

Response to Member Questions, Hearing entitled “Examining Proposals that Provide Access to Care for Patients and Support Research for Rare Diseases”

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All questions are from Hon Frank Pallone Jr.

1. “In our legislative hearing on June 14, a number of studies were referenced in regards to gender-affirming care. Can you provide a summary of the scientific and clinical evidence around gender-affirming care?”

The diagnosis of gender dysphoria and provision of transitioning medications are grounded in a large body of research showing that appropriate use of such care confers key benefits to transgender people, including youth. The number of studies establishing the benefits of gender-affirming care for transgender youth has increased steadily since 2013 (see table below). These benefits include improvements in anxiety and depression, social functioning, self-esteem, and body image, as well as reductions in suicidal ideation.

Table: Characteristics of studies demonstrating the benefits of gender-affirming care for transgender youth

Citation	Population	Study description	Outcomes
De Vries, A. L. et al (2011). Puberty suppression in adolescents with gender identity disorder : A prospective follow-up study. The Journal of Sexual Medicine, 8(8), 2276-2283.	N = 70, mean age at enrollment 13.7 years	Prospective cohort study comparing the psychological functioning before and after puberty suppression in transgender youth receiving care in the Netherland. Participants received puberty suppression for nearly 2 years.	Behavioral and emotional problems and depressive symptoms decreased; general functioning improved; feelings of anxiety and anger did not change; gender dysphoria and body satisfaction did not change; all participants progressed to cross-sex hormone treatment.
De Vries, A. L., et al (2014). Young adult psychological outcome after puberty suppression and gender	N = 55, assessed at 3 different ages (means 13.6, 16.7, 20.7).	Prospective cohort study of the mental health effects of gender-affirming care at varying stages in adolescence among a cohort of transgender youth in the Netherlands. Age-	Gender dysphoria and psychological functioning improved. Well-being was similar to or better than cisgender age-matched controls.

reassignment. Pediatrics, 134(4), 696-704.		matched controls from the general adult population were used to compare mental health outcomes in the oldest cohort of patients.	
Costa, R., et al (2015). Psychological support, puberty suppression, and psychosocial functioning in adolescents with gender dysphoria. The Journal of Sexual Medicine, 12(11), 2206-2214.	N = 201, 15.5 before puberty blockers, 16.4 at start of treatment	Prospective cohort study of transgender youths' global functioning after receiving psychological support and puberty blockers, in the UK, over 18 months.	Adolescents with gender dysphoria who received puberty suppression had significantly better psychosocial functioning after 1 year of puberty blockers than with just psychotherapy.
Allen, L. R. (2019). Well-being and suicidality among transgender youth after gender-affirming hormones. Clinical Practice in Pediatric Psychology, 7(3), 302.	N = 47, 16.6	Prospective cohort study of transgender youth in a US clinic of the effects of gender-affirming care on mental health.	Improvement in general well-being and decreased suicidality.
Kaltiala, R. (2020). Adolescent development and psychosocial functioning after starting cross-sex hormones for gender	N = 52, mean age of 18.1 years at diagnosis	Retrospective chart review of psychosocial functioning and psychiatric comorbidities in transgender youth receiving care in Finland.	Decreased need for psychiatric treatment of depression, anxiety, suicidality and self-harm.

dysphoria. Nordic Journal of Psychiatry, 74(3), 213-219.			
van der Miesen, A. I. et al. (2020). Psychological functioning in transgender adolescents before and after gender- affirmative care compared with cisgender general population peers. Journal of Adolescent Health, 66(6), 699-704.	N = 272, 14.5 years	Cross-section study of 272 youth not receiving care in the Netherlands self-reporting on emotional and behavioral problems, compared to 178 transgender youth receiving care and 651 cisgender youth from the general population.	Transgender adolescents receiving puberty suppression had fewer emotional and behavioral problems than newly referred patients and had similar or fewer problems than their same-age cisgender peers.
Achille, C., et al (2020). 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(1), 1-5.	N = 50, 16.2 years	Prospective cohort study of youth receiving gender-affirming care at a US clinic, over 12 months.	Mean depression scores and suicidal ideation decreased, quality of life scores improved over time.
Kuper, L. E., et al. (2020). Body dissatisfaction and mental	N = 148, 14.9 years	Prospective cohort of youth receiving gender- affirming care at a US clinic	Large improvement in body dissatisfaction, small to moderate improvement in depression and anxiety

health outcomes of youth on gender-affirming hormone therapy. Pediatrics, 145(4).			
Turban, J. L. et al (2020). Pubertal suppression for transgender youth and risk of suicidal ideation. Pediatrics, 145(2).	20,619, with subset of 3,494; mean age of 23.4	Cross-sectional study of 20,619 transgender adults in the US who self-reported on receiving puberty suppression during adolescence. The association with suicidality was analyzed.	Access to pubertal suppression was associated with a lower odds of lifetime suicidal ideation.
Carmichael, P., Butler, G., Masic, U., Cole, T. J., De Stavola, B. L., Davidson, S., ... & Viner, R. M. (2021). 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, 16(2), e0243894.	N = 44 at 12 months, 24 at 24 months, 14 at 36 months; Mean age at enrollment was 13.6 years.	Prospective cohort study evaluating the physical and mental health effects of puberty blockers in transgender youth in the UK's Gender Identity Development Service, with follow up periods ranging from 12 to 36 months.	Overall patient experience of changes on puberty blockers was positive, based on qualitative interviews. Stability of psychological functioning identified.
Grannis, C., et al. (2021). Testosterone treatment, internalizing symptoms, and body image	N = 42, mean ages of those treated with and without were testosterone 15.8 years and 17.0 years respectively	Cross sectional study on the effects of testosterone, comparing self-reported anxiety, depression and body dissatisfaction between 19 youth treated with	Those receiving testosterone had lower scores in generalized anxiety, social anxiety, depression, and body image dissatisfaction compared to

dissatisfaction in transgender boys. Psychoneuroendocrinology, 132, 105358.		testosterone and 23 untreated youth in a US clinic.	those not receiving hormones.
Hisle-Gorman, E., et al (2021). Mental healthcare utilization of transgender youth before and after affirming treatment. The Journal of Sexual Medicine, 18(8), 1444-1454.	N = 3754 transgender adolescents (and 6603 cisgender siblings who served as controls), 10 years at study initiation and 18 years at study completion	Retrospective cohort study over 8 years, using US military data among transgender youth on mental healthcare utilization and prescription of psychiatric medication with cisgender siblings used as controls	Among 963 transgender youth using gender-affirming pharmaceuticals, mental healthcare did not significantly change and psychotropic medications increased following gender-affirming pharmaceutical initiation; older age was associated with less mental healthcare and prescription of psychiatric medications.
Green, A. E., (2021). Association of gender-affirming hormone therapy with depression, thoughts of suicide, and attempted suicide among transgender and nonbinary youth. Journal of Adolescent Health.	5753 (number of only adolescent participants)		Access to gender-affirming hormones was associated with lower odds of recent depression and suicide attempts compared to those who desired but did not access gender-affirming hormones.
Turban, J. L., et al. (2022). Access to gender-affirming hormones during adolescence and mental health outcomes	N = 21598 survey respondents, all adults (18+)	Cross-sectional analysis of US Transgender Survey data on mental health outcomes, comparing those who did receive and did not receive gender-affirming care.	Accessing gender-affirming care was associated with lower odds of past-year suicidal ideation and past year severe psychological distress. Access to gender-affirming care during adolescence was associated with a lower odds of these same adverse mental health

among transgender adults. PLoS One, 17(1), e0261039.			outcomes when compared to not accessing gender-affirming hormones until adulthood.
Tordoff, D. M., et al. (2022) Mental Health Outcomes in Transgender and Nonbinary Youths Receiving Gender-Affirming Care. JAMA Network Open, 5(2), e220978.	N = 104, 15.8	Prospective, longitudinal cohort study of transgender youth in the US receiving gender-affirming care over one year.	Lower odds of depression and suicidality among those who started gender-affirming medical care, when compared to those who did not.
Chen, D., et al. (2023). Psychosocial Functioning in Transgender Adolescent after 2 Years of Hormones. <i>New England Journal of Medicine</i> , 388(3), 240-250.	N = 315, 16	Prospective, longitudinal cohort study of transgender youth receiving gender-affirming care at four clinical sites in the US over two years.	Appearance congruence, positive affect, and life satisfaction increased, and depression and anxiety symptoms decreased. Appearance congruence correlated positively with increases in positive affect and life satisfaction and decreases in depression and anxiety symptoms.
Sorbara JC, et al. Mental Health and Timing of Gender-Affirming Care. <i>Pediatrics</i> . 2020;146(4):e20193600	N = 300, 116 youth presenting before age 15 (median 13.9) and 184 youth presenting at 15 or older (median 16.3)	Cross-sectional chart review of transgender youth receiving care in a Canadian clinic, comparing mental health measures in those younger than 15 and those 15 or older.	After presentation, more older than younger youth reported a diagnosis of depression, had self-harmed, had considered suicide, had attempted suicide, and required psychoactive medications. Late puberty was associated with depressive disorders and anxiety disorders. Late pubertal stage and older age were found to be associated with worse mental health.

<p>de Lara, D. L. et al (2020). Psychosocial assessment in transgender adolescents. <i>Anales de Pediatría (English Edition)</i>, 93(1), 41-48.</p>	<p>N = 23 transgender youth compared to 30 cisgender controls, mean age 16 years</p>	<p>Prospective cohort study of 23 transgender youth who received gender-affirming care over a year at a clinic in Spain.</p>	<p>At baseline, trans adolescents had worse measures of mental health than the cisgender control adolescents. The transgender adolescents in the study who received gender affirming hormones had statistically significant improvements in anxiety and depression.</p>
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2. Can you address the claim that there is only “low-quality evidence” in regards to gender-affirming care?

“Low quality evidence” describes evidence that is derived from research that is *not* a randomized controlled trial. There are different ways a clinical research study can be designed to evaluate the effect of an intervention. The randomized controlled trial design offers a model where the independent effects of an intervention are assessed in comparison to a control group. It is often the case that subjects enrolled in a randomized controlled trial are “blinded,” meaning that they are unaware of whether they receive placebo or the intervention being studied. However, randomized controlled trials are not universally feasible, ethical, necessary or even superior to other study designs. Observational study designs can offer practical and naturalistic ways to study the effect of an intervention. Notably, in pediatrics, the vast majority of evidence informing clinical care is derived from observational study.

The pros and cons of these study designs have been discussed in the context of gender-affirming care for youth by subject matter experts. In summary, randomized controlled trials are not, and cannot be, the gold standard method to study the effects of gender-affirming care, due to practical and ethical constraints. Gender-affirming care has long been shown, by reliable scientific methods, to address gender dysphoria and improve mental health, recommended by rigorous clinical practice guidelines, and endorsed by every major medical organization. Given this evidence-based medical consensus it would be unethical to conduct an randomized controlled trial that involved denying standard medical care to a control group of individuals. (Ashley et al. 2023)

“Low-quality evidence” is a technical term that routinely informs strong recommendations for clinical care (Balshem et al. 2011). “Low-quality evidence” is crucial in guiding care for rare conditions, as in the case of gender dysphoria. Indeed, less than 15% of medical treatments are supported by “high quality” evidence (Fleming et al. 2016). And while one might presume that over time and with further study, the quality of evidence will improve, that does not seem to be the case. According to a metaepidemiological analysis of systematic reviews, the quality of evidence does not worsen or improve with subsequent study (Howick et al. 2020). This suggests that there may be practical limit of evidence quality achievable in many fields of medicine. If reliance on “low-quality evidence” was universally considered grounds for banning care, most healthcare would be subject to similar legal interference. As a pediatrician, I have used low-quality guidance to inform treatment of (1) viral croup with steroids, (2)

depression, anxiety, and post-traumatic stress syndrome with various medications and referrals to different types of psychotherapy, (3) anorexia and bulimia nervosa with certain therapy modalities and psychiatric medications, (4) heavy menstrual bleeding with hormonal therapies, (5) fertility preservation in adolescents receiving chemotherapy.

3) How are clinical standards of care established?

The use of evidence-informed guidelines to unify and improve clinical practice is convention in medicine. Innumerable medical conditions are treated according to documents referred to as “clinical practice guidelines” or “standards of care.” Such guidelines are produced through iterative discussions amongst experts and researchers with strict standards on how to utilize the best available evidence. Independent review is common practice to reduce bias, mitigate conflicts of interest and enhance good-faith scientific debate. A few discrete processes exist by which such guidelines can be developed, all of which utilize independent review. The two guideline-development processes pertinent to the provision of GAC are outlined by the National Academy of Medicine, upon which WPATH’s Standards of Care were developed, and the GRADE Working Group, which informed development of the Endocrine Society’s Clinical Practice Guidelines.

Balshem, H., M. Helfand, H. J. Schunemann, A. D. Oxman, R. Kunz, J. Brozek, G. E. Vist, Y. Falck-Ytter, J. Meerpohl, S. Norris, and G. H. Guyatt. 2011. "GRADE guidelines: 3. Rating the quality of evidence." *J Clin Epidemiol* 64 (4): 401-6.

<https://doi.org/10.1016/j.jclinepi.2010.07.015>.

<https://www.ncbi.nlm.nih.gov/pubmed/21208779>.

Fleming, P. S., D. Koletsi, J. P. Ioannidis, and N. Pandis. 2016. "High quality of the evidence for medical and other health-related interventions was uncommon in Cochrane systematic reviews." *J Clin Epidemiol* 78: 34-42. <https://doi.org/10.1016/j.jclinepi.2016.03.012>.

<https://www.ncbi.nlm.nih.gov/pubmed/27032875>.

Howick, J., D. Koletsi, N. Pandis, P. S. Fleming, M. Loef, H. Walach, S. Schmidt, and J. P. A. Ioannidis. 2020. "The quality of evidence for medical interventions does not improve or worsen: a metaepidemiological study of Cochrane reviews." *J Clin Epidemiol* 126: 154-159. <https://doi.org/10.1016/j.jclinepi.2020.08.005>.

<https://www.ncbi.nlm.nih.gov/pubmed/32890636>.