3] The average cost to develop a new drug, including dollars spent on products that never gain approval, is between $1 billion and $2 billion.[4] Without an adequate time window to recoup these investments, drug manufacturers and capital investors are likely to redirect these investments away from small-molecule therapies.

While the IRA does include some exceptions in price setting for drugs developed to treat rare diseases, they are inadequate to protect innovation. According to CMS guidance, an orphan drug that is exempt from price caps would become eligible once the drug receives a second orphan drug designation to treat another rare disease. This disincentivizes manufacturers from producing drugs for rare diseases and harms patients.

HLC urges Congress to work with the administration to prioritize innovation and fix the IRA before it has these adverse effects. Implementation of the IRA's drug pricing provisions must be transparent and meaningfully engage stakeholders, centering the patient-experience. Collaboration with the private sector is also critical as we work towards the shared goal to reduce the cost of prescription drugs without significantly increasing health plan costs or sacrificing access or innovation.

HLC looks forward to working with Congress to increase innovation and access to care. Please reach out to Debbie Witchey with any questions.

Sincerely,

Mary R. Grealy
President

[3] Continuing Trends in U.S. Brand-Name and Generic Drug Competition, Journal of Medical Economics, (August 2, 2021), https://doi.org/10.1080/13696998.2021.1952795.
[4] Research and Development in the Pharmaceutical Industry, Congressional Budget Office, (April 8, 2021), https://www.cbo.gov/publication/57126.

CHILDREN'S HOSPITAL ASSOCIATION

Champions for Children's Health

Children's Hospital Association Statement for the Record

House Energy and Commerce Committee Subcommittee on Health Hearing, "Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases."

June 14, 2023

On behalf of the more than 200 nation's children's hospitals and the millions of children and families we serve, the Children's Hospital Association is submitting this statement for the record for today's legislative hearing. We appreciate the committee taking up several bills today that will help the patients and families children's hospitals and the specialized physicians important to their care serve, such as the PREEMIE Reauthorization Act and the Sickle Cell Disease and Other Heritable Blood Disorders Research, Surveillance, Prevention and Treatment Act. We urge the committee to promptly move legislation to reauthorize the Children's Hospitals Graduate Medical Education (CHGME) program, the only federal program focused exclusively on the training of pediatricians and pediatric specialists, without making any policy changes to this vital program. CHGME is critical to the national goal of providing needed care for America's children, including children in military families and those in underserved rural and urban communities. To this end, we support Rep. Schrier's bill, H.R. 3841, which would be a clean, five-year reauthorization of CHGME. In doing so, Congress can build upon its legacy of overwhelming bipartisan support for reauthorizing this critical program. We appreciate Rep. Schrier introducing H.R. 3841 and look forward to it moving promptly and in a bipartisan fashion.

As we face a critical pediatric provider shortage, CHGME is vital to ensuring our nation's children and their families have access to the routine care they need. The purpose of the program is to train doctors. How those physicians provide care is dependent on the scope of state law and what is supported by medical evidence in consultation with consenting families. CHA opposes tying the availability of physician training funding to any type of care provided at a hospital independently of its training programs as is suggested in H.R. 3887, which is why we oppose this legislation. To do so only threatens the critical pipeline of needed pediatricians.

Congress created the bipartisan CHGME program in 1999 recognizing that a dedicated source of support for training pediatricians and pediatric specialists in children's hospitals was key to building and sustaining a robust pediatric workforce and providing access to care for our nation's children. CHGME was established specifically to address the disparity between the funding that adult-focused hospitals access through Medicare Graduate Medical Education (GME) and the funding children's hospitals receive to train the pediatric physician workforce. Because children's hospitals care for extremely few children covered by Medicare, they receive very little Medicare GME funding—the primary source of federal support for training physicians. Before CHGME, pediatric physician training programs suffered from minimal federal support, leading to shortages of pediatricians which created access to care challenges for the nation's children. These challenges continue today.

Contact us: public.policy@childrenshospitals.org
600 13th St., NW | Suite 500 | Washington, DC 20005 | 202-753-5500
16011 College Blvd. | Suite 250 | Lenexa, KS 66219 | 913-262-1436
www.childrenshospitals.org | © Children's Hospital Association

Children's hospitals are pediatric workforce training hubs, responsible for training the next generation of pediatricians and pediatric specialists as well as pediatric nurses, therapists, advanced practitioners and technicians. They also serve as a vital safety net for all children regardless of insurance status, including those that are uninsured, underinsured and enrolled in Medicaid and the Children's Health Insurance Program (CHIP). Children's hospitals serve the majority of children with serious, chronic, and complex conditions, providing **95% of all pediatric cancer care**, and care to most children in need of major surgery.

CHGME children's hospitals have the patient volume necessary to train pediatric specialists. The residents and fellows whose training is supported by CHGME learn from experienced pediatric-focused practitioners, gain hands-on experience treating highly complex cases and participate in pediatric research ensuring the highest quality of care.

The Success of CHGME

Since its inception, CHGME has enabled children's hospitals to dramatically increase pediatric physician training overall and grow the supply of pediatric specialists. The 59 children's teaching hospitals that now receive CHGME support train **more than half of all pediatricians and pediatric subspecialists**, including pediatric cardiologists, child and adolescent psychiatrists, and pediatric oncologists. In some fields, such as pediatric rehabilitation medicine, virtually all physicians receive their training at CHGME children's hospitals. CHGME children's hospitals also train adult medical specialists, such as family medicine residents, who rotate through for their pediatrics training. In 2022, **over 15,000 pediatric residents trained in CHGME children's hospitals**.

Furthermore, CHGME is critical to the national goal of providing comprehensive and timely access to care for all of America's children. CHGME-trained physicians provide critical access to care to **children in military families and children in underserved rural and urban communities, serve as medical homes and address health care disparities**. Although CHGME-funded hospitals make up just 1% of all hospitals nationwide, these hospitals provide close to one-third of the inpatient hospital care received by children covered by Medicaid.

It is also important to note that approximately **60% of CHGME-funded physicians** who complete their training programs choose to practice in the states where they complete their residency – ensuring access to care for some of the most underserved children. This was critically important as the COVID-19 pandemic, RSV and the children's mental health crisis exacerbated existing pediatric workforce shortages and created a record-breaking demand for access to children's health care.

The Continuing Need for CHGME

While the CHGME program has helped the nation make great strides toward a more robust pediatric workforce to care for our nation's children, serious shortages in many pediatric specialties persist. Addressing those shortages by bolstering our pediatric workforce training programs is more important than ever as our nation's youth are grappling with a worsening mental, emotional, and behavioral health crisis. We cannot keep up the momentum to enhance the pediatric workforce and remove barriers to children's access to both physical and mental health care without the CHGME program.

Again, we urge the committee to promptly move Rep. Schrier's legislation (H.R. 3841) to reauthorize CHGME without making policy changes to this vital program. CHGME is an essential training program to our country's pediatric health care and ensuring children now and in the future have access to the specialized care they need.

BILL PASCRELL, JR.
9TH DISTRICT, NEW JERSEY

2409 RAYBURN HOUSE OFFICE BUILDING
WASHINGTON, D.C. 20515
(202) 225-5751
(202) 225-5782 FAX

ROBERT A. ROE FEDERAL BUILDING
200 FEDERAL PLAZA, SUITE 500
PATERSON, NJ 07505
(973) 523-5152
(973) 523-0637 FAX

http://pascrell.house.gov
bill.pascrell@mail.house.gov

Congress of the United States
House of Representatives

COMMITTEE ON WAYS AND MEANS
RANKING MEMBER, SUBCOMMITTEE ON OVERSIGHT
SUBCOMMITTEE ON SOCIAL SECURITY

DEMOCRATIC STEERING AND
POLICY COMMITTEE

Testimony of the Honorable Bill Pascrell, Jr. for
The House Energy and Commerce Subcommittee on Health Legislative Hearing
"Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases."
Wednesday, June 14, 2023

I thank Chair Cathy McMorris Rodgers, Ranking Member Frank Pallone, Health Subcommittee Chair Brett Guthrie, and Ranking Member Anna Eshoo for your important work in holding this critical hearing. This committee has an important opportunity to show needed leadership and support for protecting the health of our nation's firefighters.

Supporting research for deadly diseases is one of the most effective ways in which the federal government can invest in improving the health outcomes of our citizenry. I am grateful that my bipartisan bill, the Firefighter Cancer Registry Reauthorization Act of 2023 (H.R. 3821), is a part of today's discussion. I appreciate the support of Reps. Brian Fitzpatrick, Steny Hoyer, and Mike Bost, who are the co-chairs of the Congressional Fire Services Caucus and are my co-leads on H.R. 3821.

While the immediate, physical toll of the firefighting profession is tangible, the effects of exposure to deadly toxins and carcinogens can take years to develop. In 2015, National Institute for Occupational Safety and Health (NIOSH) published a multi-year study which found that firefighters are nine percent more likely to develop cancer and 14 percent more likely to die from cancer relative to the general population. Cancer is now the leading cause of death for firefighters.

Nearly three years ago, Paterson, New Jersey firefighter Jerry Behnke tragically lost his life to cancer. He was a leader in our community. He embodied the very best of public service. He was my dear friend.

We have found that this story is too common. Eduardo Diaz of Hasbrouck Heights was a career firefighter at North Hudson Regional who we lost to cancer six years ago at the age of 53.

When someone is diagnosed with cancer, information about their cancer is reported to the cancer registry in their state. However, specific details about their work are not taken into account. By collecting occupational information, the National Firefighter Registry allows researchers to better understand cancer and its risk factors in the fire service.

Congress created the Firefighter Cancer Registry by passing my bill (H.R. 931) into law in 2018 to study the relationship between long-term exposure to dangerous fumes and toxins and the

incidence of cancer in firefighters. In April 2023, the registry officially opened. Since then, the volunteer registry has already signed up thousands of firefighters. This is the largest effort in our nation's history to understand and reduce cancer among firefighters.

H.R. 3821 would simply reauthorize the registry for five years at a modest level of funding needed to continue this important mission.

I am pleased to have worked with the many prominent firefighting organizations on this legislation to ensure our government is doing more to combat this pernicious disease. Thank you to the International Association of Fire Fighters, New Jersey Firefighters Mutual Benevolent Association, International Association of Fire Chiefs, Congressional Fire Services Institute, and National Volunteer Fire Council.

Congress should act expeditiously to reauthorize the Firefighter Cancer Registry and I thank the committee for holding this hearing on our bipartisan bill.

Bill Pascrell, Jr.
Member of Congress

InterACT
Advocates for Intersex Youth
365 Boston Post Road, Suite 163 Sudbury, MA 01776

Testimony of interACT: Advocates for Intersex Youth
In opposition to H.R. 3887, by Rep. Crenshaw, R-TX
Before the House Energy and Commerce Subcommittee on Health
June 14, 2023

In the interest of the intersex youth for whom we advocate, we write in opposition to H.R. 3887, which would withhold program funding from facilities that offer gender-affirming care to young people. As the nation's preeminent advocacy organization working to advance the rights of children and youth with intersex variations, we condemn any policy effort that diminishes individuals' decision-making authority over the most personal aspects of their own bodies and lives. This bill is not only a remorseless attempt to obstruct access to crucial care that transgender young people seek and need; it is a double-edged sword that purports to authorize the continued practice of imposing unnecessary medical interventions on intersex children without their consent. If these hateful intentions are made law, H.R. 3887 will cause grave harm to millions of Americans, exacerbating health inequities for transgender and intersex communities alike for years to come.

We urgently request your help in preventing this outcome and urge you not to advance this legislation.

Intersex traits, a range of innate variations in physical sex characteristics that can cause an individual's body to differ from stereotypical notions of male or female, have an estimated prevalence of 1.7% in the general population. Although intersex variations rarely give rise to any need for urgent surgical intervention in childhood, intersex children are often subjected to operations to make their bodies conform more closely to expectations associated with the assigned sex. These surgeries are most commonly carried out before the age of two – long before an intersex individual will have the ability to make an informed decision about how they want their body to look and function. As such, these procedures are performed on the basis of stereotypes and assumptions rather than an individual's own stated wishes and priorities, let alone their evaluation of the risks and benefits of any proposed intervention – and the risks are far from trivial. The physical and psychological consequences of subjecting intersex infants to surgeries on their genitals or reproductive organs include risks of sterilization, permanent loss of sexual function, chronic pain, urinary incontinence, depression, and post-traumatic stress disorder.

In this context, it is hard to justify rushing an intersex infant through an irreversible surgery they may never even want or need. Nonetheless, in state legislation aiming to restrict transgender patients' access to gender-affirming care, language is commonly

included that expressly exempts medical interventions on children with intersex variations – usually referred to in these bills as "medically verifiable disorder[s] of sex development," and/or with language describing the presence of variations in bodily characteristics such as genitals, gonads, chromosomes, and hormone function.

H.R. 3887 takes the same tack, declaring that all of the enumerated procedures would still be permissible to perform on a child who has "both ovarian and testicular tissue," or who "does not have normal sex chromosome structure, sex steroid hormone production, or sex steroid hormone action." This framework, monstrously, seeks to hinder the availability of *consensual and medically necessary* treatment for gender dysphoria while giving approval to the paradigm of "normalizing" interventions to which young intersex patients *cannot consent* and that are otherwise *not medically necessary.*[1] Because procedures on intersex infants are carried out prior to a child having the ability to express their gender or care needs, this is *not* gender-affirming care,[2] but rather a choice made by the child's caregivers that may aim to "encourage" or enforce cisgender and heteronormative appearance and behavioral expectations based on the sex assigned (which will not always match the gender identity that the child develops). It is telling that proponents of H.R. 3887 and similar policy efforts prefer to preserve the availability of operations that serve one of the latter purposes than to allow children to discover who they are without coercion and constraint.

Both transgender youth and intersex youth deserve to be empowered in their medical decision-making, which requires not only supportive families and healthcare providers, but also the opportunity to exercise bodily autonomy and self-determination. H.R. 3887 sets up a double standard that works in the exact opposite way that it should: it denies transgender youth the ability to obtain care that meets their needs, consigns intersex children to a continuing risk of injury and violation, and ultimately protects no one. For these reasons, we urge you to oppose the harmful provisions of this bill.

Respectfully submitted,

Erika Lorshbough, Executive Director, interACT
[redacted]

[1] Only a small minority of surgeries on intersex infants and young children are performed for medical reasons that would be urgent enough to require intervention prior to the point when the individual could lead the decision.
[2] On the other hand, older intersex youth, like transgender youth, may choose to access hormonal and/or surgical interventions that meet their medical needs and help them feel at home in their body. Some intersex individuals view this as gender-affirming care, while others may not feel that the term accurately encompasses their experience. In this context, care that an intersex individual seeks and consents to could be described as affirming their bodily self-determination (instead of, or in addition to, affirming their gender).

JENNIFER WEXTON
10TH DISTRICT, VA

COMMITTEE ON APPROPRIATIONS

TRANSPORTATION, AND HOUSING AND URBAN DEVELOPMENT, AND RELATED AGENCIES

LEGISLATIVE BRANCH

COMMITTEE ON THE BUDGET

Congress of the United States
House of Representatives
Washington, DC 20515

WASHINGTON, DC
1210 LONGWORTH HOUSE OFFICE BUILDING
WASHINGTON, DC 20515
(202) 225-5135

LEESBURG
210 WIRT ST. SW, UNIT 102
LEESBURG, VA 20175
PHONE: (703) 234-3800

MANASSAS
9408 GRANT AVE., UNIT 403
MANASSAS, VA 20110
PHONE: (703) 236-1300

Statement for the Record of Congresswoman Jennifer Wexton
Subcommittee on Health
House Committee on Energy and Commerce
Regarding the Hearing: *"Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases."*
June 14, 2023

I would like to start by thanking Chair Rodgers, Chair Guthrie, Ranking Member Pallone, Ranking Member Eshoo, and all the members of the subcommittee for providing this opportunity to testify in strong support of two bipartisan pieces of legislation close to my heart - the National Plan to End Parkinson's Act and the Gabriella Miller Kids First Research Act 2.0.

As many of you know, on World Parkinson's Disease Day earlier this year, I shared that I have been diagnosed with Parkinson's Disease. Over the past several months, I have been touched by the messages of care and support and the desire for action from both sides of the aisle. If there's one thing that we can all agree on, it's that we must do better to fight this terrible disease. I am grateful to have a platform to be a voice for those struggling with Parkinson's and to fight to help bring greater resources to the search for a cure, and the National Plan to End Parkinson's Act will do just that. By bringing together key stakeholders to build a national plan to prevent and cure Parkinson's, this bill is taking a critical and historic step for the more than one million Americans with Parkinson's and their families. I urge you to advance this critical legislation.

I am grateful to have the opportunity to also testify on another critical piece of legislation – the Gabriella Miller Kids First Research Act 2.0. I introduced this legislation earlier this year in honor of my constituent Gabriella Miller who passed away at 10 years old from an inoperable brain tumor. Gabriella was a fierce advocate for childhood cancer research and changed the lives of countless other young children battling these illnesses. This bipartisan legislation would reauthorize and make a critical investment in the National Institutes of Health's (NIH) Gabriella Miller Kids First Pediatric Research Program (Kids First) to research new treatments and cures for childhood cancer and other rare pediatric diseases.

Cancer is the single leading cause of death among American children past infancy of any disease. Over 15,000 children are diagnosed with cancer annually. Despite the heartbreaking number of families impacted, childhood diseases are still poorly understood, and additional investment is desperately needed to bolster existing research efforts and advance new discoveries for children.

In April 2014, Congress took the first steps towards addressing this crucial problem for families across the country by passing the Gabriella Miller Kids First Research Act to uncover new insights into the biology of childhood disease. The law authorized $12.6 million annually in funds for childhood disease research representing important areas of emerging scientific opportunities, rising public health challenges, and knowledge gaps.

Since this time, the Kids First program has made significant progress toward understanding childhood cancer and disease. It has sequenced more than 30,000 samples from childhood cancer and structural birth defect cohorts and initiated the Gabriella Miller Kids First Data Resource Center—a comprehensive data resource for research and patient communities meant to advance discoveries. We must not settle for abysmal survival rates for one of our nation's most vulnerable populations and make this desperately needed investment to further this important research.

No family should have to face the horrors of pediatric cancer and disease or Parkinson's disease. I urge you to join me in reaffirming Congress' commitment to finding treatments and cures for Parkinson's disease and pediatric diseases by advancing the Gabriella Miller Kids First Research Act 2.0 and the National Plan to End Parkinson's Act.

Jennifer Wexton
Member of Congress

ADA American Dental Association®

1111 14th Street, N.W.
Suite 1200
Washington, DC 20005

T 202.898.2400
F 202.898.2437
www.ada.org

June 8, 2023

The Honorable Brett Guthrie
Chair, Health Subcommittee
Committee on Energy & Commerce
2125 Rayburn House Office Building
Washington, DC 20515

The Honorable Anna Eshoo
Ranking Member, Health Subcommittee
Committee on Energy & Commerce
2232 Rayburn House Office Building
Washington, DC 20515

Dear Chair Guthrie and Ranking Member Eshoo:

On behalf of the over 159,000 members of the American Dental Association (ADA), we are writing to share our support of H.R. 3843, which would reauthorize the Action for Dental Health (ADH) program, a crucial workforce grant program focused on providing access to care for those most in need. We would also like to thank the Energy and Commerce Committee for its attention to dental and other health workforce issues.

These issues are among the ADA's top priorities and are closely linked because one-third of dentists have told the ADA that they are actively recruiting dental hygienists and dental assistants, and 87% of dentists tell the ADA that recruiting for these positions is extremely challenging despite incentives offered to prospective dental team members. Dental practice staffing difficulties limit the number of patients dentists can see, and this problem is especially acute in underserved areas.

The ADA has long championed the ADH program, which provides federal grants for the dental health needs of underserved populations. ADH funding is directed towards dental disease prevention through improved oral health education, reduction of geographic and language barriers, and improved access to care, among other initiatives. Programs supported by ADH advance the important goal of decreasing dental health disparities in communities where better access to care is most needed.

The ADA is asking the Committee to advance H.R. 3843 to reauthorize the Action for Dental Health Act of 2018 (P.L. 115-302) grants for innovative programs for a five-year period, from fiscal year 2024 through fiscal year 2028. In order to ensure program accountability and transparency, the ADA also asks that Congress require the Secretary of Health & Human Services (HHS) to submit a report to Congress on the extent to which the grants increased access to dental services in designated dental health professional shortage areas.

Once again, we thank you for your attention to dental workforce issues and to ADH. The nation's dentists stand ready to work with you to ensure Americans have a sufficient dental workforce to meet their oral health needs. Should you or your staff have any questions, please contact Natalie Hales at [redacted] or [redacted].

Sincerely,

George R. Shepley, D.D.S.
President

Raymond A. Cohlmia, D.D.S.
Executive Director

GRS:RAC:nh