EXHIBIT 34

APRIL 29, 2022

CURRICULUM VITAE

PERSONAL INFORMATION:

Name:	Morissa J. Ladinsky, MD, FAAP
Citizenship:	United States
Other Languages:	Spanish
Address	7 Carla Circle, Birmingham, AL 35213
Phone:	205-504-1748

CURRENT RANK/TITLE:

2015-present	Associate Professor of Pediatrics, UAB School of Medicine
2015-present	Associate Professor, Medical Education, UAB School of Medicine
Business address:	Department of Pediatrics Division of Academic General Pediatrics 310 Children's Park Place 1 1600 7th Avenue South Birmingham, AL 35233-1711
Phone: Fax Email	205-638-9585 205-975-6502 mladinsky@uabmc.edu

HOSPITAL APPOINTMENTS:

Medical Staff: Children's Hospital of Alabama, Birmingham, AL 2015-

Medical Staff: UAB Hospital Birmingham, AL 2015-

EDUCATION:

Year	Degree	Institution
1990	Doctor of Medicine	Baylor College of Medicine,

	With Honor	Houston, TX
1985	Bachelor of Arts Human Biology Magna cum laude	Brown University Providence, RI

LICENSURE

Alabama	#34204
Ohio	#35-07-7337 (inactive)
Maryland	#D47256 (inactive)
Texas	#J0053 (inactive)

BOARD CERTIFICATION:

American Board of Pediatrics, Certificate # 51388
October 13, 1993
Recertified 2001, 2008, 2014, 2019 Participating in MOC

POSTDOCTORAL TRAINING:

Year	Degree	Institution
1995-1997	Fellowship, General Academic Pediatrics and Program Development	Johns Hopkins School of Medicine
1990-1993	Residency in Pediatrics	Baylor College of Medicine

ACADEMIC APPOINTMENTS:

Year	Rank/Title	Institution
2015-present	Associate Professor	UAB School of Medicine Department of Pediatrics Division of Academic General Pediatrics
2005-2015	Assistant Professor	Division of General and Community Pediatrics Cincinnati Children's Hospital Cincinnati, OH
2000-2005	Assistant Professor	Division of Ambulatory Pediatrics

		Ohio State University School of Medicine Nationwide Children's Hospital Columbus, OH
1997-1999	Instructor in Pediatrics	Johns Hopkins University School of Medicine
1997-1999	Clinical Assistant Professor Pediatrics	University of Maryland School of Medicine

OTHER EMPLOYMENT:

1981-1983	Brown University, Research Assistant, Department of Genetics Providence, Rhode Island
1985-1986	Rural Eight County Family Planning Program Clinic Assistant, Counselor, San Marcos, Texas
1989	Bearskin Meadow Camp Medical Assistant, Diabetes Educator, CA Diabetic Youth Foundation, San Francisco, California
1993-1995	Ashford Pediatric Associates, Pediatrician (private practice) Houston, Texas
1995-1999	Franklin Square Hospital Center Pediatrician- Department of Pediatrics Consultant Baltimore, Maryland
1995-1997	Attending, Johns Hopkins Hospital Division of Pediatric/Emergency Medicine
1999	Baltimore City Dept. of Health, Physician-School based health center, Northwestern High School, Baltimore, Maryland
1999-2000	Physician- Locum Tenens, Walnut Hills Health Center, Cincinnati, Ohio
2006-2015	Pediatrician, Private Practice, Group Health Associates Cincinnati, Ohio

AWARDS/HONORS:

Phi Beta Kappa, Brown University	inducted 1984
Sigma Xi Scientific Honor Society, Brown University	inducted 1983
Academic Achievement Award: Brown University Division of Biology and Medicine	1983-1985
Alpha Omega Alpha, Baylor College of Medicine	inducted 1989
Who's Who in America	2004-present
Who's Who of American Women	2005-present
Dayton Business Journal Best Doctors:	2010-2015
Cincy Magazine Best Doctors:	2010-2015

Cover Physician, Dec. 2011

Best Doctors in America:	2011-2022
America's Top Doctors (Castle Connolly/US News):	2012-2022
Birmingham Magazine Best Doctors	2015- 2021
UAB Department of Pediatrics Educational Excellence Award	2017-2021
UAB Multicultural and Diversity Programs Research and Initiative Award	2018
TAKE of Birmingham, AL: Hope for Tomorrow Award	2018, 2019
UAB Department of Pediatrics Ralph Tiller Distinguished Faculty Award	2018
UAB Department of Pediatrics Sergio Stagno Friend of the Housestaff Award	2018

American Academy of Pediatrics, Special Achievement Award	2018
UAB Research in Medical Education Annual Symposium, First Place Award for Educational Innovation: *"Closing Healthcare Gaps for Marginalized Populations: A Transgender Standardized Patient Approach"*	2019
Castle Connolly's Exceptional Women in Medicine	2019, 2021
American Academy of Pediatrics, Alabama Chapter President's Award	2021
UAB School of Medicine Dean's Excellence Award for Diversity	2022

PROFESSIONAL SOCIETIES/MEMBERSHIPS

Fellow of the American Academy of Pediatrics	1993-present
Member, Section on LGBT Health and Wellness	2015-present
Member Section on Minority Health, Equity and Inclusion	2020-present
Ambulatory Pediatric Association	1995-present
American Medical Women's Association	1997-present

STATE OF ALABAMA, JEFFERSON COUNTY COUNCILS AND COMMITTEES:

2015	Magic City Acceptance Project, Training Committee. Council of agencies representing at risk Birmingham Youth. Advocacy for and training of service providers in law, education, social services around needs of sexual minority and gender variant youth.
2015-present	West Alabama Area Health Education Coalition, (taking teams of trainees to the West Alabama Black Belt for reciprocal training and mentoring)
2016	Curriculum Developer/Participant, HERO Project/UAB Dept. of Pediatrics Health Education Project with Washington K-8/ Birmingham Public Schools.
2016	Organized first Community (now statewide) Support Group for Spanish Speaking Parents of Children with Autism. Joint project: UAB Dept. of Pediatrics/Alabama Autism Society/HICA

2016-present	Board of Directors, TAKE (Transgender Advocates Knowledgeable Empowering) Community Empowerment and Support for Transgender Women of Color in Alabama.
2017-present	Alabama Stakeholder Workgroup: Data Driven Prevention Initiative for Heroin/Opioid Overuse/Abuse
2017-2018	Advisory Board, Central Alabama PRIDE
2017-2020	Alabama Department of Public Health, Alabama's Adolescent Vaccine Task Force
2017-present	Alabama Department of Public Health Office of Women's Health/Alabama American Academy of Pediatrics Opioid Misuse in Women/Neonatal Abstinence Syndrome Taskforce, Protocols Committee Co-Chair
2017-present	Alabama Governor's Opioid Council, Implementation Team, Treatment and Recovery Support Subcommittee
2018-present	Board of Directors, Children's Policy Council of Jefferson County. Multi-sector and agency policy network united around child advocacy.
2019-present	Alabama Medicaid Agency-Medical Care Advisory Committee
2019-present	Mayor's LGBTQ Advisory Board, Office of Mayor Randall Woodfin, Birmingham, Alabama
2019-present	Alabama Perinatal Quality Collaborative -Steering Committee for Neonatal Opioid Withdrawal Syndrome Statewide QI Initiative
2020	Advisory Board, Junior League of Birmingham
2021	Council on Accreditation, Medical Association of the State of Alabama
2021	Council on Medical Education, Medical Association of the State of Alabama
2021	Ethics Committee, Jefferson County Medical Society

NATIONAL COUNCILS AND COMMITTEES

2000-2002	Medical Consultant, Chances for Children (Former US Charity of UK Duchess Sarah Ferguson)
2013-2015	Practice Alliance/Translation Workgroup **Co-Chair**, Autism Treatment Network/Autism Speaks, National Offices, Princeton, New Jersey
2015-present	American Academy of Pediatrics, Section on LGBTQ Health and Wellness
2018-present	Co-Leader. Multi-agency Social Justice Experience. GLIDE Center for Social Justice, UCSF Department of Pediatrics, UAB Pediatrics. Annual experience uniting leaders in medicine, faith, tech and criminal justice from San Francisco and Alabama to empower coalition building around equity and social justice.

UAB AND CHILDREN'S of ALABAMA COUNCILS, COMMITTEES, ACTIVITIES

2015-2018	Center For Aids Research/Community and Behavioral Sciences Core/UAB School of Public Health. Faith and Spirituality-Health Equity Interface Programming
2017-2019	Family-Centered Care Initiatives Council: Hispanic, Other Non-English Speaking and Low SES Families (COA)
2017-2019	Faculty Advisor, Medical Student MedPride Gay/Straight Alliance, UAB School of Medicine
2018-present	Advisory Board, Psychiatric Intake and Response Center (PIRC), Children's of Alabama Departments of Psychiatry and Emergency Medicine
2019-present	Advisory Board, UAB Comprehensive Center for Addiction in Pregnancy Program
2020-present	UAB Department of Pediatrics Diversity, Equity and Inclusion Faculty Committee
2021	UAB Department of Pediatrics Residency Program Evaluation Committee
2021	UAB School of Medicine Community Engaged Teaching Roundtable

2021	UAB School of Public Health LGBTQ Endowed Professorship Executive Committee

LOCAL/REGIONAL COUNCILS AND COMMITTEES AT OTHER INSTITUTIONS

1981-1984	Steering Committee. Meiklejohn Academic Advising Brown University
1983-1985	Student representative and advisor, Brown University Office of Undergraduate Admissions
1987-1990	Baylor Medical School Admissions Committee
1998	Sinai Hospital of Baltimore Pediatric Residency Selection Committee
2012-2015	Quality Improvement Team, Physician Member, The Kelly O'Leary Center for Autism/Autism Treatment Network, Cincinnati Children's Hospital Medical Center
2014-2015	Access to Care Workgroup, Center for Developmental Disabilities and Behavioral Pediatrics Cincinnati Children's Hospital Medical Center

MAJOR RESEARCH INTERESTS:

1) Impact of faith and community on quality of health for at risk youth including LGBTQ youth living in the Deep South.

2) Implementation of AAMC Curricular Guidelines around LGBTQ health care using Standardized Patient Methodology.

3) Developmental outcomes for infants facing neonatal opioid withdrawal syndrome.

TEACHING and MENTORING EXPERIENCE:
(Academic appointments listed earlier)

1995-1997	Preceptor, Harriet Lane Pediatric Primary Care Clinic Johns Hopkins Hospital
1995-1997	Pediatric Inpatient Co-Attending Physician Johns Hopkins Hospital

1997-1999	Faculty Attending Pediatrician/Preceptor Greenspring Pediatric Associates, Department of Pediatrics, Sinai Hospital of Baltimore
2007-2015	Revision and presentations of Pediatrician section. Pre-natal Course series, Bethesda North Hospital/TriHealth, Cincinnati, Ohio
2009-2013	Pediatrician Preceptor for Family Nurse Practitioner students during Pediatric Clerkship. University of Cincinnati School of Nursing, Good Samaritan Hospital/TriHealth School of Nursing
2009-2015	Pediatrician preceptor for residents during outpatient ambulatory clerkship, Cincinnati Children's Hospital/University of Cincinnati
2015-present	Faculty Attending Primary Care Preceptor for 14-16 residents providing both continuity and acute care, 4-5 sessions weekly
2015-present	Faculty Attending Pediatrician, Multidisciplinary Transgender Health Team, Children's of Alabama
2015-present	Children's of Alabama Staff Training for Inpatient Psychiatry, ER, Child Abuse Program, Laboratory Medicine, Social Work, Patient Relations teams: *Delivering Quality and Affirming Care to LGBTQ Patients. Focus on transgender and gender non-binary youth.*
2015-present	Faculty Mentor for several Pediatric Residents, all share mutual interest in health disparities and marginalized populations.
2016-2017	UAB Department of Pediatrics Faculty Scholars Program
2016	Lead Physician for Children's of Alabama's Primary Care Clinic HPV Vaccine QI Initiative
2017-present	Curricular Development and execution of Standardized Patient/OSCE models in training medical and allied health students around LGB and transgender healthcare. UAB School of Medicine
2018-present	LGBTQ Healthcare and Education, Special Topics Course Developer and Leader, UAB School of Medicine
2018-present	Annual guest lecturer, *Cultural Humility and Spirituality in Public Health*, Samford University, School for the Health Professions. Birmingham, AL

2019-present	Mentor for 2 ongoing pediatric resident QI initiatives. Firearm Injury Prevention in a Primary Care Clinic and After Visit Anticipatory Guidance for Spanish Speaking Families.
2020-present	Health Equity Scholars Co-Lead. Development and execution of UAB Pediatrics Residency curriculum and special interest team around improving health equity through understanding of structural racism and impact on social determinants of health.
2021	Faculty Facilitator: Case Studies in Diversity in Healthcare. Pilot initiative within UAB School of Medicine

MAJOR NATIONAL LECTURES:

"Autism Spectrum Disorders in the Community, the Role of the PCP" Invited Guest Speaker, Autism Treatment Network/Autism Intervention Research Network on Physical Health Fall Program Meeting. Denver, CO, November 8, 2012

"Primary Care Physician Engagement in the Care of Children with Autism; Lessons Learned from ADHD", Invited Guest Speaker, Autism Speaks/Autism Treatment Network Steering Committee, National Meeting, Washington, DC, July 11, 2013

"Enhancing Medical Student Competencies in Transgender Healthcare: A Transgender Standardized Patient Approach", AAMC Learn Serve Lead National Conference, Phoenix, AZ, November 10, 2019

"Clinical Advocacy and Care for Transgender Youth", Harvard Medical School, Equity and Social Justice Series. Boston, MA October 27, 2021

GRANT SUPPORT:

1996-1997	The Thomas Wilson Sanitarium for the Children of Baltimore City.
1997	Baltimore Council on Human Resources "Startup funding for Reach out and Read, The Harriet Lane Primary Care Center at Johns Hopkins"
	"The WHO Oral Rehydration Solution in US Pediatric Practice: An Evaluation of Parent Satisfaction" Principal Investigator

2017-2019	Community Foundation of Greater Birmingham, "Expansion of the Multidisciplinary Gender Clinic, Pediatric Endocrinology, Children's of Alabama"
2017-2022	UAB Health Services Foundation, General Endowment Fund, "Curricular Advancement of LGBT Healthcare Competencies Using Standardized Patients"

MANUSCRIPTS:

1. Novack DH, Detering BJ, Arnold R, Forrow L, **Ladinsky, M**, Pezullo JC. Physicians' Attitudes Toward Using Deception to Resolve Difficult Ethical Problems. JAMA. 1989;261:2980-2985.

2. Raef H, **Ladinsky MJ**, Arem R. Concomitant euthyroid Graves' ophthalmopathy and isolated ocular Myasthenia Gravis. Postgraduate Medical Journal. 1990;66:849-852.

3. Musher DM, Hamill RJ, **Ladinsky MJ**, Winsor DK, Baughn RF. Acute Glomerulonephritis Due to Shigella Flexnerii Dysentery with Demonstration of a Virulence Protein of Shigella in Circulating Immune Complexes. The Journal of Infectious Diseases. 1990;161:366-377

4. Ladinsky M, Lehmann H, Santosham M. The Cost-Effectiveness of Oral Rehydration Therapy for US Children with Acute Diarrhea. Medical Interface. 1996;9:113-119.

5. Ladinsky M, Goepp J, Santosham M. Outpatient Oral Rehydration Therapy: Safe, Effective, and Rapid. Annals of Emergency Medicine. 1997;29(4):551-552.

6. Ladinsky M, Duggan A, Santosham M, Wilson M. The World Health Organization Oral Rehydration Solution in US Pediatric Practice; A Randomized Trial to Evaluate Parent Satisfaction. Archives of Pediatrics & Adolescent Medicine. 2000;154:700-705.

7. Johnson C, Hurtubise L, Castrop J, French G, Groner J, **Ladinsky M**, McLaughlin D, Mahan J. Learning management systems: technology to measure the medical knowledge competency of the ACGME. Medical Education. 2004;1365-1374

8. Shah, K, Zabielinski, M, **Ladinsky, M.** Isolated pustular nodule on the thumb, JAMA Pediatrics, 2015 Nov 1;169(11): doi: 10.1001/jamapediatrics.2015.1301, 1061-1062

9. Ladinsky, M, Cohen, M. Mind the Gap. J Pediatr. 2020 May 31. pii: S0022-3476(20)30692-2. doi: 10.1016/j.jpeds.2020.05.054

10. Kirpalani H, Bell EF, Hintz SR, Tan S, Schmidt B, Chaudhary AS, Johnson KJ, Crawford MM, Newman JE, Vohr BR, Carlo WA, D'Angio CT, Kennedy KA, Ohls RK, Poindexter BB, Schibler K, Whyte RK, Widness JA, Zupancic JAF, Wyckoff MH, Truog WE, Walsh MC,

Chock VY, Laptook AR, Sokol GM, Yoder BA, Patel RM, Cotten CM, Carmen MF, Devaskar U, Chawla S, Seabrook R, Higgins RD, Das A; Eunice Kennedy Shriver NICHD Neonatal Research Network (**Ladinsky, M**) Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants. N Engl J Med. 2020 Dec 31;383(27):2639-2651. doi: 0.1056/NEJMoa2020248. PMID: 33382931 Clinical Trial.

11. Bell EF, Hintz SR, Bann CR, Wyckoff MR, DeMauro SB, Walsh MC, Carlo WA, VanMeurs KP, Vohr VR, Eunice Kennedy Shriver NICHD Neonatal Research Network (**Ladinsky, M**). Mortality, In-Hospital Morbidity, Care Practices, and 2-Year Outcomes for Extremely Preterm Infants in the US, 2013-2018. JAMA, 2022 Jan 18:327(3): 248-263

BOOKS AND BOOK CHAPTERS:

Cohen, MB, **Ladinsky M**, and Marino, B. Pediatric Gastroenterology in Pediatric Blueprints 6th Edition, ed, Marino and Fine. Lippincott Williams & Wilkins, 2012

Published Abstracts and Poster Exhibits

1. Ladinsky MJ, Duggan A, Santosham M, Goepp JG, Wilson MH. Why is the WHO-ORS Underused by US Pediatric Practitioners? Ambulatory Pediatric Association Region IV Meeting, January 20, 1996 and National Annual Meeting, May 7, 1996. (Archives of Pediatrics & Adolescent Medicine. 1996;150:P29)

2. Goepp J, Edwards L, **Ladinsky M**, Gilger M, Oberherman R. Effect of an Oral Rehydration Training Program on Residents' Knowledge and Attitudes. Ambulatory Pediatric Association 3. 3. National Annual Meeting, May 7, 1996. (Archives of Pediatrics & Adolescent Medicine. 1996;150:P21)

4. Webb A, **Ladinsky, M.** Early Initiation of Hormone Therapy: A Lifesaving Treatment for a Transgender Teen with Anorexia Nervosa. *J Investig Med*, 2018; 66: 506

ORAL PRESENTATIONS

Scientific/Scholarly papers presented at national meetings:

Morissa Ladinsky, MD "Why is the WHO-ORS Underused by US Pediatric Practitioners?" Ambulatory Pediatric Association Region IV Meeting, January 20, 1996.
Ambulatory Pediatric Association National Annual Meeting, May 7, 1996.

Morissa Ladinsky, MD "The WHO Oral Rehydration Solution in US Pediatric Practice; A Randomized Trial to Assess Parent Satisfaction." Ambulatory Pediatric Association National Annual Meeting, May 4, 1998

Shawn Galin, PhD, **Morissa Ladinsky, MD** "Enhancing Medical Student Competencies in Transgender Healthcare: A Transgender Standardized Patient Approach", Learn, Serve, Lead 2019: The AAMC National Annual Meeting, Phoenix, AZ. November 9, 2019

Shawn Galin, PhD, Morissa Ladinsky, MD "Enhancing Medical Student Competencies in Transgender Healthcare: A Transgender Standardized Patient Approach", International Meeting on Simulation in Healthcare (IMSH), San Diego, CA January 20, 2020

Tina Simpson, MD, MPH, Chrystal Rutledge, MD, Morissa Ladinsky, MD "Developing a Health Equity Scholars Program for Pediatric Residents in the Heart of the Civil Rights Movement" American Society of Pediatric Department Chairs (AMSPDC), Virtual. March 6, 2021

Invited Workshops at local and regional meetings:

Morissa Ladinsky, MD, Teaching Oral Rehydration Therapy So It's Used. Workshop presented at the Ambulatory Pediatric Association National Annual Meeting, May 3, 1997.

Morissa Ladinsky, MD , Provision of Affirming Care to Transgender and Gender Diverse Patients, Children's Hospital of Alabama Divisions of: Pathology (September, 2015), Emergency Medicine (January, 2016), Inpatient Psychiatry (March, 2016), Child Abuse/CHIPS Teams (May, 2016), UAB Medical Student 1st and 2nd year Interest Group (May 2016), Second year medical student class (February, 2017-20).

Morissa Ladinsky, MD, Nefertiti Durant, MD, MPH, Group CME/MOC Part 2 Lead/Facilitator. Adolescent Medicine Self-Assessments. Alabama American Association of Pediatrics 2016 Annual Meeting and Fall Pediatric Update. Birmingham, AL October 2, 2016

Morissa Ladinsky, MD, Hussein Abdul-Latif, MD, Marianthe Grammas, MD "How Providers Can Support Trans and Gender Variant Youth" Jefferson County Medical Society Provider Workshop. October 27, 2017

Morissa Ladinsky, MD "Trans/Gender Non-Conforming Affirming Healthcare," Webinar addressing importance of medical education in healthcare. May 19, 2020

Morissa Ladinsky, MD , Shajuane Jones, MS "A Community Approach to Implementing Plans of Safe Care in Jefferson and Jackson Counties, Alabama" National Quality Improvement Center for Collaborative Community Court Teams Webinar. The Children's Bureau. July 10, 2020.

Morissa Ladinsky, MD, Heather Austin PhD, "LGBTQ: The Reality for Youth and Families", Alabama Psychological Association 2021 Annual Conference, Orange Beach, AL June 12, 2021

Morissa Ladinsky, MD , Samantha Hill, MD, MPH, Matthew Kiszla, BS, MS-2, "What's on the Books: Sexual and Gender Minority Health in Alabama Post 2020", Blackburn Institute 2021 Annual Symposium, University of Alabama, Tuscaloosa, August 27, 2021

Morissa Ladinsky, MD, Shajuane Jones, MS "Understanding Substance Dependence when Serving Pregnant and Parenting Women", Addiction and The Law Training, Dallas County Court and DHR. Montgomery, AL September 9, 2021

Invited lectures at local/regional meetings:

Oral Rehydration Therapy, an Update" Pediatric Grand Rounds at Sinai Hospital of Baltimore, February 2, 1998.

"Current Research in Pediatric Obesity and Realities in Clinical Practice" Regional Annual Meeting, National Association of Pediatric Nurse Practitioners. Cincinnati, OH. November 12, 2006

"Care Coordination for our NICU Grads in Alabama", Perinatal Grand Rounds, UAB Departments of Neonatology, OB/GYN and Pediatrics, March 30, 2016

"Pediatricians Preparing Youth for College, Can We Still Anticipate and Guide?" Alabama American Academy of Pediatrics, Spring Meeting and Pediatric Update, Point Clear, AL, April 29, 2016

"Office Based Care for LGBTQ Youth in 2016" at Raising the Resilient Teen, It Takes a Village Children's of Alabama, Adolescent Health Symposium, April 8, 2016

"Office Based Care for LGBTQ Youth in 2016" Alabama American Academy of Pediatrics, Spring Meeting and Pediatric Update, Point Clear, AL, April 30, 2016

"How Pediatricians can Support Trans and Gender Variant Youth in 2016", at American Academy of Pediatrics District II and VII Executive Leadership Annual Meeting", Washington, DC, June 25, 2016

"Pediatricians Preparing Youth for College, Can we Still Anticipate and Guide?" Pediatric Grand Rounds, Children's of Alabama, July 7, 2016

"Beyond Bathrooms, Understanding Trans and Gender Variant Youth in 2016". Grand Rounds, Children's of Alabama, October, 13, 2016.

"Gender Dysphoria, Eating Disorders and Health Challenges for Trans/Gender Variant Youth", Intensive Course in Pediatric Nutrition, Department of Pediatrics, UAB. February 24, 2016, 2019 and 2020

"Neonatal Abstinence Syndrome" at *The Opioid Crisis in Alabama; From Silos to Solutions*. A public policy conference. Montgomery, AL. March 10, 2017.

"Neonatal Abstinence Syndrome", National Association of Pediatric Nurse Practitioners Annual Meeting, UAB School of Nursing, May 21, 2017

"Who are LGBTQ Youth, Who Am I? Alabama Mental Health Symposium, Children's Hospital of Alabama, May 19, 2017.

"You are the Key to HPV Cancer Prevention". Provider Education and Networking Event, Alabama Area Health Education Coalition, Tuscaloosa, AL, May 24, 2017

"Opioid Use in Pregnancy and Neonatal Abstinence Syndrome", Alabama American Academy of Pediatrics, Fall Annual Meeting, Birmingham, AL, October 1, 2017

"HPV Vaccine Update" at Progress in OB/GYN 2018, Alabama ACOG, UAB Department of OB/GYN Annual Meeting, Birmingham, AL February 16, 2018

"Neonatal Opioid Withdrawal Syndrome, Drugs and the Brain" at Alabama Department of Health, Women's Health Update, Birmingham, AL August 3, 2018

"Opioid Use in Pregnancy and Neonatal Opioid Withdrawal Syndrome", Statewide Opioid Clinical Conference, Birmingham, AL, August 10, 2018

"The Opioid Crisis: National and State Initiatives", Annual Perinatal Conference:, Huntsville Hospital for Women and Children, Huntsville, AL, September 21, 2018

"Sound the Alarm: Opioid Use in Pregnancy and Neonatal Opioid Withdrawal Syndrome" 34th Annual Statewide Early Intervention and Preschool Conference, Birmingham, AL. October 16, 2018

"The Opioid Epidemic as a Child Health Crisis. State and National Initiatives, Outcomes and Insights", Grand Rounds, Children's of Alabama, Birmingham, AL. November 29, 2018

"Stakeholder Unity to Improve the Future for Substance Dependent Women and their Children", First Annual Alabama Child Protective Services/Department of Human Resources Conference, Birmingham, AL February 28, 2019

"Neurologic Outcomes of NICU Graduates", UAB Perinatal Conference, Birmingham, AL, June 30, 2019

"The Alabama 2020 Legislative Session, Bills affecting Child Health", First Fridays Community Stakeholder Conference, February 8, 2020

"Understanding Medication Assisted Treatment for Opioid Dependent Alabamians Within the Criminal Justice System", Annual Meeting of Family Court Judges, Alabama Association of Drug Court Professionals, AL Administrative Office of Courts. January 9, 2021

"Understanding Medication Assisted Treatment for Opioid Use Disorder", Alabama Association of Drug Court Professionals Annual Conference, Opening Plenary Session speaker, February 9, 2021

INVITED MEDIA APPEARANCES, INTERVIEWS, PANEL PARTICIPATION:

Invited Participant, US Department of Justice Roundtable Discussion on LGBTQ Issues, Office of US Attorney Joyce Vance for the Northern District of Alabama, July 12, 2016.

Panelist, "Legal Rights Intersection with LGBTQ Health", Senator Doug Jones, Moderator, UAB, October 14, 2016

Panelist, "LGBTQ Rights", Rep. Patricia Todd, Moderator, Vestavia Hills Library, January 21, 2017

Panelist, "Forum on The Future of the Affordable Care Act", Congresswoman Terri Sewell, Organizer and Moderator. Princeton Hospital. January 20, 2017.

Panelist, Your Voice, Your Future Roundtable, "Transgender in Alabama", Sinclair Broadcast Group, ABC33/40. Birmingham, AL. April 18, 2017

Panelist, "Anti-bullying Community Forum", Hadassah/Birmingham Community Foundation, April 20, 2017

Helio Health, Invited editorial response to "PCP-Transgender Patient Relationships Needs Improvement", November 27, 2018. *https://www.healio.com/news/primary-care/20181127/pcptransgender-patient-relationships-need-improvement*

Helio Health, "How PCP's Can Meet Needs of Transgender Patients", March 5, 2019, *https://www.healio.com/news/primary-care/20190305/how-pcps-can-meet-needs-of-transgender-patients*

NBC News, "Alabama Moves Closer to Transgender Health Ban for Minors", March 10, 2020. *https://www.nbcnews.com/feature/nbc-out/alabama-moves-closer-transgender-health-care-ban-minors-n1154791*

Alabama Media Group, "Doctors Call New Alabama Abortion Bill 'Medically Implausible'", March 11, 2020. *https://www.al.com/politics/2020/03/doctors-call-new-alabama-abortion-bill-medically-implausible.html*

Reuters Media Group, "Anxieties Mount for Transpeople as Coronavirus Delays Surgeries", April 9, 2020, *https://www.openlynews.com/i/?id=380a10c1-b93c-4a25-8691-0d1f84e39a7b*

American Academy of Pediatrics Voices, "Stripping of Transgender Protections Does not Have to Hamstring our Ability To Help All Patients" July 23, 2020. *https://services.aap.org/en/news-room/aap-voices/stripping-of-transgender-protections-does-not-have-to-hamstring-our-ability-to-help-all-patients/*

https://www.birminghamal.gov/2021/03/08/city-of-birminghams-lgbtq-advisory-board-issues-statement-on-hb1sb10/?fbclid=IwAR2aHeKeYh04PYOjYDXj2GN_28nVyptL7kMVHKTDa1KNJQ5vFyxPwJzv4O0 Primary Statement Author

Health Highlights with Dr. Kay, Podcast. "Teaching Medical Students About Transgender Healthcare with Drs. Morissa Ladinsky and Shawn Galin". March 19, 2021. https://podcasts.apple.com/us/podcast/teaching-medical-students-about-transgender-health/id1555978677?i=1000513735920

VICENews https://www.youtube.com/watch?v=ZQ4o1RqYJmc March 29, 2021. Alabama Wants to Send Doctors to Prison for Treating Trans Kids

Let's Think On It Live, Radio Show and Podcast with Dr. Mark Westfall. "Current Medical Understanding of Being Transgender". Live radio event on 107.3 FM and livestream http://bhammountainradio.com . Podcast http://letsthinkonitnow.com April 8, 2021

https://www.npr.org/2021/03/28/981225604/its-hurtful-trans-youth-speaks-out-as-alabama-debates-banning-medical-treatment National NPR with Melissa Block

Birmingham Aids Outreach Community Conversations on HB-1, SB-10. Facebook Live panelist. March 29, 2021 https://www.facebook.com/events/1587818304941823
https://www.alreporter.com/2021/03/23/the-dad-and-daughter-asking-lawmakers-to-stop-the-trans-health-care-ban/

Politifact. April 2021, Assistance with fact checking regarding proposed legislation prohibiting receipt of gender affirming healthcare

https://www.al.com/opinion/2021/05/im-a-doctor-and-alabama-could-arrest-me-for-doing-my-job.html

Maynard Cooper and Gayle (Legal Firm with Birmingham and national offices), Pride Month Dialogue, Pro-Bono Legal Document Clinic and Its Far Reaching Impact for Trans identified Clients. June 16, 2021

"Caring for Trans and Gender Diverse Youth; From Tavistock to US State Legislatures" 60 Minutes, Australia. Interviewer Sarah Abo. Taped September 3, 2021.

https://time.com/6146269/doctors-trans-youth-gender-affirming-care-harassment/
Time Magazine national. February 16, 2022

DIRECT LEGISLATIVE ADVOCACY AND POLICY ENGAGEMENT

Gave testimony to Alabama House of Representatives in support of HB-76, Childcare Safety Act. February 2, 2018. The bill was signed into law March 27, 2018 saving many lives by equalizing accountability around safety and hiring in licensure of faith based **and** secular day care centers in Alabama.

Delivered the pediatrician perspective to several hundred attendees rallying against the Trump Administration Family Separation policy. Speaker, "Families Belong Together Rally", Kelly Ingram Park, Birmingham, AL, June 30, 2018

Alabama Media Group and House/Senate Proceedings, 2019 Alabama Legislative Session:
https://www.al.com/news/2019/05/doctors-question-need-for-alabama-born-alive-bill.html

Nominated and asked by the Jefferson County Medical Society to run for a Delegate At Large position on the Board of Censors of the Medical Society of the State of Alabama. (MASA). Involved statewide travel and campaigning. February-April, 2019

Together with AL DHR Commissioner Nancy Buckner, Chief of Prosecution Services Barry Matson, authored proposal for pre-arrest diversion pathway for pregnant substance dependent women accused of non-violent crimes in AL. November 20, 2019
Proposal presented in person to Governor Ivey's Task Force on Prison Reform, December 4, 2019, Montgomery, AL.

Gave testimony to Alabama House and Senate Subcommittees on Health in opposition to HB303/SB 219, Vulnerable Child Advocacy and Protection Act (VCAP), February 26, 2020. Such act would criminalize pediatricians, pharmacists and teachers who prescribe, fill or discuss administration of puberty blocking or hormonal medications to minors suffering gender dysphoria.

With 3 pediatric colleagues and executive leadership of the AL American Academy of Pediatrics, met with AL State Rep. Wesley Allen (R-Troy), author of VCAP bill pre-filed as HB-1 for 2021 Legislative Session. Mutually beneficial education session around standards of care for pediatric and adolescent management of gender dysphoria. August 26, 2020

Gave testimony to House Judiciary and Senate Health in opposition to HB-1/SB-10, Vulnerable Child Advocacy and Protection Act (VCAP). February 19, 2021

Gave testimony to House Health in opposition to HB-1/SB-10, Vulnerable Child Advocacy and Protection Act (VCAP). March 10, 2021

Opinion editorial published in the Alabama Political Reporter
https://www.alreporter.com/2021/08/01/uab-pediatrician-theres-a-lot-we-know-about-covid-vaccines/ August 1, 2021

Additional invited media appearances, interviews and reporting on testimony given by myself relative to the 2021 Legislative Session's VCAP Bill HB-1, SB-10

https://www.pinknews.co.uk/2021/02/11/david-fuller-cop-trans-daughter-alabama-bill-puberty-blockers-federal-crime/ International reporting

https://www.rocketcitynow.com/article/news/local/transgender-treatment-minors-alabama-criminalize-bill/525-3d0980fd-63c1-44fb-9cd8-b8433e7cdb02
https://www.advocate.com/transgender/2021/2/12/alabama-father-testifies-passionately-against-trans-treatment-ban

https://www.al.com/news/2021/02/father-of-transgender-daughter-tells-alabama-lawmakers-treatment-ban-is-misguided.html?e=5eb4073b1edbca3e5a2ac3b00086c885&utm_source=Sailthru&utm_medium=email&utm_campaign=Newsletter_politics%202021-02-11&utm_term=Newsletter_politics

https://www.montgomeryadvertiser.com/story/news/2021/02/11/alabama-bill-would-criminalize-transgender-treatment-minors/4448260001/

https://www.alreporter.com/2021/02/12/alabama-senate-committee-votes-to-criminalize-treatment-for-transgender-minors/

https://www.them.us/story/alabama-anti-trans-student-legislation?fbclid=IwAR1SxrDQ8M9oqTPoz3qTnsQBMRTLOyexTuHQ4cQkoTkURoTFCnDVqOwygfg

https://www.metroweekly.com/2021/02/anti-trans-health-care-bill-would-force-alabama-schools-to-out-transgender-students-to-their-parents/?fbclid=IwAR1auaz0XKgN4KX3IqK57CWyjsQ8QVGI3hb2SP8f0OIvqFRiKjBe625QQAg

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https://www.gadsdentimes.com/story/news/politics/2021/02/23/alabama-bill-criminalizing-transgender-therapy-kids-prompts-debate/6793134002/

https://www.gadsdentimes.com/story/news/local/2021/02/23/transgender-minors-bill-alabama-legislature-impact-gadsden-dad/6754825002/

https://www.rocketcitynow.com/article/news/local/local-parent-says-transgender-medical-care-bill-for-youth-are-steps-backward-gender-dysphoria/525-257093f1-9834-4ac7-b608-3f22a6cda9b2

https://www.al.com/news/2021/03/alabama-senate-passes-bill-banning-transgender-treatments-for-minors.html

https://www.alreporter.com/2021/04/20/opponents-of-alabamas-transgender-youth-treatment-ban-implore-lawmakers-to-stop/

https://www.al.com/news/2021/04/alabama-gov-kay-ivey-weighs-possible-economic-ramifications-over-restricting-transgender-rights.html

https://abc3340.com/news/local/transgender-advocates-push-back-on-proposed-alabama-laws

https://theaggie.org/2021/04/19/call-it-what-it-is-alabamas-vulnerable-child-compassion-and-protection-act-is-discrimination/

https://theaggie.org/2021/04/19/call-it-what-it-is-alabamas-vulnerable-child-compassion-and-protection-act-is-discrimination/
https://www.newsweek.com/alabama-considering-making-transgender-treatment-minors-felony-even-if-parents-approve-it-1575478?amp=1

https://www.audacy.com/wearechannelq/latest/pediatrician-who-treats-trans-youth-might-be-arrested

https://www.montgomeryadvertiser.com/story/news/2021/04/20/alabama-transgender-youth-bill-banning-medical-treatment-advocates-urge-rejection/7307227002/

https://www.them.us/story/alabama-pediatrician-fears-anti-trans-healthcare-bill

https://www.axios.com/transgender-youth-bills-doctors-health-care-bdefd950-b41d-4728-af11-26afd2f484f0.html

UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

REV. PAUL A. EKNES-TUCKER; BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; JAMES ZOE, individually and on behalf of his minor son, ZACHARY ZOE; MEGAN POE, individually and on behalf of her minor daughter, ALLISON POE; KATHY NOE, individually and on behalf of her minor son, CHRISTOPHER NOE; JANE MOE, Ph.D.; and RACHEL KOE, M.D.

Plaintiffs,

v.

KAY IVEY, in her official capacity as Governor of the State of Alabama; STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; DARYL D. BAILEY, in his official capacity as District Attorney for Montgomery County; C. WILSON BAYLOCK, in his official capacity as District Attorney for Cullman County; JESSICA VENTIERE, in her official capacity as District Attorney for Lee County; TOM ANDERSON, in his official capacity as District Attorney for the 12th Judicial Circuit; and DANNY CARR, in his official capacity as District Attorney for Jefferson County.

Defendants.

Civil Action No. 2:22-cv-184-LCB

DECLARATION OF MORISSA J. LADINSKY, MD, FAAP, IN SUPPORT OF PLAINTIFFS' MOTION FOR TEMPORARY RESTRAINING ORDER & PRELIMINARY INJUNCTION

I, Morissa J. Ladinsky, declare as follows:

1. I am an Associate Professor of Pediatrics at the University of Alabama at Birmingham ("UAB") School of Medicine.

2. I am a practicing physician and a member of the medical staff at the Children's Hospital of Alabama and UAB Hospital, both in Birmingham. I am co-lead of the multi-disciplinary gender clinic at UAB Hospital.

3. I obtained a bachelor's degree (magna cum laude) in Human Biology from Brown University in 1985. I obtained my medical degree (with honors) from Baylor University in 1990.

4. I was certified by the American Board of Pediatrics in 1993. I am licensed to practice medicine in Alabama. I have past licensure in Ohio, Maryland, and Texas when I previously practiced and resided in these states.

5. For the last 31 years, I have dedicated my practice to the medical care of young people. Throughout my career, my patients included transgender young people. Presently, those transgender patients live in Alabama, Mississippi, Florida, and Georgia.

6. Since starting at the gender clinic at UAB, I have treated approximately 250 transgender young people for gender dysphoria.

7. The treatment of gender dysphoria is well-established in the medical profession. This is not a pioneering or experimental area of medicine. There are comprehensive standards of care governing the treatment of gender dysphoria that were developed by the World Professional Association for Transgender Health (WPATH), founded in 1979, and Endocrine Society, in collaboration with the Pediatric Endocrine Society. These guidelines are recognized as the prevailing standard of care by the major associations of medical professionals, including the American Medical Association, American Academy of Pediatrics, and the Society for Adolescent Health and Medicine, to name a few. The current version of the WPATH standards of care have been in place for more than a decade.

8. The treatment of gender dysphoria is also part of medical school curricula across the country and world. In fact, this subject is taught as part of the endocrine module to all students at the UAB School of Medicine. The broader topic of transgender medicine is also found on every state board medical exam, including in Alabama.

9. Incorporated within the standards of care is a process each patient must follow before beginning any treatment for gender dysphoria. And, as with any treatment, we also follow a protocol for obtaining informed consent as part of that process. Standard protocol requires that medical treatment for gender dysphoria is

not prescribed until a patient meets the rigorous requirements outlined in the standards of care and consistent with an informed-consent process.

10. The informed consent procedures used by the gender clinic at UAB are very comprehensive. Patients at the clinic begin that process with their primary care provider and often community based mental health provider before they even have an initial appointment with a doctor like me. The patient's mental health provider thoroughly assesses the patient's mental health, maturity, presence and acuity of dysphoria and if indicated, ultimate readiness to undergo medical treatment for gender dysphoria. Using those assessments as our baseline, our multidisciplinary team begins its evaluation. We meet with the patient and their parents/legal guardians, review the risks, benefits, and alternatives of treatment, as medical and mental health providers do for all treatments. After that initial meeting, we meet with our patients at regular intervals for follow up, allowing us to monitor the patient's gender dysphoria as well as their overall physical and mental health over time. The team also provides families with materials to review and community-based supports and resources to connect with in the time between appointments.

11. Most of our patients are in the care of the gender clinic for one to three years before initiating medical treatment for gender dysphoria, depending on when they first come to the clinic and their individual healthcare needs. Even after that extended observation and assessment period, we will not prescribe any treatment

unless the full multidisciplinary team agrees that treatment is appropriate, and the patient and the patient's parents fully understand, have the capacity to consent, and sign the informed-consent forms. This process is intentionally set up to ensure all involved are making an informed, measured decision, from the healthcare providers to the patients and their parents.

12. Throughout this evaluation information-sharing process, patients are encouraged to avail themselves of the various services offered as part of our multidisciplinary clinic, including pastoral care. The purpose of these services is to get a full picture of a patient's health, wellbeing, household support, and functioning. Each of those data points help determine whether a potential treatment option may be appropriate for any given patient.

13. Once a patient begins medical treatment, their progress is monitored at regular intervals, typically every six months, to assess the efficacy of the prescribed treatment through a physical examination or laboratory tests. This ongoing monitoring also ensures ongoing evaluation of a patient's mental health and the chance to address any questions the patient or their parents may have.

14. I understand that Governor Ivey signed the Vulnerable Child Compassion and Protection Act (the "Act"). My understanding is that the Act expressly prohibits physicians, and others, from doing or saying anything that could cause a transgender young person, under age 19, in Alabama to undergo medical

treatment for gender dysphoria. I further understand that violating the Act exposes Alabama healthcare providers and others to criminal prosecution, which could result in a prison sentence or substantial fine.

15. Puberty-blocking medication and hormone-replacement therapy have greatly improved the physical and mental health and wellbeing of my patients. Denying my patients access to these well-established medical treatments will cause the mental health of many of my patients to regress, including increasing their suicidality and likelihood of attempting suicide. To cease ongoing care, without a medical basis, would violate my professional, ethical, and legal obligations by forcing me to harm my patient.

16. In the days since the Act was signed into law, I have met with numerous patients who are experiencing significant psychological distress due to the prospect of the Act going into effect. One teenage patient was visibly trembling in fear. Parents are regularly calling the clinic in tears. The uncertainty weighs heavily on the minds of my patients and their parents. And, for some, their worst fears have already started to materialize: several of my patients have reported to me that their pharmacies are refusing to fill prescriptions relating to the treatment of their gender dysphoria, including for menstrual suppression medications which are supposedly not criminalized by the Act.

I declare under penalty of perjury that the foregoing is true and correct.

Executed this 20 th day of April , 2022.

Morissa J. Ladinsky, MD, FAAP

University of Alabama System

University of Alabama System
Office of Counsel
1720 2nd Avenue South, AB 820
Birmingham, AL 35294-0108
205.934.3474

March 3, 2023

Via Email: *bbarnes@cooperkirk.com*

Brian Barnes
Cooper & Kirk, PLLC
1523 New Hampshire Ave. NW
Washington, DC 20036

RE: ***Boe, et al. v. Marshall, et al.***
U.S. District Court for the Middle District of Alabama
Case. No. 22-cv-00184-LCB-CWB

Dear Counsel:

I represent UAB Medicine Enterprise ("UABME") and The Board of Trustees of the University of Alabama (the "Board")[1], including its operating unit The University of Alabama at Birmingham ("UAB"), with respect to the subpoena Defendants issued to UABME dated December 13, 2022. Please direct all future communication regarding this matter to me.

As an initial matter, please note that UABME is not the proper entity to respond to this subpoena. UABME is a non-profit corporation that does not own patient care facilities, provide clinical services to patients, employ medical providers, or develop policies relating to the care of patients. The subpoena should have been directed to the Board, which owns UAB Hospital inpatient and outpatient operations, as well as other clinical enterprises including the UAB Gender Health Clinic and the UAB Department of Pediatric Endocrinology. In an effort to avoid unnecessary administrative burden, however, we have accepted the subpoena as if it was served on the Board and are responding accordingly.

Please also note that the Gender Health Clinic (whose treatment of minors is limited to 18-year-olds only) and the UAB Pediatric Endocrinology Department, which includes the UAB Pediatrics Multidisciplinary Gender Health Clinic, are the only areas within UAB that we believe have any responsive documents. As I have mentioned previously, while we are producing responsive documents from the Gender Health Clinic, the vast majority of its patients are not minors (it has only treated eleven 18-year-olds) and the documents produced may have never been used to treat a minor. Although I have discussed some of our concerns regarding this subpoena with you already, I am writing to provide UAB's formal written objections pursuant to FED. R. CIV. P. 45(d)(2)(B). In addition to these objections, I am also providing non-privileged, non-confidential, responsive documents Bates stamped UAB 0001 - 0661.

[1] See Ala. Code § 16-47-1, et seq.

I. OBJECTIONS AND RESPONSES

A. GENERAL OBJECTIONS

General Objection 1: UAB objects to the subpoena to the extent it seeks documents protected by attorney-client privilege and/or work product doctrine, including protections due to UAB and its employees.

General Objection 2: UAB objects to the subpoena to the extent it seeks documents protected by privileges associated with peer review, accreditation, credentialing, and quality assurance.

General Objection 3: UAB objects to the subpoena to the extent it seeks documents protected by contractual obligation and/or federal and state privileges or protections related to trade secrets, intellectual property, research confidentiality, or other confidential business material that has nothing to do with this litigation.

General Objection 4: UAB objects to the subpoena to the extent it seeks documents containing Protected Health Information of individual patients. UAB also objects to the extent that any request seeks confidential communications between patients/patient representatives and mental health providers, which are protected by state and federal privileges. Moreover, non-party patients/potential patients/parents or guardians are entitled to at least the level of anonymity granted to party patients/potential patients/parents or guardians. Non-party treatment providers are also entitled to at least the level of anonymity granted to party treatment providers. Non-party UAB should not bear the burden of reviewing and redacting every bit of medical and other records for every single potential patient over the years. To the extent the information requested exists only in patient charts, notes, or communications with patients, potential parents, and/or their parents or legal guardians, UAB objects to producing these documents.

B. OBJECTIONS TO INSTRUCTIONS

Objection to introductory paragraph and Instructions 1-4: UAB objects to instructions that require anything different from and/or more than the Federal Rules of Civil Procedure and other applicable law. UAB's obligations to do anything are limited to those outlined on page three of the subpoena form, and UAB is also entitled to every protection outlined therein. *See* FED. R. CIV. P. 45.

Objection to Instruction 6: UAB objects to a six-year scope of time on grounds that it is overly broad and unduly burdensome. The Gender Health Clinic did not open until July 10, 2020, and therefore has no potentially responsive documents prior to that time. Subject to and without waiving these objections, and in a good faith effort to respond, UAB has worked diligently to identify and produce responsive documents and data dating back to 2017 to the extent such documents and data exist.

C. OBJECTIONS TO DEFINITIONS

Objection to Definitions 1-5: UAB objects to the extent these definitions require anything different from and/or more than the Federal Rules of Civil Procedure and other applicable law. UAB's obligations to do

anything are limited to those outlined on page three of the subpoena form, and UAB is also entitled to every protection outlined therein. *See* FED. R. CIV. P. 45.

D. OBJECTIONS AND RESPONSES TO SPECIFIC DOCUMENT REQUESTS

Request No. 1. Produce all versions of uncompleted patient intake forms You have used for Minor patients. This request does not include completed or partially completed patient intake forms that contain information about individual patients.

Objections and Response to Request No. 1: UAB is producing blank intake forms currently used for patients in the UAB Pediatric Endocrinology Department and the Gender Health Clinic. See documents Bates stamped UAB 0001-0012.

Request No. 2. Produce all versions of Documents and Communications You have used to disclose to Minor patients, potential Minor patients, or parents or guardians of Minor patients, the risks of Puberty Blockers, Cross-sex Hormones, or other Transitioning treatments.

Objections and Response to Request No. 2: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB is producing documents, to the extent they exist, used by both the UAB Pediatric Endocrinology Department and the Gender Health Clinic to disclose risks of the treatments they provide to patients, potential patients, and/or their parents and guardians. See documents Bates stamped UAB 0013-0030.

Request No. 3. Produce all versions of Documents and Communications UAB Medicine Enterprise has used to disclose to Minor patients, potential Minor patients, or parents or guardians of Minor patients, the risks of Puberty Blockers or sex hormones for purposes other than transitioning (e.g., using Puberty Blockers to treat precocious puberty, providing testosterone to a biological male with a testosterone deficiency, and providing estrogen to a biological female with an estrogen deficiency).

Response to Request No. 3: See objections and responses to Request No. 2.

Request No. 4. Produce all versions of Documents and Communications You possess, from Your program or others, that disclose to Minor patients, potential Minor patients, or parents or guardians of Minor patients, the risks of Puberty Blockers or sex hormones for purposes other than transitioning (e.g., using Puberty Blockers to treat precocious puberty, providing testosterone to a biological male with a testosterone deficiency, and providing estrogen to a biological female with an estrogen deficiency).

Objections and Response to Request No. 4: See objections and responses to Request No. 2.

Request No. 5. Produce all Documents and Communications that set forth, contain, or reflect Your policies and procedures for obtaining, recording, and/or memorializing informed consent for the administration of Transitions treatments to Minors. This request includes any versions of uncompleted informed consent forms You have used; it does not include informed consent forms memorializing informed consent by specific patients, prospective patients, or parents or guardians.

Objections and Response to Request No. 5: See objections and responses to Request No. 2.

Request No. 6. Produce all Documents and Communications that set forth, contain, or reflect Your policies and procedures for discussing the risk of suicide in Minors suffering from Gender Dysphoria or a Related Condition.

Objections and Response to Request No. 6: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB is producing documents currently used by both the UAB Pediatric Endocrinology Department and the Gender Health Clinic to screen patients for depression, anxiety, and suicidal ideation. See documents Bates stamped UAB 0031-0032.

Request No. 7. Produce all Documents and Communications You have used to provide information to Minor patients, or the parents or guardians of Minor patients, concerning any coverage by Medicaid, medical insurance carriers, or other sources of funding for Transitioning treatments for Minors.

Objections and Response to Request No. 7: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that the UAB Pediatric Endocrinology Department does not provide information to its patients, potential patients, and/or their parents or guardians related to insurance coverage or treatment funding. The Gender Health Clinic maintains some reference documents related to insurance coverage, which are being produced. See documents Bates stamped UAB 0033-0111.

Request No. 8. Produce Documents and Communications sufficient to identify the ICD codes You use for coverage of Transitioning treatments for Minors.

Objections and Response to Request No. 8: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB is producing documents identifying ICD codes relating to the treatment of Gender Dysphoria or Related Conditions. See documents Bates stamped UAB 0033-0112.

Request No. 9. Produce all Documents and Communications containing, disclosing, or setting forth Your policies and procedures concerning the administration or prescription of, or referral for, Transitioning treatments for Minors.

Objections and Response to Request No. 9: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that the UAB Pediatric Endocrinology Department does not possess any responsive documents. UAB also states that it does not refer Minors for Transitioning treatments. UAB further states that the Gender Health Clinic is producing responsive documents, to the extent they exist. See documents Bates stamped UAB 0113-0163.

Request No. 10. Produce all Documents and Communications containing, disclosing, or setting forth Your policies and procedures for monitoring Minors who are receiving or have received Transitioning treatments from You or at Your direction.

Objections and Response to Request No. 10: See objections and responses to Request No. 9.

Request No. 11. Produce Documents and Communications sufficient to determine the annual number of your Minor patients who received, were prescribed, or were referred by You to another healthcare provider for Puberty Blockers since 2014.

Objections and Response to Request No. 11: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Specifically, this request appears to require non-party UAB to investigate, select, and review documents for an expanded time scope to generate statistical reports that do not already exist, which is beyond the scope of what a non-party is required to do in responding to a subpoena under FED. R. CIV. P. 45. Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that since 2017 the UAB Pediatric Endocrinology Department provided 17 minor patients with puberty blockers and the Gender Health Clinic did not provide any minor patients with puberty blockers. UAB further states that it does not refer Minors for Transitioning treatments.

Request No. 12. Produce Documents and Communications sufficient to determine the annual number of your Minor patients who received, were prescribed, or were referred by You to another healthcare provider for Cross-sex Hormones since 2014.

Objections and Response to Request No. 12: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Specifically, this request appears to require non-party UAB to investigate, select, and review documents for an expanded time scope to generate statistical reports that do not already

exist, which is beyond the scope of what a non-party is required to do in responding to a subpoena under FED. R. CIV. P. 45. Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that since 2017 the UAB Pediatric Endocrinology Department provided hormone treatment therapy to 110 patients and the Gender Health Clinic provided hormone treatment therapy to 11 Minor patients. UAB also states that it does not refer Minors for Transitioning treatments.

> Request No. 13. Produce Documents and Communications sufficient to determine the annual number of your Minor patients who received, were prescribed, or were referred by You to another healthcare provider for Transitioning surgeries since 2014.

Objections and Response to Request No. 13: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Specifically, this request appears to require non-party UAB to investigate, select, and review documents for an expanded time scope to generate statistical reports that do not already exist, which is beyond the scope of what a non-party is required to do in responding to a subpoena under FED. R. CIV. P. 45. Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that no Minor patients were referred to another healthcare provider for purposes of providing a Transitioning surgery. UAB further states that the UAB Pediatric Endocrinology Department does not provide Transitioning surgeries to minors and does not refer them to other providers for such treatment. Since opening in July 2020, the Gender Health Clinic has conducted one transitioning surgery for an 18-year-old, but no longer provides such treatment to 18-year-olds. The Gender Health Clinic does not refer Minors to other providers for such treatment. See Bates stamped documents UAB 0164-0165.

> Request No. 14. Produce Documents and Communications reflecting how many, and rates of, Your Minor patients who began Puberty Blockers and went on to Cross-sex Hormones since 2014.

Objections and Response to Request No. 14: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Specifically, this request appears to require non-party UAB to investigate, select, and review documents for an expanded time scope to generate statistical reports that do not already exist, which is beyond the scope of what a non-party is required to do in responding to a subpoena under FED. R. CIV. P. 45. Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that of the 17 patients in the UAB Pediatric Endocrinology Department since 2017 who received puberty blockers, seven went on to receive hormone treatment therapy. UAB does not track a patient once that patient leaves the care of UAB. No Minor patients of the Gender Health Clinic receive Puberty Blockers.

> Request No. 15. Produce Documents and Communications reflecting how many, and rates of, Your Minor patients who began Transitioning treatments and later discontinued them (while still a Minor or not) since 2014.

Objections and Response to Request No. 15: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Specifically, this request appears to require non-party UAB to investigate, select, and review documents for an expanded time scope to generate statistical reports that do not already exist, which is beyond the scope of what a non-party is required to do in responding to a subpoena under FED. R. CIV. P. 45. Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that the UAB Pediatric Endocrinology Department has had one patient discontinue Transitioning treatment. UAB does not track a patient once that patient leaves the care of UAB. None of the Minor patients of the Gender Health Clinic have discontinued treatment.

> Request No. 16. Produce all Documents or Communications reflecting, noting, or recording any incidents or possible incidents of Desistance or Detransition in any of Your current or former patients since 2014.

Objections and Response to Request No. 16: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Specifically, this request appears to require non-party UAB to investigate, select, and review documents for an expanded time scope to generate statistical reports that do not already exist, which is beyond the scope of what a non-party is required to do in responding to a subpoena under FED. R. CIV. P. 45. Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that the UAB Pediatric Endocrinology Department has had one patient discontinue Transitioning treatment. UAB does not track a patient once that patient leaves the care of UAB. None of the Minor patients of the Gender Health Clinic have experienced Desistance or Detransition as of the time of this response.

> Request No. 17. Produce all Documents and Communications containing, disclosing, or setting forth Your policies and procedures concerning surgical Transitioning treatments. This request includes referral policies or practices.

Objections and Response to Request No. 17: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that the UAB Pediatric Endocrinology Department does not possess any responsive documents because it does not perform surgical Transitioning treatments, and UAB does not refer patients for such treatment. UAB will produce responsive documents from the Gender Health Clinic to the extent they exist. See documents Bates stamped UAB 0166-0174.

> Request No.18. If any of Your healthcare providers have given any presentations or lectures or participated in any panel discussions about providing Transitioning treatments to Minors, produce all Documents and Communications regarding those presentations, including any handouts, slide decks, and video or audio recordings of the events.

Objections to Request No. 18: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). UAB also objects to this request to the extent it encompasses documents regarding administrative arrangements and other irrelevant material. Subject to and without waiving these objections, and in a good faith effort to respond, UAB produces available copies of PowerPoint presentations given by Drs. Ladinsky and Latif regarding providing Transitioning treatments to Minors. Statements made in the presentation materials are the views of Drs. Ladinksy and Latif and do not necessarily reflect the views and policies of UAB. Neither Dr. Ladinsky nor Dr. Latif possess any recordings of their presentations. See documents Bates stamped UAB 0175-0661.

> Request No. 19. Produce all Documents and Communications regarding WPATH Standards of Care 8. *See* E. Coleman et al., *Standards of Care for the Health of Transgender and Gender Diverse People, Version 8*, Int'l J. of Transgender Health (2022), https://www.tandfonline.com/doi/pdf/10.10830/26895269.2022.2100644.

> Request No. 20. Produce all non-privileged Documents and Communications regarding Alabama's Vulnerable Child Compassion and Protection Act, including non-privileged Documents and Communications regarding *Boe v. Marshall*, M.D. Ala. No. 22-cv-184; *Ladinsky v. Ivey*, N.D. Ala. No. 22-cv-447; and *Walker v. Marshall*, M.D. Ala. No. 22-cv-167.

Objections and Response to Requests No. 19 and 20: UAB entities are part of one of the largest academic medical centers in the United States. As an academic institution, UAB entities support and encourage individual employee rights to engage in professional debate and private or public commentary on issues of public and professional concern, including published articles and legislation. UAB objects to these requests on grounds that they have a chilling effect on free speech by allowing State of Alabama law enforcement officials to compile non-party opinions about legislation it seeks to enforce and/or policies and practices to which State of Alabama officials are politically opposed. Also, non-parties are entitled to at least the level of anonymity granted to parties.

In addition, UAB objects on grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1), and would be unduly burdensome to identify and collect. For example, just searching the emails of well over 50,000 employees and students would require an enormous amount of time and money.

> Request No. 21. Produce all Documents and Communications regarding any ongoing or completed research or studies You are or have conducted related to Transitioning Minors, as well as the results, data, protocols, posters, presentations, and grants or funding related to such research.

Objections to Request No. 21: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim

or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that no UAB physician in either the UAB Pediatric Endocrinology Department or the Gender Health Clinic is conducting research on the topic of providing Transitioning treatments to Minors.

> Request No.22. Produce all Documents and Communications regarding what health care providers You refer Minor patients to for Transitioning treatments.

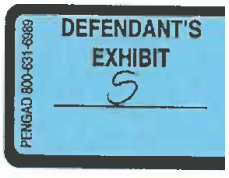
Objections to Request No. 22: UAB asserts the General Objections from Section II. (A)-(B) herein. In addition, UAB objects on the grounds that the requested documents are not relevant to any claim or defense nor proportional to the needs of the case as required by FED. R. CIV. P. 26(b)(1). Subject to and without waiving these objections, and in a good faith effort to respond, UAB states that it does not refer Minor patients for Transitioning treatments.

I appreciate your flexibility in providing us with extra time over the holiday season to respond to your subpoena. We have worked diligently to identify and produce responsive documents.

Sincerely,

/s/Emily T. Vande Lune
Emily T. Vande Lune
University Counsel
evandelune@uasystem.edu

EXHIBIT 1



IN THE UNITED STATES DISTRICT COURT
FOR THE MIDDLE DISTRICT OF ALABAMA
NORTHERN DIVISION

BRIANNA BOE, individually and on behalf of her minor son, MICHAEL BOE; *et al.*, Plaintiffs, and UNITED STATES OF AMERICA, Plaintiff-Intervenor, v. STEVE MARSHALL, in his official capacity as Attorney General of the State of Alabama; *et al.*, Defendants.	Case No. 2:22-cv-00184-LCB-CWB Honorable Liles C. Burke

PLAINTIFFS' DISCLOSURE OF EXPERT REPORT OF MORISSA J. LADINSKY, MD, FAAP

I, Morissa J. Ladinsky, have been retained by counsel for Plaintiffs as an expert in connection with the above-captioned litigation. I have actual knowledge of the matters stated in this report and relied in its preparation on the medical and scientific literature cited herein. In addition, I relied on my scientific education and training, my research experience, my knowledge of the scientific literature in the pertinent fields, and my clinical experience treating transgender adolescents with gender dysphoria, as set out in my curriculum vitae (Exhibit A). The materials I have relied upon in preparing this report are the same types of materials that experts in my field regularly rely upon when forming opinions on these subjects. I may wish to supplement these opinions or the bases for them as a result of new scientific research or publications or in response to statements and issues that may arise in my area of expertise.

BACKGROUND AND QUALIFICATIONS

I am a Professor of Pediatrics at the University of Alabama at Birmingham ("UAB") School of Medicine. A true and correct copy of my Curriculum Vitae is attached hereto as Exhibit A.

I am a practicing physician and a member of the medical staff at the Children's Hospital of Alabama and UAB Hospital, both in Birmingham. I am co-lead of the multi-disciplinary gender clinic at UAB Hospital. I also lead our primary care clinic and co-lead our regional Neonatal Intensive Care Unit (NICU) follow-up clinic.

I obtained a bachelor's degree (magna cum laude) in Human Biology from Brown University in 1985. I obtained my medical degree (with honors) from Baylor College of Medicine in 1990.

I was certified by the American Board of Pediatrics in 1993. I am licensed to practice medicine in Alabama. I have past licensure in Ohio, Maryland, and Texas when I previously practiced and resided in those states.

For the last 31 years, I have dedicated my practice to the medical care of young people. Throughout my career, my patients have included transgender young people.

Since starting at the gender clinic at UAB, I have personally treated approximately 250 transgender young people for gender dysphoria. The clinic itself has treated a few hundred transgender young people for gender dysphoria using GnRH agonists and/or hormonal therapies. The number of patients who are minors who receive transitioning medications at the UAB clinic represents only a portion of all young people who are seen by the clinic team, as some young people are seen at the clinic and never receive these medications, while others are not yet candidates for them.

As part of my practice, I stay familiar with the latest medical science and treatment protocols related to differences or disorders of sex development and gender dysphoria.

In the past four years, I have not been deposed or testified at trial as an expert in any other case. I did, however, testify at the preliminary injunction hearing in this case in May 2022.

I am being compensated at an hourly rate of $450 per hour for preparation of expert declarations and reports as well as for time spent preparing for or giving deposition or trial testimony. My compensation does not depend on the outcome of this litigation, the opinions I express, or the testimony I provide.

SUMMARY OF OPINIONS

The purpose of this report is to provide my expert opinions regarding: (1) the treatment protocols as established by medical standards and in use at UAB for transgender adolescents with gender dysphoria, including the provision of pubertal suppression treatment and hormone therapy; and (2) the severe harm to these adolescents that would be caused by withholding or withdrawing this medical treatment where such treatment is medically necessary.

TREATMENT PROTOCOLS FOR GENDER DYSPHORIA

Being transgender is not itself a mental disorder or a medical condition to be cured. But gender dysphoria is a serious medical condition that, if left untreated, can result in severe anxiety and depression, self-harm, and suicidality.[1]

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[1] Spack, N.P., Edwards-Leeper, L., Feldmain, H.A., *et al.* Children and Adolescents with Gender Identity Disorder Referred to a Pediatric Medical Center. *Pediatrics*. 2012; 129(3):418-425; Olson, K.R., Durwood, L., DeMeules, M., &

Before receiving treatment, many individuals with gender dysphoria experience anxiety, depression, and self-harming behaviors. I have seen in my patients that, without appropriate treatment, this distress impacts every aspect of life. When appropriately treated, gender dysphoria is manageable. I currently treat many transgender patients.

The treatment of gender dysphoria is well-established in the medical profession. There are comprehensive standards of care governing the treatment of gender dysphoria that were developed by the World Professional Association for Transgender Health (WPATH), founded in 1979, and Endocrine Society, in collaboration with the Pediatric Endocrine Society. These guidelines are based on considerable scientific and medical research and represent the best evidence-based practice guidelines available for treating this condition.[2] These guidelines are

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McLaughlin, K.A. Mental Health of Transgender Children Who Are Supported in Their Identities. *Pediatrics*. 2015; 137(3):1-8.

[2] Hembree, W.C., Cohen-Kettenis, P.T., Gooren, L., *et al*. Endocrine Treatment of Gender- Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism*. 2017; 102(11):3869- 3903 (hereafter, "Endocrine Society Guideline"); Coleman, E., Bockting, W., Botzer, M., *et al*. Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (7th Version). *The World Professional Association for Transgender Health*. 2012. *Available at* https://www.wpath.org/media/cms/Documents/SOC%20v7/SOC%20V7_English2012.pd f?_t=1613669341 (hereafter, "WPATH SOC 7"); *see also* E. Coleman, A. E. Radix, W. P. Bouman, *et al.* (2022) Standards of Care for the Health of Transgender and Gender Diverse People, Version 8, International Journal of Transgender Health, 23:sup1, S1-S259, DOI: 10.1080/26895269.2022.2100644 (hereafter "WPATH SOC 8").

recognized as the prevailing standard of care by the major associations of medical professionals, including the American Medical Association, American Academy of Pediatrics, and the Society for Adolescent Health and Medicine, to name a few. The American Academy of Pediatrics, founded in 1930, is an association representing more than 67,000 pediatricians. The Endocrine Society, founded in 1916, is an organization representing more than 18,000 endocrinologists. These groups represent the largest professional associations in these fields of medicine in the United States.

The treatment of gender dysphoria is also part of medical school curricula across the country and world. In fact, this subject is taught as part of the endocrine module to students at the UAB School of Medicine. The topic of transgender medicine is found on state board medical exams across the country, including in Alabama.

The precise treatment for gender dysphoria depends on each person's individualized need, and the medical standards of care differ depending on whether the treatment is for a pre-pubertal child, an adolescent, or an adult.

Treatment for gender dysphoria is aimed at eliminating the clinically significant distress a patient experiences by helping the patient live in alignment with their gender identity. This treatment is sometimes referred to as "gender transition,"

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"transition-related care," or "gender-affirming care." All the major medical professional groups in the United States, including the American Academy of Pediatrics, the American Medical Association, and the American Academy of Child and Adolescent Psychiatry, agree that this care is safe, effective, and medically necessary treatment for the health and wellbeing of children and adolescents suffering from gender dysphoria.[3]

The Endocrine Society Clinical Practice Guideline (the "Endocrine Society Guideline") was developed through a rigorous scientific process that "followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the

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[3] Rafferty, J., Committee on Psychosocial Aspects of Child and Family Health, Committee on Adolescence and Section on Lesbian, Gay, Bisexual, & Transgender Health and Wellness. Policy Statement: Ensuring Comprehensive Care and Support for Transgender and Gender Diverse Children and Adolescents. *Pediatrics*. 2018; 142(4):2018-2162. *Available at*: https://pediatrics.aappublications.org/content/142/4/e20182162; Beers, L.S. American Academy of Pediatrics Speaks Out Against Bills Harming Transgender Youth. *American Academy of Pediatrics*. 2021. *Available at*: https://services.aap.org/en/news- room/news-releases/aap/2021/american-academy-of-pediatrics-speaks-out-against-bills- harming-transgender-youth/; AACAP Statement Responding to Efforts to Ban Evidence- Based Care for Transgender and Gender Diverse Youth. *American Academy of Child & AdolescentPsychiatry*. 2019. *Available at*: https://www.aacap.org/AACAP/Latest_News/AACAP_Statement_Responding_to_Effort s-to_ban_Evidence Based_Care_for_Transgender_and_Gender_Diverse.aspx; State Advocacy Update. *American Medical Association*. 2021. *Available at*: https://www.ama-assn.org/health-care-advocacy/advocacy-update/march-26-2021-state-advocacy-update.

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development and implementation of evidence- based guidelines."[4] The guideline establishes that patients with gender dysphoria may require "a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender."[5]

Before puberty, treatment for gender dysphoria does not include any medications or surgical interventions; prepubertal treatment may include "social transition," which means allowing a transgender child to live and be socially recognized in accordance with their gender identity.[6] This can include allowing children to wear clothing, to cut or grow their hair, to use names and pronouns, and to access restrooms and other sex-separated facilities and activities in line with their gender identity instead of the sex assigned to them at birth. The goal of social transition is to support the child in living comfortably consistent with their gender identity.

For many transgender adolescents with gender dysphoria, going through endogenous puberty significantly worsens their dysphoria. At the clinic, we see this manifest as anxiety, depression, academic decline, and social withdrawal. Puberty-delaying treatment allows patients to delay going through puberty, thereby avoiding

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[4] Endocrine Society Guideline at 3872.
[5] Endocrine Society Guideline at 3869.
[6] Endocrine Society Guideline at 3877-79; WPATH SOC 7 at 15-17.

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the heightened gender dysphoria and permanent physical changes that puberty would cause. This fully reversible treatment also gives a young person time to further understand their gender identity without the distress caused by the changes to their body that result from puberty and before initiating hormone therapy if it becomes medically indicated.

Puberty-delaying treatment works by pausing endogenous puberty at the stage it has reached when the treatment begins. This has the impact of limiting the influence of a person's endogenous hormones on the body. For example, after the initiation of puberty-delaying treatment, a girl who is transgender will stop experiencing the impacts of testosterone on her body for the duration of the treatment.

For some adolescents with gender dysphoria, initiating puberty consistent with gender identity through hormone therapy may also be medically necessary. When prescribed hormone therapy—testosterone for transgender boys, and testosterone suppression and estrogen for transgender girls—the adolescent will go through hormonal puberty consistent with their gender identity on a comparable timeline to their non-transgender peers.

Before any medical intervention is initiated, the Endocrine Society Guideline and the WPATH Standards of Care for the Treatment of Gender Dysphoria ("WPATH SOC") provide that extensive mental health evaluations should be

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conducted. The Endocrine Society Guideline specifies that mental health clinicians trained "in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex."[7] It further explains: "[i]n cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues."[8] The Endocrine Society Guideline takes very seriously the importance of ongoing mental health evaluation for purposes of accurate diagnosis as well as effective treatment.

These requirements are also echoed in the WPATH SOC, which provide 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."[9] The WPATH SOC 7 make clear that mental health professionals assessing for a gender dysphoria diagnosis should, among other things, conduct an "[a]ssessment of gender dysphoria and should explore the nature and characteristics of a child's or adolescent's gender identity."[10] This "[a]ssessment should include an

[7] Endocrine Society Guideline at 3876.
[8] Endocrine Society Guideline at 3877.
[9] WPATH SOC 7 at 18.
[10] WPATH SOC 7 at 15.

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evaluation of the strengths and weaknesses of family functioning" and the WPATH SOC 7 specifically recognize that "[e]motional and behavioral problems are relatively common, and unresolved issues in a child's or youth's environment may be present."[11] The WPATH SOC 8 similarly recommend that "health care professionals working with gender diverse adolescents undertake a comprehensive biopsychosocial assessment of adolescents who present with gender identity-related concerns and seek medical / surgical transition-related care" that aims "to understand the adolescent's strengths, vulnerabilities, diagnostic profile, and unique needs to individualize their care."[12]

There is not an assumption that transitioning medications are appropriate for every patient. The WPATH SOC 7 explicitly advise that "[h]ormonal . . . interventions are appropriate for some adolescents, but not for others."[13] The WPATH SOC 8 advises that "it is important to establish the young person has experienced several years of persistent gender diversity / incongruence prior to initiating less reversible treatments such as gender-affirming hormones . . . ."[14] Similarly, the Endocrine Society Guideline provides that prior to the initiation of any

[11] WPATH SOC 7 at 15.
[12] WPATH SOC 8 at S50.
[13] WPATH SOC 7 at 16.
[14] WPATH SOC 8 at S60.

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medical intervention, "[t]ransgender individuals should be encouraged to experience living in the new gender role and assess whether this improves their quality of life."[15]

Under the Endocrine Society Guideline, transgender adolescents with gender dysphoria may be eligible for pubertal suppression if:

- A qualified mental health professional has confirmed that:
  - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
  - gender dysphoria worsened with the onset of puberty,
  - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
  - has sufficient mental capacity to give informed consent to this (reversible) treatment, and
- The adolescent:
  - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility, and
  - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
- And a pediatric endocrinologist or other clinician experienced in pubertal assessment:

[15] Endocrine Society Guideline at 3876.

- agrees with the indication for GnRH agonist treatment,
- has confirmed that puberty has started in the adolescent, and
- has confirmed that there are no medical contraindications to GnRH agonist treatment.[16]

Under the Endocrine Society Guideline, transgender adolescents may be eligible for therapy if:

- A qualified mental health professional has confirmed:
  - the persistence of gender dysphoria,
  - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
  - the adolescent has sufficient mental capacity to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
- And the adolescent:
  - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
  - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other

[16] Endocrine Society Guideline at 3878.

caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,

- And a pediatric endocrinologist or other clinician experienced in pubertal induction:
    - agrees with the indication for sex hormone treatment,
    - has confirmed that there are no medical contraindications to sex hormone treatment.[17]

I have been treating transgender patients as part of an interdisciplinary, specialty-level team at UAB for 7 years. As a primary care pediatrician, I have also cared for youth receiving hormonal therapies for an additional 28 years. I have prescribed and cared for youth receiving estrogen-containing hormonal therapies for all these years.

Together with our Gender Team, I am currently a provider to about 200 transgender adolescents with gender dysphoria at the UAB clinic. Our clinic follows the process outlined in the Endocrine Society Guideline and the WPATH SOC before beginning any treatment for gender dysphoria. And, as with any treatment, we also follow a protocol for obtaining informed consent as part of that process. Standard protocol requires that medical treatment for gender dysphoria is not prescribed until a patient meets the rigorous requirements outlined in the standards of care and consistent with an informed-consent process.

[17] Endocrine Society Guideline at 3878.

The informed consent procedures used by the gender clinic at UAB are comprehensive. Patients at the clinic begin that process with their primary care provider and often a community-based mental health provider before they even have an initial appointment with a doctor like me. The patient's mental health provider thoroughly assesses the patient's mental health, maturity, presence and acuity of dysphoria, and, if indicated, ultimate readiness to undergo medical treatment for gender dysphoria. Using those assessments as our baseline, our multidisciplinary team begins its evaluation. We meet with the patient and their parents/legal guardians, review the risks, benefits, and alternatives of treatment, as medical and mental health providers do for all treatments. After that initial meeting, we meet with our patient at regular intervals for follow-up, allowing us to monitor the patient's gender dysphoria as well as their overall physical and mental health over time. The team also provides families with materials to review and community-based supports and resources to connect with in the time between appointments. The full team consists of myself, a pediatric endocrinologist, a primary care doctor in pediatric and adolescent medicine, a psychologist, a social worker, and a pediatric and adolescent gynecologist when indicated.

Our clinical practice is to extensively evaluate our patients before initiating transitioning medical treatments for gender dysphoria. It is only after a longitudinal observation and assessment period that we prescribe any treatment and only after the

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multidisciplinary team agrees that treatment is appropriate, and the patient's parents fully understand and sign the informed-consent forms. This process is intentionally set up to ensure that all involved are making an informed, measured decision, from the healthcare providers to the parents to the patients.

Throughout this evaluation and information-sharing process, patients and their families are encouraged to avail themselves of the various services and resources offered as part of our multidisciplinary clinic. The purpose of these services is to get a full picture of a patient's health, wellbeing, household support, and functioning. Each of those data points help determine whether a potential treatment option may be appropriate for any given patient.

Once a patient begins medical treatment, their progress is monitored at regular intervals, typically every six months, to assess the efficacy of the prescribed treatment through a physical examination and laboratory tests when indicated. This ongoing monitoring ensures continuous evaluation of a patient's physical and mental health and provides the opportunity to address any questions that arise during treatment.

Consistent with the established treatment guidelines described above, I prescribe puberty-delaying treatment starting at the Tanner 2 or early Tanner 3 stages of puberty. For people assigned male at birth, these stages of puberty are typically between ages 9 and 15, and for people assigned female at birth, typically between

ages 8 and 13. Depending on the patient's needs and the changes that have already been caused by their endogenous puberty, I either initiate pubertal suppression and wait to initiate hormones until they are ready and it is medically indicated; or, initiate puberty consistent with their gender identity with hormones when a patient is ready and it is medically indicated. The goal is to minimize the patient's dysphoria and initiate puberty consistent with gender identity within the typical age range. In my extensive clinical experience, I have observed the substantial benefits of pubertal suppression and hormone therapy, when medically indicated.

PUBERTY BLOCKERS AND HORMONE THERAPY ARE SAFE AND EFFECTIVE TREATMENTS FOR TRANSGENDER YOUTH

I have reviewed the "Vulnerable Child Compassion and Protection Act" (the "Act") passed by the Alabama Legislature and signed by Governor Ivey, in April 2022. If the law goes into effect, based on my expert opinion, it will cause serious harms to my patients as well as other transgender youth throughout Alabama.

Puberty-blocking medication and hormone therapy have greatly improved the physical and mental health and wellbeing of my patients. Denying my patients access to these well-established medical treatments will cause the mental health of many of my patients to regress, including increasing their suicidality and likelihood of attempting suicide. To cease ongoing care without a medical basis would violate my professional, ethical, and legal obligations by forcing me to harm my patient.

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The Endocrine Society's treatment protocols for providing puberty blockers and hormone therapy provide a safe and effective treatment approach for gender dysphoria. The American Academy of Pediatrics and every major medical association in the United States support the use of pubertal suppression and hormone therapy to treat gender dysphoria where medically indicated in adolescent patients.

Puberty blockers began to be used in the United States to treat gender dysphoria around 2004, which is not considered recent in medicine. We also have over 30 years of data on the impact of puberty blockers on children who undergo precocious puberty that we can apply to the transgender population. From the more than 30 years of data that we have, there is no scientific evidence of short- or long-term negative effects on patients who receive puberty blockers that would outweigh the benefits of this treatment. And for youth with gender dysphoria (as compared to those treated for precocious puberty), the treatment is used for a much shorter period of time, in order to pause puberty before either initiating puberty with cross-sex hormones or resuming endogenous puberty.

Pubertal suppression in youth with gender dysphoria does not delay puberty beyond the typical age range during which adolescents go through puberty. Pubertal development has a very wide variation among individuals. Puberty in individuals assigned male at birth typically begins anywhere from ages 9 to 15, and sometimes does not complete until a person's early twenties. For those individuals assigned

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female at birth, puberty typically begins anywhere from ages 8 to 13 and tends to be complete around age 15 on average. Protocols used for transgender youth would tend to put them in the latter third of typical puberty but nothing outside of the typical range. In our clinic at UAB, most patients who are prescribed puberty blocking medication are prescribed puberty blocking medication for one or two years.

In a 2020 study published in *Pediatrics*, the official journal of the American Academy of Pediatrics, researchers concluded that "[t]reatment with pubertal suppression among those who wanted it was associated with lower odds of lifetime suicidal ideation when compared with those who wanted pubertal suppression but did not receive it. Suicidality is of particular concern for this population because the estimated lifetime prevalence of suicide attempts among transgender people is as high as 40%."[18]

As noted above, under the Endocrine Society Clinical Guideline, once an adolescent establishes further maturity and competence to comprehensively understand decisions about additional treatment, it may then be medically necessary

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[18] Turban, J.L., King, D., Carswell, J.M., *et al.* Pubertal Suppression for Transgender Youth and Risk of Suicidal Ideation. *Pediatrics*. 2020;145(2):e20191725, at *5; *see also* Wiepjes, C.M., Nota, N.M., de Blok, C.J., *et al.* The Amsterdam Cohort of Gender Dysphoria Study (1972–2015): Trends in Prevalence, Treatment, and Regrets. *The Journal of Sexual Medicine*. 2018; 15(4):582-590; De Vries, A.L., McGuire, J.K., Steensma, T.D., *et al.* Young Adult Psychological Outcome After Puberty Suppression and Gender Reassignment. *Pediatrics*. 2014; 134(4):696-704.

and appropriate to provide hormone therapy to initiate puberty consistent with gender identity. For girls who are transgender this means administering both testosterone suppressing treatment as well as estrogen to initiate hormonal puberty consistent with the patient's female gender identity. For boys who are transgender this means administering testosterone.

There is nothing unique about undergoing hormone treatment to sustain one's health; it is a common practice in many non-transgender patients for reasons unrelated to treatment of gender dysphoria. It is not uncommon, for instance, for adolescents to have genetic or metabolic congenital conditions where the body may not produce ample amounts of estrogen or testosterone. Estrogen is also commonly prescribed to teenage girls to manage acne, to deal with inordinately heavy menstruation, and for polycystic ovary syndrome. It is the standard of care to prescribe estrogen or testosterone in these situations to supplement endogenous hormones. Many adults with gender dysphoria have been on hormone therapy for decades and no reputable medical organization has concluded that the risk of any negative outcome would outweigh the substantial benefit of the treatment. Likewise, many non-transgender individuals require hormone treatment for the majority of their lives as standard of care medicine for particular medical conditions. This includes patients with various intersex conditions such as Turner syndrome and Klinefelter syndrome, or medical conditions such as premature ovarian failure and childhood onset cancer.

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In addition to my patients with intersex traits, I regularly manage non-transgender patients receiving the same hormones that are provided to transgender patients. For example, nontransgender girls with hypogonadotropic hypogonadism (delayed puberty due to lack of estrogen caused by a problem with the pituitary gland or hypothalamus) may be treated with estrogen to initiate puberty. I also treat nontransgender girls with Polycystic Ovarian Syndrome (PCOS) with hormonal birth control or testosterone suppression to reduce some symptoms of the condition including excess facial hair.

I regularly prescribe hormone treatment to my patients—non-transgender and transgender—for various medical needs. The care is always specifically calibrated to the individual, their baseline hormone levels, and their particular medical needs. The legislative findings in the Act cite a risk of "irreversible sterility." When I recommend a treatment that may impact fertility, I counsel the patient and their parents about this potential side effect. At the UAB Clinic, if there is any risk that a treatment may impact fertility, patients and their families are informed of this risk and referred to a reproductive endocrinologist for discussion of fertility preservation if desired. Many people undergo fertility preservation before any treatment that could compromise fertility, including for instance, some types of pediatric cancers and autoimmune conditions. Puberty blockers do not impair long-term fertility in either transgender or non-transgender patients.

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The legislative findings in the Act also claim that "cross-sex hormones" cause "increased risks of cardiovascular disease, thromboembolic stroke, asthma, COPD, and cancer." Each of these risks is rare when this treatment is provided and supervised by a clinician. Moreover, these very same risks are present when hormone therapy is used to treat non-transgender individuals and individuals with intersex traits. None of these risks are unique to transition care for transgender patients. In my years of treating transgender patients, I have never seen the aforementioned complications afflict any of my patients.

The goal of treatment for gender dysphoria is to resolve the distress associated with the disconnect between a person's assigned sex at birth and their gender identity. Denying puberty blockers and hormones to a transgender adolescent who needs the treatment will not cause the adolescent to stop being transgender. It will only cause the minor to experience distress from lack of treatment.

Puberty-delaying medication and hormones are only provided after careful evaluation where a patient is experiencing consistent and persistent gender identification different from their assigned sex and clinically significant distress related to the incongruence. Each stage of the treatment is carefully evaluated and can be changed by carefully tapering a patient off the treatment if appropriate. In the case of puberty-blocking medication, once stopped, a patient's endogenous puberty

begins immediately. With hormone therapy, once stopped, a patient's naturally occurring hormones will continue to circulate.

All medical intervention comes with risk, and any medication can have side effects. In the case of medical treatment for gender dysphoria, decades of data have shown that the risk of adverse side effects from either puberty blockers or hormone therapy is low, and the benefits of the care greatly outweigh it.

In sum, the medical interventions described above are safe, effective, and essential for the well-being of many transgender young people. My patients who receive medically appropriate treatment for gender dysphoria experience significant improvement in their health. Medical treatment recommended for and provided to transgender adolescents with gender dysphoria can substantially reduce lifelong gender dysphoria and can eliminate the medical need for surgery later in life. Providing transition-based medical care can be lifesaving treatment and can improve the short- and long-term health outcomes for transgender youth.

HARMS OF WITHHOLDING OR TERMINATING TREATMENT FOR TRANSGENDER YOUTH WITH GENDER DYSPHORIA

Withholding pubertal suppression and hormone therapy from transgender young people when it is medically indicated is extremely harmful. As noted above, administration of pubertal suppression has been shown to significantly reduce suicidality in transgender patients.

If I had to pull my patients off treatment without medical indication, even for a short time, I have a very high level of concern that some could become so traumatized they would resort to self-harm and very possibly attempt suicide. Getting my patients on treatment has been lifesaving for many; taking them off mid-treatment, where the treatment is working, or denying it to those in need could be life-threatening.

ANTICIPATED ARGUMENTS FROM DEFENSE EXPERTS

I reviewed the declarations of Dr. James Cantor (Dkt. 69-2, Ex. 2), Dr. Paul Hruz (Dkt. 69-2, Ex. 5), Dr. Paul Hunter (Dkt. 69-2, Ex. 6), Dr. Quentin L. Van Meter (Dkt. 69-2, Ex. 4), and Dr. Michael Laidlaw (Dkt. 69-2, Ex. 3) that were filed earlier in this case. Anticipating that they may make similar arguments in their expert reports, I respond to some of the central points in those declarations. I do not specifically address each study or article cited but instead explain the overall problems with some of the conclusions that the Defendants' experts draw and provide data showing why such conclusions are in error. If necessary, I reserve the right to supplement my opinions as the case proceeds.

The Defendants' experts suggest that gender clinics routinely provide medical interventions to adolescents without proper mental health assessments and without informing patients and their parents of the potential risks of treatment. As described in detail above, both the Endocrine Society Clinical Practice Guideline (the

"Endocrine Society Guideline") and the World Professional Association of Transgender Health Standards of Care (the "WPATH SOC") require rigorous mental health assessments and informed consent processes before any medical treatment is initiated. In my experience treating transgender youth with gender dysphoria during my tenure at the UAB clinic, each patient undergoes an extensive psychological assessment and, if medical interventions are deemed medically appropriate, an extensive informed consent process before such interventions are provided as described above.

It is not the case that we encourage patients to initiate gender transition with no medical need as some of the Defendants' experts suggest. See, *e.g.*, Cantor ¶ 43 (referring to "transition-on-demand"); Hruz ¶¶ 75-76 (referring to "[u]nexamined 'affirming' medical interventions" and claiming that children transition without parental consent or for non-medical reasons). Consistent with the WPATH SOC and the Endocrine Society Guideline, each patient is met first by mental health providers who explore the patient's medical and mental health history and identity. Patients are not rushed into medical treatment, and treatment is not initiated without the aforementioned evaluations and informed consent process.

It appears to be the position of the Defendants' experts that waiting until a patient turns 18 years of age before initiating medical treatment for gender dysphoria would not cause harm to minor patients. See, *e. g.*, Hruz ¶¶ 56-57; Hunter ¶¶ 25, 39-

54 (claiming, falsely, that "[c]hildhood onset gender dysphoria typically remits naturally."). This is wrong. Many physiological changes that happen during endogenous puberty cause severe distress for transgender patients with gender dysphoria and can be difficult, if not impossible, to reverse with subsequent treatment. Based on my clinical experience, patients with severe dysphoria who are able to receive treatment prior to age 18 experience substantial mental health improvements.

Safety and Efficacy of Puberty Blockers

Puberty blockers have been used to treat patients with gender dysphoria for decades. We also have over 30 years of data about the safety of this treatment based on data from treating children with precocious puberty.

Dr. Laidlaw claims that "[p]sychosocial development will be necessarily stunted" with the use of puberty blocking medication since transgender children "are not developing with their peers." Laidlaw p. 15. As I explained above, pubertal suppression in youth with gender dysphoria does not delay puberty beyond the typical age range during which adolescents go through puberty. Pubertal development has a very wide variation among individuals. Puberty in individuals assigned male at birth typically begins anywhere from ages 9 to 15, and sometimes does not complete until a person's early twenties. For those individuals assigned female at birth, puberty typically begins anywhere from ages 8 to 13 and tends to be complete around

age 15 on average. As set forth above, protocols used for transgender youth would tend to put them in the latter third of typical puberty but nothing outside of the typical range.[19]

In his report, Dr. Hruz claims that patients treated with hormones will experience a range of negative health consequences. Hruz ¶ 61. For example, he says that patients treated with puberty blockers and hormones will be at an elevated risk of lower bone mineral density. *Id.* ¶¶ 61, 67. While lower bone density can sometimes occur while a young person is taking puberty blocking medication, that issue can be managed with the use of supplemental calcium and attention to weight-bearing exercise. When these medications are stopped after a brief period of use of some 1-3 years (as is our practice), followed by a hormonal puberty, we know from excellent data that bone density catch-up ensues. This is well documented[20] and matches our own clinical experience.[21] Additionally, studies have shown no

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[19] Hembree, W. C., Cohen-Kettenis, P. T., Gooren, L., *et al.* Endocrine Treatment of Gender- Dysphoric/Gender-Incongruent Persons: An Endocrine Society Clinical Practice Guideline. *The Journal of Clinical Endocrinology & Metabolism.* 2017; 102(11): 3869-903; Euling, S. Y., Herman- Giddens, M. E., Lee, P. A., *et al.* Examination of U. S. Puberty-Timing Data from 1940 to 1994 for Secular Trends: Panel Findings. *Pediatrics.* 2008; 121 (Supplemental 3): S172-S191.

[20] van der Loos, M. A., Hellinga, I., Vlot, M. C., *et al.* Development of Hip Bone Geometry During Gender-Affirming Hormone Therapy in Transgender Adolescents Resembles That of the Experienced Gender When Pubertal Suspension Is Started in Early Puberty. *Journal of Bone and Mineral Research.* 2021; 36(5): 931-41. doi: https://doi. org/10. 1002/jbmr. 4262.

[21] Dr. Hruz focuses on a study by Klink that reported some reduction in bone density at age 22 among 15 transgender women treated with blockers during

changes in bone mineralization among patients with central precocious puberty treated with pubertal suppression for a period of three years.[22] Dr. Hruz raises the issue of increased risk of fracture later in life, but we have been using pubertal suppression to treat patients with precocious puberty for over 30 years and have not observed these long-term effects. Hruz ¶ 61. And "[m]ore than 20 years of experience with GnRHa treatment … reveals that follow-up of patients several years after cessation of therapy reveals bone mineral accrual to be within the normal range compared with population norms."[23] As with all the risks of puberty suppression, the risks related to bone mineralization and the state of the evidence are discussed with patients and their parents during the informed consent process.

Additionally, Dr. Hruz says that patients on puberty-suppressing treatment will have slower rates of growth in height. Hruz ¶ 67. For transgender girls, there

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adolescence. Hruz ¶ 61. But the authors concluded that "[t]he contribution of GnRHa treatment is at best tentative," as they noted other factors that could explain the results, such as lower bone density among the transgender women before commencement of treatment, possibly due to their discomfort engaging in sports. Klink, D., Caris, M., Heijboer, A., *et al.* Bone Mass in Young Adulthood Following Gonadotropin-Releasing Hormone Analog Treatment and Cross-Sex Hormone Treatment in Adolescents With Gender Dysphoria, *The Journal of Clinical Endocrinology & Metabolism.* 2015; 100(2): E270-E275, at E274. doi: https://doi. org/10. 1210/jc. 2014-2439.

[22] Park, H. K., Lee, H. S., Ko, J. H., *et al.* The effect of gonadotrophin-releasing hormone agonist treatment over 3 years on bone mineral density and body composition in girls with central precocious puberty. *Clinical Endocrinology.* 2012; 77(5): 743-48.

[23] Eugster, Erica A. Treatment of central precocious puberty. *Journal of the Endocrine Society*, vol. 3, issue 5. May 2019; 965-72. https://doi.org/10.1210/js.2019-00036.

may be some overall reduced height growth, but the reduced height is both consistent with the gender-affirmation aspect of the care (*i.e.,* a transgender girl's treatment will aim to align her physiological characteristics, including height, consistent with what is typical for girls generally) and still within the expected overall range for the patient's height based their mid-parental average. For transgender boys, pubertal suppression could lead to *increased* height growth, which is likewise consistent with the gender-affirmation aspect of the care and also still within the expected overall range for what their adult height would be.

Dr. Hruz's suggestion that "alteration of normal adolescent brain maturation" may be another "possible side effect" of puberty blockers is not accurate. See Hruz ¶ 67. I have not seen this in my practice and science does not support the statement.[24]

Safety and Efficacy of Hormone Therapy

Dr. Hruz repeats many of the alleged risks of hormone therapy discussed in the law's legislative findings including "high blood pressure, weight gain, abnormal glucose tolerance, breast cancer, liver disease, thrombosis, and cardiovascular disease," Hruz ¶ 67, as well as "blood clots and strokes." *Id.* ¶ 80. As I explained

[24] Staphorsius, A. S., Kreukels, B. P., Cohen-Kettenis, P. T., *et al.* Puberty suppression and executive functioning: An fMRI-study in adolescents with gender dysphoria. *Psychoneuroendocrinology*. 2015; 56: 190-99. doi: https://doi. org/10. 1016/j. psyneuen. 2015. 03. 007.

above, we rarely see these side effects in patients with well-managed treatment through trained clinical providers.

When treating patients with hormones, the staff and physicians at the UAB Gender Clinic closely monitor dosing and circulating hormone levels to minimize any risk of adverse effects. This is true for patients with gender dysphoria and any other conditions requiring hormonal treatment. With transgender men and boys treated with testosterone, we have not seen red blood cell counts that are atypically concerning for men.[25]

Dr. Hunter claims that transgender children will be "bitterly disappointed later when they realize that they will be medically dependent for life," including with respect to cross-sex hormones. Hunter ¶ 148. In my experience, this is not true. To the contrary, I have observed happiness and positive adjustments in my adolescent patients as they age into adulthood.

In my clinical experience spanning more than three decades, transition-related medical care drastically improves the health and well-being of transgender adolescents with gender dysphoria for whom the care is medically indicated. My clinical experience has also shown that transgender adolescents who receive needed

[25] Wierckx K., Mueller, S., Van Caenegem, E., *et al.* Long-term evaluation of cross-sex hormone treatment in transsexual persons. *The Journal of Sexual Medicine*. 2012; 9(10): 2641-51. doi: https://doi. org/10. 1111/j. 1743-6109. 2012. 02876. x.

medical treatment for gender dysphoria have improved social and romantic relationships and are able to develop peer relationships with non-transgender and transgender people alike. I have seen hundreds of children and adolescents avoid the most serious consequences of gender dysphoria including severe anxiety, depression, and self-harming behaviors, specifically because they received medical treatment. Many of my patients, for instance, have transformed from being sullen, withdrawn, and struggling in school to kids, adolescents, and young adults who are now thriving academically and socially.

If my clinic is barred from providing this care, it is foreseeable and certain that transgender youth in Alabama will suffer serious medical and mental health consequences, including declining mental health, suicide ideation, suicide attempts, and possibly completed suicides. There is a well-established and known standard of medical care to treat transgender adolescents, and this law would prohibit doctors from caring for their patients and abiding by the Hippocratic oath.

I hold each of the opinions expressed in this report with a reasonable degree of scientific certainty based on the materials I have reviewed and based on my education, experience, and knowledge. I reserve the right to supplement, amend, or modify my opinions upon review of further information, including, but not limited to, testimony, documents, and reports I receive after the date of this report.

Executed this 12 th day of February, 2023.

Morissa J. Ladinsky, MD, FAAP

EXHIBIT A

CURRICULUM VITAE

PERSONAL INFORMATION:

Name:	Morissa J. Ladinsky, MD, FAAP
Citizenship:	United States
Other Languages:	Spanish

CURRENT RANK/TITLE:

2015-present	Professor of Pediatrics, UAB School of Medicine
2015-present	Professor, Medical Education, UAB School of Medicine
Business address:	Department of Pediatrics Division of Academic General Pediatrics 310 Children's Park Place 1 1600 7th Avenue South Birmingham, AL 35233-1711

HOSPITAL APPOINTMENTS:

Medical Staff: Children's Hospital of Alabama, Birmingham, AL	2015-
Medical Staff: UAB Hospital Birmingham, AL	2015-

EDUCATION:

Year	Degree	Institution
1990	Doctor of Medicine With Honor	Baylor College of Medicine, Houston, TX
1985	Bachelor of Arts Human Biology Magna cum laude	Brown University Providence, RI

LICENSURE

Alabama	#34204
Ohio	#35-07-7337 (inactive)
Maryland	#D47256 (inactive)

Texas #J0053 (inactive)

BOARD CERTIFICATION:

American Board of Pediatrics, Certificate # 51388
October 13, 1993
Recertified 2001, 2008, 2014, 2019. Participating in MOC

POSTDOCTORAL TRAINING:

Year	Degree	Institution
1995-1997	Fellowship, General Academic Pediatrics and Program Development	Johns Hopkins School of Medicine
1990-1993	Residency in Pediatrics	Baylor College of Medicine

ACADEMIC APPOINTMENTS:

Year	Rank/Title	Institution
2015-2022	Associate Professor	UAB School of Medicine Department of Pediatrics Division of Academic General Pediatrics
2005-2015	Assistant Professor	Division of General and Community Pediatrics Cincinnati Children's Hospital Cincinnati, OH
2000-2005	Assistant Professor	Division of Ambulatory Pediatrics Ohio State University School of Medicine Nationwide Children's Hospital Columbus, OH
1997-1999	Instructor in Pediatrics	Johns Hopkins University School of Medicine
1997-1999	Clinical Assistant Professor Pediatrics	University of Maryland School of Medicine

OTHER EMPLOYMENT:

1981-1983	Brown University, Research Assistant, Department of Genetics Providence, Rhode Island
1985-1986	Rural Eight County Family Planning Program Clinic Assistant, Counselor, San Marcos, Texas
1989	Bearskin Meadow Camp Medical Assistant, Diabetes Educator, CA Diabetic Youth Foundation, San Francisco, California
1993-1995	Ashford Pediatric Associates, Pediatrician (private practice) Houston, Texas
1995-1999	Franklin Square Hospital Center Pediatrician-Department of Pediatrics Consultant Baltimore, Maryland
1995-1997	Attending, Johns Hopkins Hospital Division of Pediatric/Emergency Medicine
1999	Baltimore City Dept. of Health, Physician-School based health center, Northwestern High School, Baltimore, Maryland
1999-2000	Physician- Locum Tenens, Walnut Hills Health Center, Cincinnati, Ohio
2006-2015	Pediatrician, Private Practice, Group Health Associates Cincinnati, Ohio

AWARDS/HONORS:

Phi Beta Kappa, Brown University	inducted 1984
Sigma Xi Scientific Honor Society, Brown University	inducted 1983
Academic Achievement Award: Brown University Division of Biology and Medicine	1983-1985

Alpha Omega Alpha, Baylor College of Medicine	inducted 1989
Who's Who in America	2004-present
Who's Who of American Women	2005-present
Dayton Business Journal Best Doctors:	2010-2015
Cincy Magazine Best Doctors:	2010-2015

Cover Physician, Dec. 2011

Best Doctors in America:	2011-2023
America's Top Doctors (Castle Connolly/US News):	2012-2023
Birmingham Magazine Best Doctors	2015- 2022
UAB Department of Pediatrics Educational Excellence Award	2017-2022
UAB Multicultural and Diversity Programs Research and Initiative Award	2018
TAKE of Birmingham, AL: Hope for Tomorrow Award	2018, 2019
UAB Department of Pediatrics Ralph Tiller Distinguished Faculty Award	2018
UAB Department of Pediatrics Sergio Stagno Friend of the Housestaff Award	2018
American Academy of Pediatrics, Special Achievement Award	2018
UAB Research in Medical Education Annual Symposium, First Place Award for Educational Innovation: *"Closing Healthcare Gaps for Marginalized Populations: A Transgender Standardized Patient Approach"*	2019
Castle Connolly's Exceptional Women in Medicine	2019, 2021, 2022

American Academy of Pediatrics, Alabama Chapter President's Award	2021
UAB School of Medicine Dean's Excellence Award for Diversity Enhancement	2022
Central Alabama Pride Ally Award	2022
American Academy of Pediatrics-Marsha Raulerson Advocacy Award-Alabama Chapter	2022
Champion of Justice-Courage Award. National Center for Lesbian Rights (NCLR).	2022
Insider Magazine T100 List of Leaders Driving Unprecedented Change and Innovation. One of 10 healthcare leaders awarded nationally.	2022

PROFESSIONAL SOCIETIES/MEMBERSHIPS

Fellow of the American Academy of Pediatrics	1993-present
Member, Section on LGBT Health and Wellness	2015-present
Member Section on Minority Health, Equity and Inclusion	2020-present
Ambulatory Pediatric Association	1995-present
American Medical Women's Association	1997-present

STATE OF ALABAMA, JEFFERSON COUNTY COUNCILS AND COMMITTEES:

2015	Magic City Acceptance Project, Training Committee. Council of agencies representing at risk Birmingham Youth. Advocacy for and training of service providers in law, education, social services around needs of sexual minority and gender variant youth.
2015-present	West Alabama Area Health Education Coalition, (taking teams of trainees to the West Alabama Black Belt for reciprocal training and mentoring)
2016	Curriculum Developer/Participant, HERO Project/UAB Dept. of Pediatrics Health Education Project with Washington K-8/ Birmingham Public Schools.

2016	Organized first Community (now statewide) Support Group for Spanish Speaking Parents of Children with Autism. Joint project: UAB Dept. of Pediatrics/Alabama Autism Society/HICA
2016-present	Board of Directors, TAKE (Transgender Advocates Knowledgeable Empowering) Community Empowerment and Support for Transgender Women of Color in Alabama.
2017-present	Alabama Stakeholder Workgroup: Data Driven Prevention Initiative for Heroin/Opioid Overuse/Abuse
2017-2018	Advisory Board, Central Alabama PRIDE
2017-2020	Alabama Department of Public Health, Alabama's Adolescent Vaccine Task Force
2017-2022	Alabama Department of Public Health Office of Women's Health/Alabama American Academy of Pediatrics Opioid Misuse in Women/Neonatal Abstinence Syndrome Taskforce, Protocols Committee Co-Chair
2017-present	Alabama Governor's Opioid Council, Implementation Team, Treatment and Recovery Support Subcommittee Maternal and Child Health Subcommittee
2018-present	Board of Directors, Children's Policy Council of Jefferson County. Multi-sector and agency policy network united around child advocacy.
2019-present	Alabama Medicaid Agency-Medical Care Advisory Committee
2019-present	Mayor's LGBTQ Advisory Board, Office of Mayor Randall Woodfin, Birmingham, Alabama
2019-present	Alabama Perinatal Quality Collaborative -Steering Committee for Neonatal Opioid Withdrawal Syndrome Statewide QI Initiative
2020	Advisory Board, Junior League of Birmingham
2021	Council on Accreditation, Medical Association of the State of Alabama
2021-present	Council on Medical Education, Medical Association of the State of Alabama

2021-present	Ethics Committee, Jefferson County Medical Society

NATIONAL COUNCILS AND COMMITTEES

2000-2002	Medical Consultant, Chances for Children (Former US Charity of UK Duchess Sarah Ferguson)
2013-2015	Practice Alliance/Translation Workgroup **Co-Chair**, Autism Treatment Network/Autism Speaks, National Offices, Princeton, New Jersey
2015-present	American Academy of Pediatrics, Section on LGBTQ Health and Wellness
2018-present	Co-Leader. Multi-agency Social Justice Experience. GLIDE Center for Social Justice, UCSF Department of Pediatrics, UAB Pediatrics. Annual experience uniting leaders in medicine, faith, tech and criminal justice from San Francisco and Alabama to empower coalition building around equity and social justice.
2022-present	Board of Directors, Out Care, a national comprehensive resource for LGBTQ+ health care resources, mentorship, medical education and cultural humility training.

UAB AND CHILDREN'S of ALABAMA COUNCILS, COMMITTEES, ACTIVITIES

2015-2018	Center For Aids Research/Community and Behavioral Sciences Core/UAB School of Public Health. Faith and Spirituality-Health Equity Interface Programming
2017-2019	Family-Centered Care Initiatives Council: Hispanic, Other Non-English Speaking and Low SES Families (COA)
2017-2019	Faculty Advisor, Medical Student MedPride Gay/Straight Alliance, UAB School of Medicine
2018-present	Advisory Board, Psychiatric Intake and Response Center (PIRC), Children's of Alabama Departments of Psychiatry and Emergency Medicine
2019-present	Advisory Board, UAB Comprehensive Center for Addiction in Pregnancy Program
2020-present	UAB Department of Pediatrics Diversity, Equity and Inclusion Faculty Council. Co-Chair, 2022-present

2021-present	UAB Department of Pediatrics Residency Program Evaluation Committee
2021	UAB School of Medicine Community Engaged Teaching Roundtable
2021	UAB School of Public Health LGBTQ Endowed Professorship Executive Committee
2022	UAB Faculty Senate Subcommittee on Diversity, Equity and Inclusion

LOCAL/REGIONAL COUNCILS AND COMMITTEES AT OTHER INSTITUTIONS

1981-1984	Steering Committee. Meiklejohn Academic Advising Brown University
1983-1985	Student representative and advisor, Brown University Office of Undergraduate Admissions
1987-1990	Baylor Medical School Admissions Committee
1998	Sinai Hospital of Baltimore Pediatric Residency Selection Committee
2012-2015	Quality Improvement Team, Physician Member, The Kelly O'Leary Center for Autism/Autism Treatment Network, Cincinnati Children's Hospital Medical Center
2014-2015	Access to Care Workgroup, Center for Developmental Disabilities and Behavioral Pediatrics Cincinnati Children's Hospital Medical Center

MAJOR RESEARCH INTERESTS:

1) Impact of faith and community on quality of health for at risk youth including LGBTQ youth living in the Deep South.

2) Implementation of AAMC Curricular Guidelines around LGBTQ health care using Standardized Patient Methodology.

3) Developmental outcomes for infants facing neonatal opioid withdrawal syndrome.

TEACHING and MENTORING EXPERIENCE:
(Academic appointments listed earlier)

1995-1997	Preceptor, Harriet Lane Pediatric Primary Care Clinic Johns Hopkins Hospital
1995-1997	Pediatric Inpatient Co-Attending Physician Johns Hopkins Hospital
1997-1999	Faculty Attending Pediatrician/Preceptor Greenspring Pediatric Associates, Department of Pediatrics, Sinai Hospital of Baltimore
2007-2015	Revision and presentations of Pediatrician section. Pre-natal Course series, Bethesda North Hospital/TriHealth, Cincinnati, Ohio
2009-2013	Pediatrician Preceptor for Family Nurse Practitioner students during Pediatric Clerkship. University of Cincinnati School of Nursing, Good Samaritan Hospital/TriHealth School of Nursing
2009-2015	Pediatrician preceptor for residents during outpatient ambulatory clerkship, Cincinnati Children's Hospital/University of Cincinnati
2015-present	Faculty Attending Primary Care Preceptor for 14-16 residents providing both continuity and acute care, 4-5 sessions weekly
2015-present	Faculty Attending Pediatrician, Multidisciplinary Transgender Health Team, Children's of Alabama
2015-present	Children's of Alabama Staff Training for Inpatient Psychiatry, ER, Child Abuse Program, Laboratory Medicine, Social Work, Patient Relations teams: *Delivering Quality and Affirming Care to LGBTQ Patients. Focus on transgender and gender non-binary youth.*
2015-present	Faculty Mentor for several Pediatric Residents, all share mutual interest in health disparities and marginalized populations.
2016-2017	UAB Department of Pediatrics Faculty Scholars Program
2016	Lead Physician for Children's of Alabama's Primary Care Clinic HPV Vaccine QI Initiative

2017-present	Curricular Development and execution of Standardized Patient/OSCE models in training medical and allied health students around LGB and transgender healthcare. UAB School of Medicine
2018-present	LGBTQ Healthcare and Education, Special Topics Course Developer and Leader, UAB School of Medicine
2018-present	Annual guest lecturer, *Cultural Humility and Spirituality in Public Health*, Samford University, School for the Health Professions, Birmingham, AL
2019-present	Mentor for 2 ongoing pediatric resident QI initiatives. Firearm Injury Prevention in a Primary Care Clinic and After Visit Anticipatory Guidance for Spanish Speaking Families.
2020-present	Health Equity Scholars Co-Lead. Development and execution of UAB Pediatrics Residency curriculum and special interest team around improving health equity through understanding of structural racism and impact on social determinants of health.
2021	Faculty Facilitator: Case Studies in Diversity in Healthcare. Pilot initiative within UAB School of Medicine

MAJOR NATIONAL LECTURES:

"Autism Spectrum Disorders in the Community, the Role of the PCP" Invited Guest Speaker, Autism Treatment Network/Autism Intervention Research Network on Physical Health Fall Program Meeting. Denver, CO, November 8, 2012

"Primary Care Physician Engagement in the Care of Children with Autism; Lessons Learned from ADHD", Invited Guest Speaker, Autism Speaks/Autism Treatment Network Steering Committee, National Meeting, Washington, DC, July 11, 2013

"Enhancing Medical Student Competencies in Transgender Healthcare: A Transgender Standardized Patient Approach", AAMC Learn Serve Lead National Conference, Phoenix, AZ, November 10, 2019

"Clinical Advocacy and Care for Transgender Youth", Harvard Medical School, Equity and Social Justice Series. Boston, MA October 27, 2021

"On the Front Lines of Advocacy in the Deep South", Pediatric Academic Societies (PAS) National Annual Meeting, Denver, CO. April 24, 2022.

"Standing up for Gender Affirming Care-from Clinics to Courts", American Academy of Pediatrics National Conference and Exhibition. Anaheim, CA. October 8, 2022

"Standing Up for Gender Affirming Care". Closing Plenary. American Academy of Pediatrics National Conference and Exhibition. Anaheim, CA. October 11, 2022

"Understanding Substance Use Disorder in Pregnancy. Can we Align Science and Law?" Association of Prosecuting Attorneys. Washington DC. February 1, 2023

GRANT SUPPORT:

1996-1997	The Thomas Wilson Sanitarium for the Children of Baltimore City.
1997	Baltimore Council on Human Resources "Startup funding for Reach out and Read, The Harriet Lane Primary Care Center at Johns Hopkins"
	"The WHO Oral Rehydration Solution in US Pediatric Practice: An Evaluation of Parent Satisfaction" Principal Investigator
2017-2019	Community Foundation of Greater Birmingham, "Expansion of the Multidisciplinary Gender Clinic, Pediatric Endocrinology, Children's of Alabama"
2017-2022	UAB Health Services Foundation, General Endowment Fund, "Curricular Advancement of LGBT Healthcare Competencies Using Standardized Patients"

MANUSCRIPTS:

1. Novack DH, Detering BJ, Arnold R, Forrow L, **Ladinsky, M**, Pezullo JC. Physicians' Attitudes Toward Using Deception to Resolve Difficult Ethical Problems. JAMA. 1989;261:2980-2985.

2. Raef H, **Ladinsky MJ**, Arem R. Concomitant euthyroid Graves' ophthalmopathy and isolated ocular Myasthenia Gravis. Postgraduate Medical Journal. 1990;66:849-852.

3. Musher DM, Hamill RJ, **Ladinsky MJ**, Winsor DK, Baughn RF. Acute Glomerulonephritis Due to Shigella Flexnerii Dysentery with Demonstration of a Virulence Protein of Shigella in Circulating Immune Complexes. The Journal of Infectious Diseases. 1990;161:366-377

4. Ladinsky M, Lehmann H, Santosham M. The Cost-Effectiveness of Oral Rehydration Therapy for US Children with Acute Diarrhea. Medical Interface. 1996;9:113-119.

5. Ladinsky M, Goepp J, Santosham M. Outpatient Oral Rehydration Therapy: Safe, Effective, and Rapid. Annals of Emergency Medicine. 1997;29(4):551-552.

6. Ladinsky M, Duggan A, Santosham M, Wilson M. The World Health Organization Oral Rehydration Solution in US Pediatric Practice; A Randomized Trial to Evaluate Parent Satisfaction. Archives of Pediatrics & Adolescent Medicine. 2000;154:700-705.

7. Johnson C, Hurtubise L, Castrop J, French G, Groner J, **Ladinsky M**, McLaughlin D, Mahan J. Learning management systems: technology to measure the medical knowledge competency of the ACGME. Medical Education. 2004;1365-1374

8. Shah, K, Zabielinski, M, **Ladinsky, M.** Isolated pustular nodule on the thumb, JAMA Pediatrics, 2015 Nov 1;169(11): doi: 10.1001/jamapediatrics.2015.1301, 1061-1062

9. Ladinsky, M, Cohen, M. Mind the Gap. J Pediatr. 2020 May 31. pii: S0022-3476(20)30692-2. doi: 10.1016/j.jpeds.2020.05.054

10. Kirpalani H, Bell EF, Hintz SR, Tan S, Schmidt B, Chaudhary AS, Johnson KJ, Crawford MM, Newman JE, Vohr BR, Carlo WA, D'Angio CT, Kennedy KA, Ohls RK, Poindexter BB, Schibler K, Whyte RK, Widness JA, Zupancic JAF, Wyckoff MH, Truog WE, Walsh MC, Chock VY, Laptook AR, Sokol GM, Yoder BA, Patel RM, Cotten CM, Carmen MF, Devaskar U, Chawla S, Seabrook R, Higgins RD, Das A; Eunice Kennedy Shriver NICHD Neonatal Research Network (**Ladinsky, M**) Higher or Lower Hemoglobin Transfusion Thresholds for Preterm Infants. N Engl J Med. 2020 Dec 31;383(27):2639-2651. doi: 0.1056/NEJMoa2020248. PMID: 33382931 Clinical Trial.

11. Bell EF, Hintz SR, Bann CR, Wyckoff MR, DeMauro SB, Walsh MC, Carlo WA, VanMeurs KP, Vohr VR, Eunice Kennedy Shriver NICHD Neonatal Research Network (**Ladinsky, M**). Mortality, In-Hospital Morbidity, Care Practices, and 2-Year Outcomes for Extremely Preterm Infants in the US, 2013-2018. JAMA, 2022 Jan 18:327(3): 248-263

BOOKS AND BOOK CHAPTERS:

Cohen, MB, **Ladinsky M**, and Marino, B. Pediatric Gastroenterology in Pediatric Blueprints 6th Edition, ed, Marino and Fine. Lippincott Williams & Wilkins, 2012

Published Abstracts and Poster Exhibits

1. Ladinsky MJ, Duggan A, Santosham M, Goepp JG, Wilson MH. Why is the WHO-ORS Underused by US Pediatric Practitioners? Ambulatory Pediatric Association Region IV Meeting, January 20, 1996 and National Annual Meeting, May 7, 1996. (Archives of Pediatrics & Adolescent Medicine. 1996;150:P29)

2. Goepp J, Edwards L, **Ladinsky M**, Gilger M, Oberherman R. Effect of an Oral Rehydration Training Program on Residents' Knowledge and Attitudes. Ambulatory Pediatric Association 3. 3. National Annual Meeting, May 7, 1996. (Archives of Pediatrics & Adolescent Medicine. 1996;150:P21)

4. Webb A, **Ladinsky, M.** Early Initiation of Hormone Therapy: A Lifesaving Treatment for a Transgender Teen with Anorexia Nervosa. *J Investig Med*, 2018; 66: 506

ORAL PRESENTATIONS

Scientific/Scholarly papers presented at national meetings:

Morissa Ladinsky, MD "Why is the WHO-ORS Underused by US Pediatric Practitioners?" Ambulatory Pediatric Association Region IV Meeting, January 20, 1996.
Ambulatory Pediatric Association National Annual Meeting, May 7, 1996.

Morissa Ladinsky, MD "The WHO Oral Rehydration Solution in US Pediatric Practice; A Randomized Trial to Assess Parent Satisfaction." Ambulatory Pediatric Association National Annual Meeting, May 4, 1998

Shawn Galin, PhD, **Morissa Ladinsky, MD** "Enhancing Medical Student Competencies in Transgender Healthcare: A Transgender Standardized Patient Approach", Learn, Serve, Lead 2019: The AAMC National Annual Meeting, Phoenix, AZ. November 9, 2019

Shawn Galin, PhD, **Morissa Ladinsky, MD** "Enhancing Medical Student Competencies in Transgender Healthcare: A Transgender Standardized Patient Approach", International Meeting on Simulation in Healthcare (IMSH), San Diego, CA January 20, 2020

Tina Simpson, MD, MPH, Chrystal Rutledge, MD, **Morissa Ladinsky, MD** "Developing a Health Equity Scholars Program for Pediatric Residents in the Heart of the Civil Rights Movement" American Society of Pediatric Department Chairs (AMSPDC), Virtual. March 6, 2021

Invited Workshops at local and regional meetings:

Morissa Ladinsky, MD, Teaching Oral Rehydration Therapy So It's Used. Workshop presented at the Ambulatory Pediatric Association National Annual Meeting, May 3, 1997.

Morissa Ladinsky, MD , Provision of Affirming Care to Transgender and Gender Diverse Patients, Children's Hospital of Alabama Divisions of: Pathology (September, 2015), Emergency Medicine (January, 2016), Inpatient Psychiatry (March, 2016), Child Abuse/CHIPS Teams (May, 2016), UAB Medical Student 1st and 2nd year Interest Group (May 2016), Second year medical student class (February, 2017-20).

Morissa Ladinsky, MD, Nefertiti Durant, MD, MPH, Group CME/MOC Part 2 Lead/Facilitator. Adolescent Medicine Self-Assessments. Alabama American Association of Pediatrics 2016 Annual Meeting and Fall Pediatric Update. Birmingham, AL October 2, 2016

Morissa Ladinsky, MD, Hussein Abdul-Latif, MD, Marianthe Grammas, MD "How Providers Can Support Trans and Gender Variant Youth" Jefferson County Medical Society Provider Workshop. October 27, 2017

Morissa Ladinsky, MD "Trans/Gender Non-Conforming Affirming Healthcare," Webinar addressing importance of medical education in healthcare. May 19, 2020

Morissa Ladinsky, MD , Shajuane Jones, MS "A Community Approach to Implementing Plans of Safe Care in Jefferson and Jackson Counties, Alabama" National Quality Improvement Center for Collaborative Community Court Teams Webinar. The Children's Bureau. July 10, 2020.

Morissa Ladinsky, MD, Heather Austin PhD, "LGBTQ: The Reality for Youth and Families", Alabama Psychological Association 2021 Annual Conference, Orange Beach, AL. June 12, 2021

Morissa Ladinsky, MD , Samantha Hill, MD, MPH, Matthew Kiszla, BS, MS-2, "What's on the Books: Sexual and Gender Minority Health in Alabama Post 2020", Blackburn Institute 2021 Annual Symposium, University of Alabama, Tuscaloosa, August 27, 2021

Morissa Ladinsky, MD, Shajuane Jones, MS "Understanding Substance Dependence when Serving Pregnant and Parenting Women", Addiction and The Law Training, Dallas County Court and DHR. Montgomery, AL September 9, 2021

Morissa Ladinsky, MD, Gender Affirming Spaces, Places and Care. The Basics. "Time To THRIVE in the Deep South", Atlanta, GA, February 4, 2023

Invited lectures at local/regional meetings:

Oral Rehydration Therapy, an Update" Pediatric Grand Rounds at Sinai Hospital of Baltimore, February 2, 1998.

"Current Research in Pediatric Obesity and Realities in Clinical Practice" Regional Annual Meeting, National Association of Pediatric Nurse Practitioners. Cincinnati, OH. November 12, 2006

"Care Coordination for our NICU Grads in Alabama", Perinatal Grand Rounds, UAB Departments of Neonatology, OB/GYN and Pediatrics, March 30, 2016

"Pediatricians Preparing Youth for College, Can We Still Anticipate and Guide?" Alabama American Academy of Pediatrics, Spring Meeting and Pediatric Update, Point Clear, AL, April 29, 2016

"Office Based Care for LGBTQ Youth in 2016" at Raising the Resilient Teen, It Takes a Village Children's of Alabama, Adolescent Health Symposium, April 8, 2016

"Office Based Care for LGBTQ Youth in 2016" Alabama American Academy of Pediatrics, Spring Meeting and Pediatric Update, Point Clear, AL, April 30, 2016

"How Pediatricians can Support Trans and Gender Variant Youth in 2016", at American Academy of Pediatrics District II and VII Executive Leadership Annual Meeting", Washington, DC, June 25, 2016

"Pediatricians Preparing Youth for College, Can we Still Anticipate and Guide?" Pediatric Grand Rounds, Children's of Alabama, July 7, 2016

"Beyond Bathrooms, Understanding Trans and Gender Variant Youth in 2016". Grand Rounds, Children's of Alabama, October, 13, 2016.

"Gender Dysphoria, Eating Disorders and Health Challenges for Trans/Gender Variant Youth", Intensive Course in Pediatric Nutrition, Department of Pediatrics, UAB. February 24, 2016, 2019 and 2020

"Neonatal Abstinence Syndrome" at *The Opioid Crisis in Alabama; From Silos to Solutions*. A public policy conference. Montgomery, AL. March 10, 2017.

"Neonatal Abstinence Syndrome", National Association of Pediatric Nurse Practitioners Annual Meeting, UAB School of Nursing, May 21, 2017

"Who are LGBTQ Youth, Who Am I? Alabama Mental Health Symposium, Children's Hospital of Alabama, May 19, 2017.

"You are the Key to HPV Cancer Prevention". Provider Education and Networking Event, Alabama Area Health Education Coalition, Tuscaloosa, AL, May 24, 2017

"Opioid Use in Pregnancy and Neonatal Abstinence Syndrome", Alabama American Academy of Pediatrics, Fall Annual Meeting, Birmingham, AL, October 1, 2017

"HPV Vaccine Update" at Progress in OB/GYN 2018, Alabama ACOG, UAB Department of OB/GYN Annual Meeting, Birmingham, AL February 16, 2018

"Neonatal Opioid Withdrawal Syndrome, Drugs and the Brain" at Alabama Department of Health, Women's Health Update, Birmingham, AL August 3, 2018

"Opioid Use in Pregnancy and Neonatal Opioid Withdrawal Syndrome", Statewide Opioid Clinical Conference, Birmingham, AL, August 10, 2018

"The Opioid Crisis: National and State Initiatives", Annual Perinatal Conference:, Huntsville Hospital for Women and Children, Huntsville, AL, September 21, 2018

"Sound the Alarm: Opioid Use in Pregnancy and Neonatal Opioid Withdrawal Syndrome" 34th Annual Statewide Early Intervention and Preschool Conference, Birmingham, AL. October 16, 2018

"The Opioid Epidemic as a Child Health Crisis. State and National Initiatives, Outcomes and Insights", Grand Rounds, Children's of Alabama, Birmingham, AL. November 29, 2018

"Stakeholder Unity to Improve the Future for Substance Dependent Women and their Children", First Annual Alabama Child Protective Services/Department of Human Resources Conference, Birmingham, AL February 28, 2019

"Neurologic Outcomes of NICU Graduates", UAB Perinatal Conference, Birmingham, AL, June 30, 2019

"The Alabama 2020 Legislative Session, Bills affecting Child Health", First Fridays Community Stakeholder Conference, February 8, 2020

"Understanding Medication Assisted Treatment for Opioid Dependent Alabamians Within the Criminal Justice System", Annual Meeting of Family Court Judges, Alabama Association of Drug Court Professionals, AL Administrative Office of Courts. January 9, 2021

"Understanding Medication Assisted Treatment for Opioid Use Disorder", Alabama Association of Drug Court Professionals Annual Conference, Opening Plenary Session speaker, February 9, 2021

INVITED MEDIA APPEARANCES, INTERVIEWS, PANEL PARTICIPATION:

Invited Participant, US Department of Justice Roundtable Discussion on LGBTQ Issues, Office of US Attorney Joyce Vance for the Northern District of Alabama, July 12, 2016.

Panelist, "Legal Rights Intersection with LGBTQ Health", Senator Doug Jones, Moderator, UAB, October 14, 2016

Panelist, "LGBTQ Rights", Rep. Patricia Todd, Moderator, Vestavia Hills Library, January 21, 2017

Panelist, "Forum on The Future of the Affordable Care Act", Congresswoman Terri Sewell, Organizer and Moderator. Princeton Hospital. January 20, 2017.

Panelist, Your Voice, Your Future Roundtable, "Transgender in Alabama", Sinclair Broadcast Group, ABC33/40. Birmingham, AL. April 18, 2017

Panelist, "Anti-bullying Community Forum", Hadassah/Birmingham Community Foundation, April 20, 2017

Helio Health, Invited editorial response to "PCP-Transgender Patient Relationships Needs Improvement", November 27, 2018. *https://www.healio.com/news/primary-care/20181127/pcptransgender-patient-relationships-need-improvement*

Helio Health, "How PCP's Can Meet Needs of Transgender Patients", March 5, 2019, *https://www.healio.com/news/primary-care/20190305/how-pcps-can-meet-needs-of-transgender-patients*

NBC News, "Alabama Moves Closer to Transgender Health Ban for Minors", March 10, 2020. *https://www.nbcnews.com/feature/nbc-out/alabama-moves-closer-transgender-health-care-ban-minors-n1154791*

Alabama Media Group, "Doctors Call New Alabama Abortion Bill 'Medically Implausible'", March 11, 2020. *https://www.al.com/politics/2020/03/doctors-call-new-alabama-abortion-bill-medically-implausible.html*

Reuters Media Group, "Anxieties Mount for Transpeople as Coronavirus Delays Surgeries", April 9, 2020, *https://www.openlynews.com/i/?id=380a10c1-b93c-4a25-8691-0d1f84e39a7b*

American Academy of Pediatrics Voices, "Stripping of Transgender Protections Does not Have to Hamstring our Ability To Help All Patients" July 23, 2020. *https://services.aap.org/en/news-room/aap-voices/stripping-of-transgender-protections-does-not-have-to-hamstring-our-ability-to-help-all-patients/*

https://www.birminghamal.gov/2021/03/08/city-of-birminghams-lgbtq-advisory-board-issues-statement-on-hb1sb10/?fbclid=IwAR2aHeKeYh04PYOjYDXj2GN_28nVyptL7kMVHKTDa1KNJQ5vFyxPwJzv4O0 Primary Statement Author

Health Highlights with Dr. Kay, Podcast. "Teaching Medical Students About Transgender Healthcare with Drs. Morissa Ladinsky and Shawn Galin". March 19, 2021. https://podcasts.apple.com/us/podcast/teaching-medical-students-about-transgender-health/id1555978677?i=1000513735920

VICENews https://www.youtube.com/watch?v=ZQ4o1RqYJmc March 29, 2021. Alabama Wants to Send Doctors to Prison for Treating Trans Kids

Let's Think On It Live, Radio Show and Podcast with Dr. Mark Westfall. "Current Medical Understanding of Being Transgender". Live radio event on 107.3 FM and livestream http://bhammountainradio.com . Podcast http://letsthinkonitnow.com April 8, 2021

https://www.npr.org/2021/03/28/981225604/its-hurtful-trans-youth-speaks-out-as-alabama-debates-banning-medical-treatment National NPR with Melissa Block

Birmingham Aids Outreach Community Conversations on HB-1, SB-10. Facebook Live panelist. March 29, 2021 https://www.facebook.com/events/1587818304941823
https://www.alreporter.com/2021/03/23/the-dad-and-daughter-asking-lawmakers-to-stop-the-trans-health-care-ban/

Politifact. April 2021, Assistance with fact checking regarding proposed legislation prohibiting receipt of gender affirming healthcare

https://www.al.com/opinion/2021/05/im-a-doctor-and-alabama-could-arrest-me-for-doing-my-job.html

Maynard Cooper and Gayle (Legal Firm with Birmingham and national offices), Pride Month Dialogue, Pro-Bono Legal Document Clinic and Its Far Reaching Impact for Trans identified Clients. June 16, 2021

"Caring for Trans and Gender Diverse Youth; From Tavistock to US State Legislatures" 60 Minutes, Australia. Interviewer Sarah Abo. Taped September 3, 2021.

https://time.com/6146269/doctors-trans-youth-gender-affirming-care-harassment/
Time Magazine national. February 16, 2022

https://www.washingtonpost.com/politics/2022/04/07/alabama-health-care-transgender-bill/
April 7, 2022

NPR National, 1A. "Doctors who provide gender affirming care are preparing for growing restrictions" April 14, 2022. Transcript at https://the1a.org/segments/doctors-who-provide-gender-affirming-care-are-preparing-for-growing-restrictions/

NPR National, Morning Edition. "Families of transgender youth in Alabama face some difficult choices." Aired May 3, 2022. https://www.npr.org/2022/05/03/1096075578/families-of-transgender-youth-in-alabama-face-some-difficult-choices

"Transgender medication law in Alabama blocked by Judge". AP interview with text forming part of articles in news features nationally and worldwide.
https://www.spokesman.com/stories/2022/may/09/transgender-treatment-doctors-threatened-by-new-al/

https://sjlmag.com/2022/05/04/fighting-for-their-lives-jewish-pediatrician-in-middle-of-alabama-transgender-battles/ May 4, 2022

https://www.washingtonpost.com/nation/2022/05/14/alabama-hormone-therapy-puberty-blockers-judge/ May 14, 2022

https://www.reuters.com/world/us/alabama-transgender-youth-can-use-medicine-during-transition-judge-2022-05-14/

https://forward.com/opinion/507291/the-only-two-doctors-in-alabama-providing-gender-affirming-care-to-trans-youth/ The Forward, the nation's largest Jewish publication. June 23, 2022

https://www.jewishchronicle.org/2022/07/05/madison-native-in-alabama-offers-gender-affirming-care-pediatrician-is-in-a-lawsuit/ July 5, 2022

"Beyond the Binary: Understanding the Diversity of Gender and Gender Affirming Care". National podcast. https://pride365plus.com/podcasts/beyond-the-binary-understanding-the-diversity-of-gender-and-gender-affirming-care Released August 2, 2022

UAB Community Engagement Institute. "CEI Perspectives: A Conversation on LGBTQ Health Equity". August 30, 2022

https://19thnews.org/2022/10/trans-youth-hospitals-justice-department/ October 3, 2022

"Securing Justice for All". National Webinar co-sponsored by the ADL and HRC. November 9, 2022

"Transgender people in rural America struggle to find doctors willing or able to provide care. https://www.cbsnews.com/news/transgender-people-health-care-doctors-rural-america/ January 20, 2023

DIRECT LEGISLATIVE ADVOCACY AND POLICY ENGAGEMENT

Gave testimony to Alabama House of Representatives in support of HB-76, Childcare Safety Act. February 2, 2018. The bill was signed into law March 27, 2018 saving many lives by equalizing accountability around safety and hiring in licensure of faith based **and** secular day care centers in Alabama.

Delivered the pediatrician perspective to several hundred attendees rallying against the Trump Administration Family Separation policy. Speaker, "Families Belong Together Rally", Kelly Ingram Park, Birmingham, AL, June 30, 2018

Alabama Media Group and House/Senate Proceedings, 2019 Alabama Legislative Session: *https://www.al.com/news/2019/05/doctors-question-need-for-alabama-born-alive-bill.html*

Nominated and asked by the Jefferson County Medical Society to run for a Delegate At Large position on the Board of Censors of the Medical Society of the State of Alabama. (MASA). Involved statewide travel and campaigning. February-April, 2019

Together with AL DHR Commissioner Nancy Buckner, Chief of Prosecution Services Barry Matson, authored proposal for pre-arrest diversion pathway for pregnant substance dependent women accused of non-violent crimes in AL. November 20, 2019
Proposal presented in person to Governor Ivey's Task Force on Prison Reform, December 4, 2019, Montgomery, AL.

Gave testimony to Alabama House and Senate Subcommittees on Health in opposition to HB303/SB 219, Vulnerable Child Advocacy and Protection Act (VCAP), February 26, 2020. Such act would criminalize pediatricians, pharmacists and teachers who prescribe, fill or discuss administration of puberty blocking or hormonal medications to minors suffering gender dysphoria.

With 3 pediatric colleagues and executive leadership of the AL American Academy of Pediatrics, met with AL State Rep. Wesley Allen (R-Troy), author of VCAP bill pre-filed as HB-1 for 2021 Legislative Session. Mutually beneficial education session around standards of care for pediatric and adolescent management of gender dysphoria. August 26, 2020

Gave testimony to House Judiciary and Senate Health in opposition to HB-1/SB-10, Vulnerable Child Advocacy and Protection Act (VCAP). February 19, 2021

Gave testimony to House Health in opposition to HB-1/SB-10, Vulnerable Child Advocacy and Protection Act (VCAP). March 10, 2021

Opinion piece published by the Alabama Media Group.
https://www.al.com/opinion/2021/05/im-a-doctor-and-alabama-could-arrest-me-for-doing-my-job.html May 10, 2021

Opinion editorial published in the Alabama Political Reporter
https://www.alreporter.com/2021/08/01/uab-pediatrician-theres-a-lot-we-know-about-covid-vaccines/ August 1, 2021

Prepared and presented summary of medical allegations in the VCAP Legislation for House Leadership. Requested by Speaker McCutcheon and Rules Chairman Mike Jones, March 25, 2022

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2022, VOL. 23, NO. S1, S1–S258
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REPORT

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Standards of Care for the Health of Transgender and Gender Diverse People, Version 8

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ABSTRACT

Background: Transgender healthcare is a rapidly evolving interdisciplinary field. In the last decade, there has been an unprecedented increase in the number and visibility of transgender and gender diverse (TGD) people seeking support and gender-affirming medical treatment in parallel with a significant rise in the scientific literature in this area. The World Professional Association for Transgender Health (WPATH) is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, public policy, and respect in transgender health. One of the main functions of WPATH is to promote the highest standards of health care for TGD people through the Standards of Care (SOC). The SOC was initially developed in 1979 and the last version (SOC-7) was published in 2012. In view of the increasing scientific evidence, WPATH commissioned a new version of the Standards of Care, the SOC-8.

Aim: The overall goal of SOC-8 is to provide health care professionals (HCPs) with clinical guidance to assist TGD people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing their overall physical health, psychological well-being, and self-fulfillment.

Methods: The SOC-8 is based on the best available science and expert professional consensus in transgender health. International professionals and stakeholders were selected to serve on the SOC-8 committee. Recommendation statements were developed based on data derived from independent systematic literature reviews, where available, background reviews and expert opinions. Grading of recommendations was based on the available evidence supporting interventions, a discussion of risks and harms, as well as the feasibility and acceptability within different contexts and country settings.

Results: A total of 18 chapters were developed as part of the SOC-8. They contain recommendations for health care professionals who provide care and treatment for TGD people. Each of the recommendations is followed by explanatory text with relevant references. General areas related to transgender health are covered in the chapters Terminology, Global Applicability, Population Estimates, and Education. The chapters developed for the diverse population of TGD people include Assessment of Adults, Adolescents, Children, Nonbinary, Eunuchs, and Intersex Individuals, and people living in Institutional Environments. Finally, the chapters related to gender-affirming treatment are Hormone Therapy, Surgery and Postoperative Care, Voice and Communication, Primary Care, Reproductive Health, Sexual Health, and Mental Health.

Conclusions: The SOC-8 guidelines are intended to be flexible to meet the diverse health care needs of TGD people globally. While adaptable, they offer standards for promoting optimal health care and guidance for the treatment of people experiencing gender incongruence. As in all previous versions of the SOC, the criteria set forth in this document for gender-affirming medical interventions are clinical guidelines; individual health care professionals and programs may modify these in consultation with the TGD person.

KEYWORDS

adolescents; assessment; children; communication; education; endocrinology; eunuch; gender diverse; health care professional; institutional settings; intersex; mental health; nonbinary; population; postoperative care; primary care; reproductive health; sexual health; SOC8; Standards of Care; surgery; terminology; transgender; voice

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INTRODUCTION

Purpose and use of the Standards of Care

The overall goal of the World Professional Association for Transgender Health's (WPATH) Standards of Care—Eighth Edition (SOC-8) is to provide clinical guidance to health care professionals to assist transgender and gender diverse (TGD) people in accessing safe and effective pathways to achieving lasting personal comfort with their gendered selves with the aim of optimizing their overall physical health, psychological well-being, and self-fulfillment. This assistance may include but is not limited to hormonal and surgical treatments, voice and communication therapy, primary care, hair removal, reproductive and sexual health, and mental health care. Healthcare systems should provide medically necessary gender-affirming health care for TGD people: See Chapter 2—Global Applicability, Statement 2.1.

WPATH is an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, public policy, and respect in transgender health. Founded in 1979, the organization currently has over 3,000 health care professionals, social scientists, and legal professionals, all of whom are engaged in clinical practice, research, education and advocacy that affects the lives of TGD people. WPATH envisions a world wherein people of all gender identities and gender expressions have access to evidence-based health care, social services, justice, and equality.

One of the main functions of WPATH is to promote the highest standards of health care for individuals through the Standards of Care (SOC) for the health of TGD people. The SOC-8 is based on the best available science and expert professional consensus. The SOC was initially developed in 1979, and the last version was published in 2012.

Most of the research and experience in this field comes from a North American and Western European perspective; thus, adaptations of the SOC-8 to other parts of the world are necessary. Suggestions for approaches to cultural relativity and cultural competence are included in this version of the SOC.

WPATH recognizes that health is not only dependent upon high-quality clinical care but also relies on social and political climates that ensure social tolerance, equality, and the full rights of citizenship. Health is promoted through public policies and legal reforms that advance tolerance and equity for gender diversity and that eliminate prejudice, discrimination, and stigma. WPATH is committed to advocacy for these policy and legal changes. Thus, health care professionals who provide care to TGD people are called upon to advocate for improved access to safe and licensed gender-affirming care while respecting the autonomy of individuals.

While this is primarily a document for health care professionals, individuals, their families, and social institutions may also use the SOC-8 to understand how it can assist with promoting optimal health for members of this diverse population.

The SOC-8 has 18 chapters containing recommendations for health care professionals working with TGD people. Each of the recommendations is followed by explanatory text with relevant references. The recommendations for the initiation of gender-affirming medical and/or surgical treatments (GAMSTs) for adults and adolescents are contained in their respective chapters (see Assessment for Adults and Adolescent chapters). A summary of the recommendations and criteria for GAMST can be found in Appendix D.

Populations included in the SOC-8

In this document, we use the phrase transgender and gender diverse (TGD) to be as broad and comprehensive as possible in describing members of the many varied communities that exist globally of people with gender identities or expressions that differ from the gender socially attributed to the sex assigned to them at birth. This includes people who have culturally specific and/or language-specific experiences, identities or expressions, which may or may not be based on or encompassed by Western conceptualizations of gender or the language used to describe it.

WPATH SOC-8 expands who is included under the TGD umbrella, and the settings in which these guidelines should be applied to promote equity and human rights.

Globally, TGD people encompass a diverse array of gender identities and expressions and have differing needs for gender-affirming care across their lifespan that is related to individual goals and characteristics, available health care resources, and sociocultural and political contexts. When standards of care are absent for certain groups this vacuum can result in a multiplicity of therapeutic approaches, including those that may be counterproductive or harmful. The SOC-8 includes recommendations to promote health and well-being for gender diverse groups that have often been neglected and/or marginalized, including nonbinary people, eunuch, and intersex individuals.

The SOC-8 continues to outline the appropriate care of TGD youth, which includes, when indicated, the use of puberty suppression and, when indicated, the use of gender-affirming hormones.

Worldwide, TGD people commonly experience transphobia, stigmatization, ignorance, and refusal of care when seeking health care services, which contributes to significant health disparities. TGD people often report having to teach their medical providers how to care for them due to the latter's insufficient knowledge and training. Intersectional forms of discrimination, social marginalization, and hate crimes against TGD people lead to minority stress. Minority stress is associated with mental health disparities exemplified by increased rates of depression, suicidality, and non-suicidal self-injuries than rates in cisgender populations. Professionals from every discipline should consider the marked vulnerability of many TGD people. WPATH urges health care authorities, policymakers, and medical societies to discourage and combat transphobia among health care professionals and ensure every effort is made to refer TGD people to professionals with experience and willingness to provide gender-affirming care.

Flexibility in the SOC

The SOC-8 guidelines are intended to be flexible to meet the diverse health care needs of TGD people globally. While adaptable, they offer standards for promoting optimal health care and for guiding treatment of people experiencing gender incongruence. As in all previous versions of the SOC, the criteria put forth in this document for gender-affirming interventions are clinical guidelines; individual health care professionals and programs may modify them in consultation with the TGD person. Clinical departures from the SOC may come about because of a patient's unique anatomic, social, or psychological situation; an experienced health care professional's evolving method of handling a common situation; a research protocol; lack of resources in various parts of the world; or the need for specific harm-reduction strategies. These departures should be recognized as such, explained to the patient, and documented for quality patient care and legal protection. This documentation is also valuable for the accumulation of new data, which can be retrospectively examined to allow for health care—and the SOC—to evolve.

The SOC-8 supports the role of informed decision-making and the value of harm reduction approaches. In addition, this version of the SOC recognizes and validates various expressions of gender that may not necessitate psychological, hormonal, or surgical treatments. Health care professionals can use the SOC to help patients consider the full range of health services open to them in accordance with their clinical needs for gender expression.

Diversity versus Diagnosis

The expression of gender characteristics, including identities, that are not stereotypically associated with one's sex assigned at birth is a common and a culturally diverse human phenomenon that should not be seen as inherently negative or pathological. Unfortunately, gender nonconformity and diversity in gender identity and expression is stigmatized in many societies around the world. Such stigma can lead to prejudice and discrimination, resulting in "minority stress." Minority stress is unique (additive to general stressors experienced by all people), socially based, and chronic, and may make TGD individuals more vulnerable to developing mental health concerns such as anxiety and depression. In addition to prejudice and discrimination in society at large, stigma can contribute to abuse and

neglect in one's interpersonal relationships, which in turn can lead to psychological distress. However, these symptoms are socially induced and are not inherent to being TGD.

While Gender Dysphoria (GD) is still considered a mental health condition in the Diagnostic and Statistical Manual of Mental Disorders, (DSM-5-TR) of the American Psychiatric Association. Gender incongruence is no longer seen as pathological or a mental disorder in the world health community. Gender Incongruence is recognized as a condition in the International Classification of Diseases and Related Health Problems, 11th Version of the World Health Organization (ICD-11). Because of historical and current stigma, TGD people can experience distress or dysphoria that may be addressed with various gender-affirming treatment options. While nomenclature is subject to change and new terminology and classifications may be adopted by various health organizations or administrative bodies, the medical necessity of treatment and care is clearly recognized for the many people who experience dissonance between their sex assigned at birth and their gender identity.

Not all societies, countries, or health care systems require a diagnosis for treatment. However, in some countries these diagnoses may facilitate access to medically necessary health care and can guide further research into effective treatments.

Health care services

The goal of gender-affirming care is to partner with TGD people to holistically address their social, mental, and medical health needs and well-being while respectfully affirming their gender identity. Gender-affirming care supports TGD people across the lifespan—from the very first signs of gender incongruence in childhood through adulthood and into older age—as well as people with concerns and uncertainty about their gender identity, either prior to or after transition.

Transgender health care is greater than the sum of its parts, involving holistic inter- and multidisciplinary care between endocrinology, surgery, voice and communication, primary care, reproductive health, sexual health and mental health disciplines to support gender-affirming interventions as well as preventive care and chronic disease management. Gender-affirming interventions include puberty suppression, hormone therapy, and gender-affirming surgeries among others. It should be emphasized there is no 'one-size-fits-all' approach and TGD people may need to undergo all, some, or none of these interventions to support their gender affirmation. These guidelines encourage the use of a patient-centered care model for initiation of gender- affirming interventions and update many previous requirements to reduce barriers to care.

Ideally, communication and coordination of care should occur between providers to optimize outcomes and the timing of gender-affirming interventions centered on the patient's needs and desires and to minimize harm. In well-resourced settings, multidisciplinary consultation and care coordination is often routine, but many regions worldwide lack facilities dedicated to transgender care. For these regions, if possible, it is strongly recommended that individual care providers create a network to facilitate transgender health care that is not available locally.

Worldwide, TGD people are sometime forced by family members or religious communities to undergo conversion therapy. WPATH strongly recommends against any use of reparative or conversion therapy (see statements 6.5 and 18.10).

Health care settings

The SOC-8 are guidelines rooted in the fundamental rights of TGD people that apply to all settings in which health care is provided regardless of an individual's social or medical circumstances. This includes a recommendation to apply the standards of care for TGD people who are incarcerated or living in other institutional settings.

Due to a lack of knowledgeable providers, untimely access, cost barriers and/or previous stigmatizing health care experiences, many TGD people take non-prescribed hormone therapy. This poses health risks associated with the use of unmonitored therapy in potentially supratherapeutic doses and the potential exposure to blood-borne illnesses if needles are shared for administration. However, for many individuals, it is the only means of acquiring medically necessary

gender-affirming treatment that is otherwise inaccessible. Non-prescribed hormone use should be approached with a harm-reduction lens to ensure individuals are connected with providers who can prescribe safe and monitored hormone therapy.

In some countries, the rights of TGD are increasingly being recognized, and gender clinics are being established that can serve as templates for care. In other countries, however, such facilities are lacking and care may be more fragmented and under-resourced. Nonetheless, different models of care are being pioneered, including efforts to decentralize gender-affirming care within primary care settings and establish telehealth services to reduce barriers and improve access. Regardless of the method of care delivery, the principles of gender-affirming care as outlined in the SOC-8 should be adapted to align with local sociocultural, political, and medical contexts.

Methodology

This version of the Standards of Care (SOC-8) is based upon a more rigorous and methodological evidence-based approach than previous versions. This evidence is not only based on the published literature (direct as well as background evidence) but also on consensus-based expert opinion. Evidence-based guidelines include recommendations intended to optimize patient care that are informed by a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility.

While evidence-based research provides the basis for sound clinical practice guidelines and recommendations, it must be balanced by the realities and feasibility of providing care in diverse settings. The process for development of the SOC-8 incorporated the recommendations on clinical practice guideline development set forth by the National Academies of Medicine and the World Health Organization, which addressed transparency, conflict-of-interest policy, committee composition, and group process.

The SOC-8 guidelines committee was multidisciplinary and consisted of subject matter experts, health care professionals, researchers, and stakeholders with diverse perspectives and geographic representation. A guideline methodologist assisted with the planning and development of questions and systematic reviews with additional input provided by an international advisory committee and during the public comment period. All committee members completed conflict of interest declarations. Recommendations in the SOC-8 are based on available evidence supporting interventions, a discussion of risks and harms, as well as feasibility and acceptability within different contexts and country settings. Consensus on the final recommendations was attained using the Delphi process that included all members of the guidelines committee and required that recommendation statements were approved by at least 75% of members. A detailed overview of the SOC-8 Methodology is included in Appendix A.

SOC-8 Chapters Summary

The SOC-8 represents a significant advancement from previous versions. Changes in this version are based upon a fundamentally different methodology, significant cultural shifts, advances in clinical knowledge, and appreciation of the many health care issues that can arise for TGD people beyond hormone therapy and surgery.

These updated guidelines continue the process started with the SOC-7 in 2011 to broaden in scope and move from a narrow focus on psychological requirements for "diagnosing transgenderism" and medical treatments for alleviation of gender dysphoria to gender-affirming care for the whole person. WPATH SOC-8 expands guidelines specifying who is included under the TGD umbrella, what should and should not be offered with gender-affirming care, and the settings in which these guidelines should be applied to promote equity and human rights.

The SOC-8 has several new chapters such as the Assessment of Adults, Education, Eunuchs, and a Nonbinary chapter. In addition, the chapter for children and adolescents of the SOC-7 has been divided into two different chapters. Overall, the SOC-8 is considerably longer than previous versions and provides a more in-depth introduction and recommendations for health care professionals. A summary of every chapter of the SOC-8 can be found below:

Chapter 1—Terminology
This new chapter lays the framework for language used in the SOC-8 and offers consensually agreed upon recommendations for the use of terminology. The chapter provides (1) terms and definitions, and (2) best practices for utilizing them. This document is accompanied by a glossary (see Appendix B) of common terms and language to provide a framework for use and interpretation of the SOC-8.

Chapter 2—Global Applicability
This chapter references key literature related to development and delivery of health care services, broader advocacy care for TGD people from beyond Western Europe and North America and provides recommendations for adapting and translating the SOC-8 to varied contexts.

Chapter 3—Population Estimates
This chapter updates the population estimates of TGD people in society. Based on the current evidence, this proportion may range from a fraction of a percent to several percentage points depending on the inclusion criteria, age group, and geographic location.

Chapter 4—Education
This new chapter provides a general review of the literature related to education in TGD health care. It offers recommendations at governmental, nongovernmental, institutional and provider levels to increase access to competent, compassionate health care. The intent is to lay the groundwork in the education area and invite a much broader and deeper discussion among educators and health care professionals.

Chapter 5—Assessment of Adults
This new chapter provides guidance on the assessment of TGD adults who are requesting gender-affirming medical and surgical treatments (GAMSTs). It describes and updates the assessment process as part of a patient-centered approach and the criteria that health care professionals may follow in order to recommend GAMSTs to TGD adults.

Chapter 6—Adolescents
This new chapter is dedicated to TGD adolescents, is distinct from the child chapter, and has been created for this 8th edition of the Standards of Care given (1) the exponential growth in adolescent referral rates; (2) the increase in studies available specific to adolescent gender diversity-related care; and (3) the unique developmental and gender-affirming care issues of this age group. This chapter provides recommendations regarding the assessment process of adolescents requiring GAMSTs as well as recommendations when working with TGD youth and their families.

Chapter 7—Children
This new chapter pertains to prepubescent gender diverse children and focuses on developmentally appropriate psychosocial practices and therapeutic approaches.

Chapter 8—Nonbinary
This new chapter in the SOC-8 consists of a broad description of the term nonbinary and its usage from a biopsychosocial, cultural, and intersectional perspective. The need for access to gender-affirming care, specific gender-affirming medical interventions, as well as an appropriate level of support is discussed.

Chapter 9—Eunuchs
This new chapter describes the unique needs of eunuchs, and how the SOC can be applied to this population.

Chapter 10—Intersex
This chapter focuses on the clinical care of intersex individuals. It addresses the evolving terminology, prevalence, and diverse presentations of such individuals and provides recommendations for providing psychosocial and medical care with their evidence-based explanations.

Chapter 11—Institutional Environments
This chapter has been expanded to include both carceral and non-carceral settings and has been built upon the last 3 versions of the SOC. This chapter describes how the SOC-8 can be applied to individuals living in these settings.

Chapter 12—Hormone Therapy

This chapter describes the initiation of gender-affirming hormone therapy, the recommended regimens, screening for health concerns before and during hormone therapy, and specific considerations regarding hormone therapy prior to surgery. It includes an expanded discussion about the safety of gonadotropin releasing hormone (GnRH) agonists in youth, various hormone regimens, monitoring to include the development of potential therapy-related health concerns, and guidance on how hormone providers should collaborate with surgeons.

Chapter 13—Surgery and Postoperative Care

This chapter describes a spectrum of gender-affirming surgical procedures for the diverse and heterogeneous community of individuals who identify as TGD. It provides a discussion about the optimal surgical training in GAS procedures, post-surgical aftercare and follow-up, access to surgery by adults and adolescents, and individually customized surgeries.

Chapter 14—Voice and Communication

This chapter describes professional voice and communication support and interventions that are inclusive of and attentive to all aspects of diversity and no longer limited only to voice feminization and masculinization. Recommendations are now framed as affirming the roles and responsibilities of professionals involved in voice and communication support.

Chapter 15—Primary Care

This chapter discusses the importance of primary care for TGD individuals, including topics of cardiovascular and metabolic health, cancer screening, and primary care systems.

Chapter 16—Reproductive Health

This chapter provides recent data on fertility perspectives and parenthood goals in gender diverse youth and adults, advances in fertility preservation methods (including tissue cryopreservation), guidance regarding preconception and pregnancy care, prenatal counseling, and chest feeding. Contraceptive methods and considerations for TGD individuals are also reviewed.

Chapter 17—Sexual Health

This new chapter acknowledges the profound impact of sexual health on physical and psychological well-being for TGD people. The chapter advocates for sexual functioning, pleasure, and satisfaction to be included in TGD-related care.

Chapter 18—Mental Health

This chapter discusses principles of care for managing mental health conditions in TGD adults and the nexus of mental health care and transition care. Psychotherapy may be beneficial but should not be a requirement for gender-affirming treatment, and conversion treatment should not be offered.

CHAPTER 1 Terminology

This chapter will lay the framework for language used in the SOC-8. It offers recommendations for use of terminology. It provides (1) terms and definitions, and (2) best practices for utilizing them. This document is accompanied by a glossary of common terms and language to provide a framework for use and interpretation of the SOC-8. See Appendix B for glossary.

Terminology

In this document, we use the phrase transgender and gender diverse (TGD) to be as broad and comprehensive as possible in describing members of the many varied communities globally of people with gender identities or expressions that differ from the gender socially attributed to the sex assigned to them at birth. This includes people who have culturally specific and/or language-specific experiences, identities or expressions, and/or that are not based on or encompassed by Western conceptualizations of gender, or the language used to describe it. TGD is used for convenience as a shorthand for transgender and gender diverse.

The decision to use transgender and gender diverse resulted from an active process and was not without controversy. Discussions centered on avoiding over-emphasis on the term transgender, integrating nonbinary gender identities and experiences, recognizing global variations in understandings of gender, avoiding the term gender nonconforming, and recognizing the changing nature of language because what is current now may not be so in coming years. Thus, the term transgender and gender diverse was chosen with the intent to be most inclusive and to highlight the many diverse gender identities, expressions, experiences, and health care needs of TGD people. A Delphi process was used wherein SOC-8 chapter authors were anonymously and iteratively surveyed over several rounds to obtain consensus on terms. The SOC-8 presents standards of care that strive to be applicable to TGD people globally, no matter how a person self-identifies or expresses their gender.

Context

The language selected in this chapter may not be (nor ever could be) comprehensive of every culture and geographic region/locale. Differences and debates over appropriate terms and specific terminologies are common, and no single term can be used without controversy. The goal of this chapter is to be as inclusive as possible and offer a shared vocabulary that is respectful and reflective of varied experiences of TGD people while remaining accessible to health practitioners and providers, and the public, for the purposes of this document. Ultimately, access to transition-related health care should be based on providing adequate information and obtaining informed consent from the individual, and not on what words TGD people, or their service providers, use to describe their identities. Using language and terminology that is respectful and culturally responsive is a basic foundation in the provision of affirming care, as is reducing the stigma and harm experienced by many TGD people seeking health care. It is vital for service providers to discuss with service users what language is most comfortable for them and to use that language whenever possible.

This chapter explains why current terms are being used in preference to others. Rather than use specific terms for medical, legal, and advocacy groups, the aim is to foster a shared language and understanding in the field of TGD health, and the many related fields (e.g., epidemiology, law), in order to optimize the health of transgender and gender diverse people.

Sex, gender, gender identity, and gender expression are used in the English language as descriptors that can apply to all people—those who are TGD, and those who are not. There are complex reasons why very specific language may be the *most* respectful, *most* inclusive, or *most* accepted by global TGD communities, including the presence or absence of words to describe these concepts in languages other than English; the structural relationship between sex and gender; legal landscapes at the local, national, and international levels; and the consequences of historical and present-day stigma that TGD people face.

Statements of Recommendations

1.1- We recommend health care professionals use culturally relevant language (including terms to describe transgender and gender diverse people) when applying the Standards of Care in different global settings.
1.2- We recommend health care professionals use language in health care settings that uphold the principles of safety, dignity, and respect.
1.3- We recommend health care professionals discuss with transgender and gender diverse people what language or terminology they prefer.

Because at present, the field of TGD health is heavily dominated by the English language, there are two specific problems that constantly arise in setting the context for terminology. The first problem is that words exist in English that do not exist in other languages (e.g., "sex" and "gender" are only represented by one word in Urdu and many other languages). The second problem is that there are words that exist outside of English that do not have a direct translation into English (e.g., *travesti*, *fa'afafine*, *hijra*, *selrata*, *muxe*, *kathoey*, *transpinoy*, *waria*, *machi*). Practically, this means the heavy influence of English in this field impacts both what terms are widely used and which people or identities are most represented or validated by those terms. The words used also shape the narratives that contribute to beliefs and perceptions. While in past versions of the Standards of Care, World Professional Association for Transgender Health (WPATH) has used only transgender as a broadly defined umbrella term, version 8 broadens this language to use TGD as the umbrella term throughout the document (see Chapter 2—Global Applicability).

Furthermore, the ever-evolving nature of language is impacted by external factors and the social, structural, and personal pressures and violence enacted on TGD people and their bodies. Many of the terms and phrases used historically have been marred by how, when, and why they were used in discussing TGD people, and have thus fallen out of use or are hotly contested among TGD people, with some individuals preferring terms others find offensive. Some wish that these Standards of Care could provide a coherent set of universally accepted terms to describe TGD people, identities, and related health services. Such a list, however, does not and cannot exist without exclusion of some people and without reinforcing structural oppressions, with regards to race, national origin, Indigenous status, socioeconomic status, religion, language(s) spoken, and ethnicity, among other intersectionalities. It is very likely that at least some of the terminology used in SOC-8 will be outdated by the time version 9 is developed. Some people will be frustrated by this reality, but it is hoped it will be seen instead as an opportunity for individuals and communities to develop and refine their own lexicons and for people to develop a still more nuanced understanding of the lives and needs of TGD people, including TGD people's resilience and resistance to oppression.

Finally, law and the work of legal professionals are within the remit of these Standards of Care. As such, language used most widely in international law is included here to help with the development of the functional definitions of these terms and encourage their usage in legal contexts in lieu of more antiquated and/or offensive terms. The currently most thorough document in international human rights law uses the term "gender diverse."[1]

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 1.1

We recommend health care professionals use culturally relevant language (including terms to describe transgender and gender diverse people) when applying the Standards of Care in different global settings.

Culturally relevant language is used to describe TGD people in different global settings. For example, the concepts of sex, gender, and gender diversity differ across contexts, as does the language used to describe them. Thus, the language used when caring

for TGD people in Thailand is not going to be the same as that used for TGD care in Nigeria. When applying the Standards of Care globally, we recommend health care professionals (HCPs) utilize local language and terms to deliver care in their specific cultural and/or geographical locale.

Gender affirmation refers to the process of recognizing or affirming TGD people in their gender identity—whether socially, medically, legally, behaviorally, or some combination of these (Reisner, Poteat et al., 2016). Health care that is gender-affirming or trans-competent utilizes culturally specific language in caring for TGD people. Gender-affirming care is not synonymous with transition-related care. Provision of transition-related care, such as medical gender affirmation via hormones or surgery, does not alone ensure provision of gender-affirming care, nor does it indicate the quality or safety of the health care provided.

Consultation and partnerships with TGD communities can help to ensure relevancy and inclusivity of the language used in providing health care locally in a particular context and setting.

Statement 1.2

We recommend health care professionals use language in health care settings that upholds the principles of safety, dignity, and respect.

Safety, dignity, and respect are basic human rights (International Commission of Jurists, 2007). We recommend HCPs utilize language and terminology that uphold these human rights when providing care for TGD people. Many TGD people have experienced stigma, discrimination, and mistreatment in health care settings, resulting in suboptimal care and poor health outcomes (Reisner, Poteat et al., 2016; Safer et al., 2016; Winter, Settle et al., 2016). Such experiences include misgendering, being refused care or denied services when sick or injured and having to educate HCPs to be able to receive adequate care (James et al., 2016). Consequently, many TGD people feel unsafe accessing health care. They may avoid health care systems and seek other means of getting health-related needs met, such as taking hormones without a medical prescription or monitoring and relying on peers for medical advice. Furthermore, previous negative experiences in health care settings are associated with future avoidance of care among TGD people.

Many TGD people have been treated unjustly, with prejudice, and without dignity or respect by HCPs, and lack of trust is often a barrier to care. Using language grounded in the principles of safety, dignity, and respect in health care settings is paramount to ensure the health, well-being, and rights of TGD people globally. Language is a significant component of gender-affirming care, but language alone does not resolve or mitigate the systematic abuse and sometimes violence TGD people face globally in care settings. Language is but one important step toward patient/client-centered and equitable health care among TGD people. Other concrete actions HCPs can take include obtaining informed consent and refraining from making assumptions about a person's needs based on their gender or TGD status.

Statement 1.3

We recommend health care professionals discuss with transgender and gender diverse people what language or terminology they prefer.

In providing health care to TGD people, we recommend HCPs discuss with their patients what language or terminology they prefer be used when referring to them. This discussion includes asking TGD people how they would like to be addressed in terms of name and pronouns, how they self-identify their gender, and about the language that should be used to describe their body parts. Utilizing affirming language or terminology is a key component of TGD-affirming care (Lightfoot et al., 2021; Vermeir et al., 2018). Furthermore, these discussions and communications can serve to build rapport and reduce the mistrust many TGD people feel toward HCPs and experience within health care systems. Discussions and usage of language or terminology can also facilitate engagement and retention in care that is not specifically TGD-related, such as uptake of routine preventive screenings and any necessary medical follow-up of findings. In electronic health records, organ/anatomical inventories can be standardly used to inform appropriate clinical care, rather than relying solely on assigned sex at birth and/or gender identity designations.

HCPs and health care settings can implement standardized procedures to facilitate these conversations such as: using intake forms that include chosen pronouns and name, inviting

all staff (regardless of gender, i.e., cisgender, TGD) to use pronouns in introductions, having pronouns accompany names on a document for all patients, and not using gendered honorifics (e.g., Ms., Mr.). Policies for HCPs and health care settings can be put in place to ensure a TGD person's privacy and right to confidentiality, including when they disclose being a TGD person, and if/how to appropriately document. For example, a clinic policy may be to record this information as private and confidential between HCPs and patients/clients, and that it should only be disclosed on a "need to know" basis.

Note

1. A/73/152, Report of the Independent Expert on protection against violence and discrimination based on sexual orientation and gender identity

CHAPTER 6 Adolescents

Historical context and changes since previous Standards of Care

Specialized health care for transgender adolescents began in the 1980s when a few specialized gender clinics for youth were developed around the world that served relatively small numbers of children and adolescents. In more recent years, there has been a sharp increase in the number of adolescents requesting gender care (Arnoldussen et al., 2019; Kaltiala, Bergman et al., 2020). Since then, new clinics have been founded, but clinical services in many places have not kept pace with the increasing number of youth seeking care. Hence, there are often long waitlists for services, and barriers to care exist for many transgender youth around the world (Tollit et al., 2018).

Until recently, there was limited information regarding the prevalence of gender diversity among adolescents. Studies from high school samples indicate much higher rates than earlier thought, with reports of up to 1.2% of participants identifying as transgender (Clark et al., 2014) and up to 2.7% or more (e.g., 7–9%) experiencing some level of self-reported gender diversity (Eisenberg et al., 2017; Kidd et al., 2021; Wang et al., 2020). These studies suggest gender diversity in youth should no longer be viewed as rare. Additionally, a pattern of uneven ratios by assigned sex has been reported in gender clinics, with adolescents assigned female at birth (AFAB) initiating care 2.5–7.1 times more frequently as compared to adolescents who are assigned male at birth (AMAB) (Aitken et al., 2015; Arnoldussen et al., 2019; Bauer et al., 2021; de Graaf, Carmichael et al., 2018; Kaltiala et al., 2015; Kaltiala, Bergman et al., 2020).

A specific World Professional Association for Transgender Health's (WPATH) Standards of Care section dedicated to the needs of children and adolescents was first included in the 1998 WPATH Standards of Care, 5th version (Levine et al., 1998). Youth aged 16 or older were deemed potentially eligible for gender-affirming medical care, but only in select cases. The subsequent 6th (Meyer et al., 2005) and 7th (Coleman et al., 2012) versions divided medical-affirming treatment for adolescents into three categories and presented eligibility criteria regarding age/puberty stage—namely fully reversible puberty delaying blockers as soon as puberty had started; partially reversible hormone therapy (testosterone, estrogen) for adolescents at the age of majority, which was age 16 in certain European countries; and irreversible surgeries at age 18 or older, except for chest "masculinizing" mastectomy, which had an age minimum of 16 years. Additional eligibility criteria for gender-related medical care included a persistent, long (childhood) history of gender "non-conformity"/dysphoria, emerging or intensifying at the onset of puberty; absence or management of psychological, medical, or social problems that interfere with treatment; provision of support for commencing the intervention by the parents/caregivers; and provision of informed consent. A chapter dedicated to transgender and gender diverse (TGD) adolescents, distinct from the child chapter, has been created for this 8th edition of the Standards of Care given 1) the exponential growth in adolescent referral rates; 2) the increased number of studies specific to adolescent gender diversity-related care; and 3) the unique developmental and gender-affirming care issues of this age group.

Non-specific terms for gender-related care are avoided (e.g., gender-affirming model, gender exploratory model) as these terms do not represent unified practices, but instead heterogenous care practices that are defined differently in various settings.

Adolescence overview

Adolescence is a developmental period characterized by relatively rapid physical and psychological maturation, bridging childhood and adulthood (Sanders, 2013). Multiple developmental processes occur simultaneously, including pubertal-signaled changes. Cognitive, emotional, and social systems mature, and physical changes associated with puberty progress. These processes do not all begin and end at the same time for a given individual, nor do they occur at the same age for all persons. Therefore, the lower and upper borders of adolescence are imprecise and cannot be defined exclusively by age. For example, physical pubertal changes may

begin in late childhood and executive control neural systems continue to develop well into the mid-20s (Ferguson et al., 2021). There is a lack of uniformity in how countries and governments define the age of majority (i.e., legal decision-making status; Dick et al., 2014). While many specify the age of majority as 18 years of age, in some countries it is as young as 15 years (e.g., Indonesia and Myanmar), and in others as high as 21 years (e.g., the U.S. state of Mississippi and Singapore).

For clarity, this chapter applies to adolescents from the start of puberty until the legal age of majority (in most cases 18 years), however there are developmental elements of this chapter, including the importance of parental/caregiver involvement, that are often relevant for the care of transitional-aged young adults and should be considered appropriately.

Cognitive development in adolescence is often characterized by gains in abstract thinking, complex reasoning, and metacognition (i.e., a young person's ability to think about their own feelings in relation to how others perceive them; Sanders, 2013). The ability to reason hypothetical situations enables a young person to conceptualize implications regarding a particular decision. However, adolescence is also often associated with increased risk-taking behaviors. Along with these notable changes, adolescence is often characterized by individuation from parents and the development of increased personal autonomy. There is often a heightened focus on peer relationships, which can be both positive and detrimental (Gardner & Steinberg, 2005). Adolescents often experience a sense of urgency that stems from hypersensitivity to reward, and their sense of timing has been shown to be different from that of older individuals (Van Leijenhorst et al., 2010). Social-emotional development typically advances during adolescence, although there is a great variability among young people in terms of the level of maturity applied to inter- and intra-personal communication and insight (Grootens-Wiegers et al., 2017). For TGD adolescents making decisions about gender-affirming treatments—decisions that may have lifelong consequences—it is critical to understand how all these aspects of development may impact decision-making for a given young person within their specific cultural context.

Gender identity development in adolescence

Our understanding of gender identity development in adolescence is continuing to evolve. When providing clinical care to gender diverse young people and their families, it is important to know what is and is not known about gender identity during development (Berenbaum, 2018). When considering treatments, families may have questions regarding the development of their adolescent's gender identity, and whether or not their adolescent's declared gender will remain the same over time. For some adolescents, a declared gender identity that differs from the assigned sex at birth comes as no surprise to their parents/caregivers as their history of gender diverse expression dates back to childhood (Leibowitz & de Vries, 2016). For others, the declaration does not happen until the emergence of pubertal changes or even well into adolescence (McCallion et al., 2021; Sorbara et al., 2020).

Historically, social learning and cognitive developmental research on gender development was conducted primarily with youth who were not gender diverse in identity or expression and was carried out under the assumption that sex correlated with a specific gender; therefore, little attention was given to gender identity development. In addition to biological factors influencing gender development, this research demonstrated psychological and social factors also play a role (Perry & Pauletti, 2011). While there has been less focus on gender identity development in TGD youth, there is ample reason to suppose, apart from biological factors, psychosocial factors are also involved (Steensma, Kreukels et al., 2013). For some youth, gender identity development appears fixed and is often expressed from a young age, while for others there may be a developmental process that contributes to gender identity development over time.

Neuroimaging studies, genetic studies, and other hormone studies in intersex individuals demonstrate a biological contribution to the development of gender identity for some

individuals whose gender identity does not match their assigned sex at birth (Steensma, Kreukels et al., 2013). As families often have questions about this very issue, it is important to note it is not possible to distinguish between those for whom gender identity may seem fixed from birth and those for whom gender identity development appears to be a developmental process. Since it is impossible to definitively delineate the contribution of various factors contributing to gender identity development for any given young person, a comprehensive clinical approach is important and necessary (see Statement 3). Future research would shed more light on gender identity development if conducted over long periods of time with diverse cohort groups. Conceptualization of gender identity by shifting from dichotomous (e.g., binary) categorization of male and female to a dimensional gender spectrum along a continuum (APA, 2013) would also be necessary.

Adolescence may be a critical period for the development of gender identity for gender diverse young people (Steensma, Kreukels et al., 2013). Dutch longitudinal clinical follow-up studies of adolescents with childhood gender dysphoria who received puberty suppression, gender-affirming hormones, or both, found that none of the youth in adulthood regretted the decisions they had taken in adolescence (Cohen-Kettenis & van Goozen, 1997; de Vries et al., 2014). These findings suggest adolescents who were comprehensively assessed and determined emotionally mature enough to make treatment decisions regarding gender- affirming medical care presented with stability of gender identity over the time period when the studies were conducted.

When extrapolating findings from the longer-term longitudinal Dutch cohort studies to present-day gender diverse adolescents seeking care, it is critical to consider the societal changes that have occurred over time in relation to TGD people. Given the increase in visibility of TGD identities, it is important to understand how increased awareness may impact gender development in different ways (Kornienko et al., 2016). One trend identified is that more young people are presenting to gender clinics with nonbinary identities (Twist & de Graaf, 2019). Another phenomenon occurring in clinical practice is the increased number of adolescents seeking care who have not seemingly experienced, expressed (or experienced and expressed) gender diversity during their childhood years. One researcher attempted to study and describe a specific form of later-presenting gender diversity experience (Littman, 2018). However, the findings of the study must be considered within the context of significant methodological challenges, including 1) the study surveyed parents and not youth perspectives; and 2) recruitment included parents from community settings in which treatments for gender dysphoria are viewed with scepticism and are criticized. However, these findings have not been replicated. For a select subgroup of young people, susceptibility to social influence impacting gender may be an important differential to consider (Kornienko et al., 2016). However, caution must be taken to avoid assuming these phenomena occur prematurely in an individual adolescent while relying on information from datasets that may have been ascertained with potential sampling bias (Bauer et al., 2022; WPATH, 2018). It is important to consider the benefits that social connectedness may have for youth who are linked with supportive people (Tuzun et al., 2022)(see Statement 4).

Given the emerging nature of knowledge regarding adolescent gender identity development, an individualized approach to clinical care is considered both ethical and necessary. As is the case in all areas of medicine, each study has methodological limitations, and conclusions drawn from research cannot and should not be universally applied to all adolescents. This is also true when grappling with common parental questions regarding the stability versus instability of a particular young person's gender identity development. While future research will help advance scientific understanding of gender identity development, there may always be some gaps. Furthermore, given the ethics of self-determination in care, these gaps should not leave the TGD adolescent without important and necessary care.

Research evidence of gender-affirming medical treatment for transgender adolescents

A key challenge in adolescent transgender care is the quality of evidence evaluating the effectiveness of medically necessary gender-affirming medical

and surgical treatments (GAMSTs) (see medically necessary statement in the Global chapter, Statement 2.1), over time. Given the lifelong implications of medical treatment and the young age at which treatments may be started, adolescents, their parents, and care providers should be informed about the nature of the evidence base. It seems reasonable that decisions to move forward with medical and surgical treatments should be made carefully. Despite the slowly growing body of evidence supporting the effectiveness of early medical intervention, the number of studies is still low, and there are few outcome studies that follow youth into adulthood. Therefore, a systematic review regarding outcomes of treatment in adolescents is not possible. A short narrative review is provided instead.

At the time of this chapter's writing, there were several longer-term longitudinal cohort follow-up studies reporting positive results of early (i.e., adolescent) medical treatment; for a significant period of time, many of these studies were conducted through one Dutch clinic (e.g., Cohen-Kettenis & van Goozen, 1997; de Vries, Steensma et al., 2011; de Vries et al., 2014; Smith et al., 2001, 2005). The findings demonstrated the resolution of gender dysphoria is associated with improved psychological functioning and body image satisfaction. Most of these studies followed a pre-post methodological design and compared baseline psychological functioning with outcomes after the provision of medical gender-affirming treatments. Different studies evaluated individual aspects or combinations of treatment interventions and included 1) gender-affirming hormones and surgeries (Cohen-Kettenis & van Goozen, 1997; Smith et al., 2001, 2005); 2) puberty suppression (de Vries, Steensma et al., 2011); and 3) puberty suppression, affirming hormones, and surgeries (de Vries et al., 2014). The 2014 long-term follow-up study is the only study that followed youth from early adolescence (pretreatment, mean age of 13.6) through young adulthood (posttreatment, mean age of 20.7). This was the first study to show gender-affirming treatment enabled transgender adolescents to make age-appropriate developmental transitions while living as their affirmed gender with satisfactory objective and subjective outcomes in adulthood (de Vries et al., 2014). While the study employed a small (n = 55), select, and socially supported sample, the results were convincing. Of note, the participants were part of the Dutch clinic known for employing a multidisciplinary approach, including provision of comprehensive, ongoing assessment and management of gender dysphoria, and support aimed at emotional well-being.

Several more recently published longitudinal studies followed and evaluated participants at different stages of their gender-affirming treatments. In these studies, some participants may not have started gender-affirming medical treatments, some had been treated with puberty suppression, while still others had started gender-affirming hormones or had even undergone gender-affirming surgery (GAS) (Achille et al., 2020; Allen et al., 2019; Becker-Hebly et al., 2021; Carmichael et al., 2021; Costa et al., 2015; Kuper et al., 2020, Tordoff et al., 2022). Given the heterogeneity of treatments and methods, this type of design makes interpreting outcomes more challenging. Nonetheless, when compared with baseline assessments, the data consistently demonstrate improved or stable psychological functioning, body image, and treatment satisfaction varying from three months to up to two years from the initiation of treatment.

Cross-sectional studies provide another design for evaluating the effects of gender-affirming treatments. One such study compared psychological functioning in transgender adolescents at baseline and while undergoing puberty suppression with that of cisgender high school peers at two different time points. At baseline, the transgender youth demonstrated lower psychological functioning compared with cisgender peers, whereas when undergoing puberty suppression, they demonstrated better functioning than their peers (van der Miesen et al., 2020). Grannis et al. (2021) demonstrated transgender males who started testosterone had lower internalizing mental health symptoms (depression and anxiety) compared with those who had not started testosterone treatment.

Four additional studies followed different outcome designs. In a retrospective chart study, Kaltiala, Heino et al. (2020) reported transgender

adolescents with few or no mental health challenges prior to commencing gender-affirming hormones generally did well during the treatment. However, adolescents with more mental health challenges at baseline continued to experience the manifestations of those mental health challenges over the course of gender-affirming medical treatment. Nieder et al. (2021) studied satisfaction with care as an outcome measure and demonstrated transgender adolescents were more satisfied the further they progressed with the treatments they initially started. Hisle-Gorman et al. (2021) compared health care utilization pre- and post-initiation of gender-affirming pharmaceuticals as indicators of the severity of mental health conditions among 3,754 TGD adolescents in a large health care data set. Somewhat contrary to the authors' hypothesis of improved mental health, mental health care use did not significantly change, and psychotropic medication prescriptions increased. In a large non-probability sample of transgender-identified adults, Turban et al. (2022) found those who reported access to gender-affirming hormones in adolescence had lower odds of past-year suicidality compared with transgender people accessing gender- affirming hormones in adulthood.

Providers may consider the possibility an adolescent may regret gender-affirming decisions made during adolescence, and a young person will want to stop treatment and return to living in the birth-assigned gender role in the future. Two Dutch studies report low rates of adolescents (1.9% and 3.5%) choosing to stop puberty suppression (Brik et al., 2019; Wiepjes et al., 2018). Again, these studies were conducted in clinics that follow a protocol that includes a comprehensive assessment before the gender-affirming medical treatment is started. At present, no clinical cohort studies have reported on profiles of adolescents who regret their initial decision or detransition after irreversible affirming treatment. Recent research indicate there are adolescents who detransition, but do not regret initiating treatment as they experienced the start of treatment as a part of understanding their gender-related care needs (Turban, 2018). However, this may not be the predominant perspective of people who detransition (Littman, 2021; Vandenbussche, 2021). Some adolescents may regret the steps they have taken (Dyer, 2020). Therefore, it is important to present the full range of possible outcomes when assisting transgender adolescents. Providers may discuss this topic in a collaborative and trusting manner (i.e., as a "potential future experience and consideration") with the adolescent and their parents/caregivers before gender-affirming medical treatments are started. Also, providers should be prepared to support adolescents who detransition. In an internet convenience sample survey of 237 self-identified detransitioners with a mean age of 25.02 years, which consisted of over 90% of birth assigned females, 25% had medically transitioned before age 18 and 14% detransitioned before age 18 (Vandenbussche, 2021). Although an internet convenience sample is subject to selection of respondents, this study suggests detransitioning may occur in young transgender adolescents and health care professionals should be aware of this. Many of them expressed difficulties finding help during their detransition process and reported their detransition was an isolating experience during which they did not receive either sufficient or appropriate support (Vandenbussche, 2021).

To conclude, although the existing samples reported on relatively small groups of youth (e.g., n = 22-101 per study) and the time to follow-up varied across studies (6 months–7 years), this emerging evidence base indicates a general improvement in the lives of transgender adolescents who, following careful assessment, receive medically necessary gender-affirming medical treatment. Further, rates of reported regret during the study monitoring periods are low. Taken as a whole, the data show early medical intervention—as part of broader combined assessment and treatment approaches focused on gender dysphoria and general well-being—can be effective and helpful for many transgender adolescents seeking these treatments.

Ethical and human rights perspectives

Medical ethics and human rights perspectives were also considered while formulating the

Statements of Recommendations

6.1- We recommend health care professionals working with gender diverse adolescents:
6.1.a- Are licensed by their statutory body and hold a postgraduate degree or its equivalent in a clinical field relevant to this role granted by a nationally accredited statutory institution.
6.1.b- Receive theoretical and evidenced-based training and develop expertise in general child, adolescent, and family mental health across the developmental spectrum.
6.1.c- Receive training and have expertise in gender identity development, gender diversity in children and adolescents, have the ability to assess capacity to assent/consent, and possess general knowledge of gender diversity across the life span.
6.1.d- Receive training and develop expertise in autism spectrum disorders and other neurodevelopmental presentations or collaborate with a developmental disability expert when working with autistic/neurodivergent gender diverse adolescents.
6.1.e- Continue engaging in professional development in all areas relevant to gender diverse children, adolescents, and families.
6.2- We recommend health care professionals working with gender diverse adolescents facilitate the exploration and expression of gender openly and respectfully so that no one particular identity is favored.
6.3- We recommend health care professionals working with gender diverse adolescents undertake a comprehensive biopsychosocial assessment of adolescents who present with gender identity-related concerns and seek medical/surgical transition-related care, and that this be accomplished in a collaborative and supportive manner.
6.4- We recommend health care professionals work with families, schools, and other relevant settings to promote acceptance of gender diverse expressions of behavior and identities of the adolescent.
6.5- We recommend against offering reparative and conversion therapy aimed at trying to change a person's gender and lived gender expression to become more congruent with the sex assigned at birth.
6.6- We suggest health care professionals provide transgender and gender diverse adolescents with health education on chest binding and genital tucking, including a review of the benefits and risks.
6.7- We recommend providers consider prescribing menstrual suppression agents for adolescents experiencing gender incongruence who may not desire testosterone therapy, who desire but have not yet begun testosterone therapy, or in conjunction with testosterone therapy for breakthrough bleeding.
6.8- We recommend health care professionals maintain an ongoing relationship with the gender diverse and transgender adolescent and any relevant caregivers to support the adolescent in their decision-making throughout the duration of puberty suppression treatment, hormonal treatment, and gender- related surgery until the transition is made to adult care.
6.9- We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiation, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated throughout the course of treatment until the transition is made to adult care.
6.10- We recommend health care professionals working with transgender and gender diverse adolescents requesting gender-affirming medical or surgical treatments inform them, prior to initiating treatment, of the reproductive effects including the potential loss of fertility and available options to preserve fertility within the context of the youth's stage of pubertal development.
6.11- We recommend when gender-affirming medical or surgical treatments are indicated for adolescents, health care professionals working with transgender and gender diverse adolescents involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent or not feasible.

The following recommendations are made regarding the requirements for gender-affirming medical and surgical treatment (All of them must be met):
6.12- We recommend health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:
6.12.a- The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care. In countries that have not implemented the latest ICD, other taxonomies may be used although efforts should be undertaken to utilize the latest ICD as soon as practicable.
6.12.b- The experience of gender diversity/incongruence is marked and sustained over time.
6.12.c- The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.
6.12.d- The adolescent's mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and gender-affirming medical treatments have been addressed.
6.12.e- The adolescent has been informed of the reproductive effects, including the potential loss of fertility and the available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.
6.12.f- The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.
6.12.g- The adolescent had at least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, including breast augmentation, orchiectomy, vaginoplasty, hysterectomy, phalloplasty, metoidioplasty, and facial surgery as part of gender-affirming treatment unless hormone therapy is either not desired or is medically contraindicated.

adolescent SOC statements. For example, allowing irreversible puberty to progress in adolescents who experience gender incongruence is not a neutral act given that it may have immediate and lifelong harmful effects for the transgender young person (Giordano, 2009; Giordano & Holm, 2020; Kreukels & Cohen-Kettenis, 2011). From a human rights perspective, considering gender diversity as a normal and expected variation within the broader diversity of the human experience, it is an adolescent's right to participate in their own decision-making

process about their health and lives, including access to gender health services (Amnesty International, 2020).

Short summary of statements and unique issues in adolescence

These guidelines are designed to account for what is known and what is not known about gender identity development in adolescence, the evidence for gender-affirming care in adolescence, and the unique aspects that distinguish adolescence from other developmental stages.

Identity exploration: A defining feature of adolescence is the solidifying of aspects of identity, including gender identity. Statement 6.2 addresses identity exploration in the context of gender identity development. Statement 6.12.b accounts for the length of time needed for a young person to experience a gender diverse identity, express a gender diverse identity, or both, so as to make a meaningful decision regarding gender-affirming care.

Consent and decision-making: In adolescence, consent and decision-making require assessment of the individual's emotional, cognitive, and psychosocial development. Statement 6.12.c directly addresses emotional and cognitive maturity and describes the necessary components of the evaluation process used to assess decision-making capacity.

Caregivers/parent involvement: Adolescents are typically dependent on their caregivers/parents for guidance in numerous ways. This is also true as the young person navigates through the process of deciding about treatment options. Statement 6.11 addresses the importance of involving caregivers/parents and discusses the role they play in the assessment and treatment. No set of guidelines can account for every set of individual circumstances on a global scale.

Statement 6.1

We recommend health care professionals working with gender diverse adolescents:

a. **Are licensed by their statutory body and hold a postgraduate degree or its equivalent in a clinical field relevant to this role granted by a nationally accredited statutory institution.**
b. **Receive theoretical and evidenced-based training and develop expertise in general child, adolescent, and family mental health across the developmental spectrum.**
c. **Receive training and have expertise in gender identity development, gender diversity in children and adolescents, have the ability to assess capacity to assent/consent, and possess general knowledge of gender diversity across the life span.**
d. **Receive training and develop expertise in autism spectrum disorders and other neurodevelopmental presentations or collaborate with a developmental disability expert when working with autistic/neurodivergent gender diverse adolescents.**
e. **Continue engaging in professional development in all areas relevant to gender diverse children, adolescents, and families.**

When assessing and supporting TGD adolescents and their families, care providers/health care professionals (HCPs) need both general as well as gender-specific knowledge and training. Providers who are trained to work with adolescents and families play an important role in navigating aspects of adolescent development and family dynamics when caring for youth and families (Adelson et al., 2012; American Psychological Association, 2015; Hembree et al., 2017). Other chapters in these standards of care describe these criteria for professionals who provide gender care in more detail (see Chapter 5—Assessment for Adults; Chapter 7—Children; or Chapter 13—Surgery and Postoperative Care). Professionals working with adolescents should understand what is and is not known regarding adolescent gender identity development, and how this knowledge base differs from what applies to adults and prepubertal children. Among HCPs, the mental health professional (MHP) has the most appropriate training and dedicated clinical time to conduct an assessment and elucidate treatment priorities and goals when working with transgender youth, including those seeking gender-affirming medical/surgical care. Understanding and managing the dynamics of family members who may share differing perspectives regarding the history and needs of the

young person is an important competency that MHPs are often most prepared to address.

When access to professionals trained in child and adolescent development is not possible, HCPs should make a commitment to obtain training in the areas of family dynamics and adolescent development, including gender identity development. Similarly, considering autistic/neurodivergent transgender youth represent a substantial minority subpopulation of youth served in gender clinics globally, it is important HCPs seek additional training in the field of autism and understand the unique elements of care autistic gender diverse youth may require (Strang, Meagher et al., 2018). If these qualifications are not possible, then consultation and collaboration with a provider who specializes in autism and neurodiversity is advised.

Statement 6.2

We recommend health care professionals working with gender diverse adolescents facilitate the exploration and expression of gender openly and respectfully so that no one particular identity is favored.

Adolescence is a developmental period that involves physical and psychological changes characterized by individuation and the transition to independence from caregivers (Berenbaum et al., 2015; Steinberg, 2009). It is a period during which young people may explore different aspects of identity, including gender identity.

Adolescents differ regarding the degree to which they explore and commit to aspects of their identity (Meeus et al., 2012). For some adolescents, the pace to achieving consolidation of identity is fast, while for others it is slower. For some adolescents, physical, emotional, and psychological development occur over the same general timeline, while for others, there are certain gaps between these aspects of development. Similarly, there is variation in the timeline for gender identity development (Arnoldussen et al., 2020; Katz-Wise et al., 2017). For some young people, gender identity development is a clear process that starts in early childhood, while for others pubertal changes contribute to a person's experience of themselves as a particular gender (Steensma, Kreukels et al., 2013), and for many others a process may begin well after pubertal changes are completed. Given these variations, there is no one particular pace, process, or outcome that can be predicted for an individual adolescent seeking gender-affirming care.

Therefore, HCPs working with adolescents should promote supportive environments that simultaneously respect an adolescent's affirmed gender identity and also allows the adolescent to openly explore gender needs, including social, medical, and physical gender-affirming interventions should they change or evolve over time.

Statement 6.3

We recommend health care professionals working with gender diverse adolescents undertake a comprehensive biopsychosocial assessment of adolescents who present with gender identity-related concerns and seek medical/surgical transition-related care, and that this be accomplished in a collaborative and supportive manner.

Given the many ways identity may unfold during adolescence, we recommend using a comprehensive biopsychosocial assessment to guide treatment decisions and optimize outcomes. This assessment should aim to understand the adolescent's strengths, vulnerabilities, diagnostic profile, and unique needs to individualize their care. As mentioned in Statement 6.1, MHPs have the most appropriate training, experience, and dedicated clinical time required to obtain the information discussed here. The assessment process should be approached collaboratively with the adolescent and their caregiver(s), both separately and together, as described in more detail in Statement 6.11. An assessment should occur prior to any medically necessary medical or surgical intervention under consideration (e.g., puberty blocking medication, gender-affirming hormones, surgeries). See medically necessary statement in Chapter 2—Global Applicability, Statement 2.1; see also Chapter 12—Hormone Therapy and Chapter 13—Surgery and Postoperative Care.

Youth may experience many different gender identity trajectories. Sociocultural definitions and experiences of gender continue to evolve over time, and youth are increasingly presenting with a range of identities and ways of describing their experiences and gender-related needs (Twist & de

Graaf, 2019). For example, some youth will realize they are transgender or more broadly gender diverse and pursue steps to present accordingly. For some youth, obtaining gender-affirming medical treatment is important while for others these steps may not be necessary. For example, a process of exploration over time might not result in the young person self-affirming or embodying a different gender in relation to their assigned sex at birth and would not involve the use of medical interventions (Arnoldussen et al., 2019).

The most robust longitudinal evidence supporting the benefits of gender-affirming medical and surgical treatments in adolescence was obtained in a clinical setting that incorporated a detailed comprehensive diagnostic assessment process over time into its delivery of care protocol (de Vries & Cohen-Kettenis, 2012; de Vries et al., 2014). Given this research and the ongoing evolution of gender diverse experiences in society, a comprehensive diagnostic biopsychosocial assessment during adolescence is both evidence-based and preserves the integrity of the decision-making process. In the absence of a full diagnostic profile, other mental health entities that need to be prioritized and treated may not be detected. There are no studies of the long-term outcomes of gender-related medical treatments for youth who have not undergone a comprehensive assessment. Treatment in this context (e.g., with limited or no assessment) has no empirical support and therefore carries the risk that the decision to start gender-affirming medical interventions may not be in the long-term best interest of the young person at that time.

As delivery of health care and access to specialists varies globally, designing a particular assessment process to adapt existing resources is often necessary. In some cases, a more extended assessment process may be useful, such as for youth with more complex presentations (e.g., complicating mental health histories (Leibowitz & de Vries, 2016)), co-occurring autism spectrum characteristics (Strang, Powers et al., 2018), and/or an absence of experienced childhood gender incongruence (Ristori & Steensma, 2016). Given the unique cultural, financial, and geographical factors that exist for specific populations, providers should design assessment models that are flexible and allow for appropriately timed care for as many young people as possible, so long as the assessment effectively obtains information about the adolescent's strengths, vulnerabilities, diagnostic profile, and individual needs. Psychometrically validated psychosocial and gender measures can also be used to provide additional information.

The multidisciplinary assessment for youth seeking gender-affirming medical/surgical interventions includes the following domains that correspond to the relevant statements:

- **Gender Identity Development:** Statements 6.12.a and 6.12.b elaborate on the factors associated with gender identity development within the specific cultural context when assessing TGD adolescents.
- **Social Development and Support; Intersectionality:** Statements 6.4 and 6.11 elaborate on the importance of assessing gender minority stress, family dynamics, and other aspects contributing to social development and intersectionality.
- **Diagnostic Assessment of Possible Co-Occurring Mental Health and/or Developmental Concerns:** Statement 6.12.d elaborates on the importance of understanding the relationship that exists, if at all, between any co-occurring mental health or developmental concerns and the young person's gender identity/gender diverse expression.
- **Capacity for Decision-Making:** Statement 6.12.c elaborates on the assessment of a young person's emotional maturity and the relevance when an adolescent is considering gender affirming-medical/surgical treatments.

Statement 6.4

We recommend health care professionals work with families, schools, and other relevant settings to promote acceptance of gender diverse expressions of behavior and identities of the adolescent.

Multiple studies and related expert consensus support the implementation of approaches that promote acceptance and affirmation of gender diverse youth across all settings, including families, schools, health care facilities, and all other organizations and communities with which they

interact (e.g., Pariseau et al., 2019; Russell et al., 2018; Simons et al., 2013; Toomey et al., 2010; Travers et al., 2012). Acceptance and affirmation are accomplished through a range of approaches, actions, and policies we recommend be enacted across the various relationships and settings in which a young person exists and functions. It is important for the family members and community members involved in the adolescent's life to work collaboratively in these efforts unless their involvement is considered harmful to the adolescent. Examples proposed by Pariseau et al. (2019) and others of acceptance and affirmation of gender diversity and contemplation and expression of identity that can be implemented by family, staff, and organizations include:

1. Actions that are supportive of youth drawn to engaging in gender-expansive (e.g., nonconforming) activities and interests;
2. Communications that are supportive when youth express their experiences about their gender and gender exploration;
3. Use of the youth's asserted name/pronouns;
4. Support for youth wearing clothing/uniforms, hairstyles, and items (e.g., jewelry, makeup) they feel affirm their gender;
5. Positive and supportive communication with youth about their gender and gender concerns;
6. Education about gender diversity issues for people in the young person's life (e.g., family members, health care providers, social support networks), as needed, including information about how to advocate for gender diverse youth in community, school, health care, and other settings;
7. Support for gender diverse youth to connect with communities of support (e.g., LGBTQ groups, events, friends);
8. Provision of opportunities to discuss, consider, and explore medical treatment options when indicated;
9. Antibullying policies that are enforced;
10. Inclusion of nonbinary experiences in daily life, reading materials, and curricula (e.g., books, health, and sex education classes, assigned essay topics that move beyond the binary, LGBTQ, and ally groups);
11. Gender inclusive facilities that the youth can readily access without segregation from nongender diverse peers (e.g., bathrooms, locker rooms).

We recommend HCPs work with parents, schools, and other organizations/groups to promote acceptance and affirmation of TGD identities and expressions, whether social or medical interventions are implemented or not as acceptance and affirmation are associated with fewer negative mental health and behavioral symptoms and more positive mental health and behavioral functioning (Day et al., 2015; de Vries et al., 2016; Greytak et al., 2013; Pariseau et al., 2019; Peng et al., 2019; Russell et al., 2018; Simons et al., 2013; Taliaferro et al., 2019; Toomey et al., 2010; Travers et al., 2012). Russell et al. (2018) found mental health improvement increases with more acceptance and affirmation across more settings (e.g., home, school, work, and friends). Rejection by family, peers, and school staff (e.g., intentionally using the name and pronoun the youth does not identify with, not acknowledging affirmed gender identity, bullying, harassment, verbal and physical abuse, poor relationships, rejection for being TGD, eviction) was strongly linked to negative outcomes, such as anxiety, depression, suicidal ideation, suicide attempts, and substance use (Grossman et al., 2005; Klein & Golub; 2016; Pariseau et al., 2019; Peng et al., 2019; Reisner, Greytak et al., 2015; Roberts et al., 2013). It is important to be aware that negative symptoms increase with increased levels of rejection and continue into adulthood (Roberts et al., 2013).

Neutral or indifferent responses to a youth's gender diversity and exploration (e.g., letting a child tell others their chosen name but not using the name, not telling family or friends when the youth wants them to disclose, not advocating for the child about rejecting behavior from school staff or peers, not engaging or participating in other support mechanisms (e.g., with psychotherapists and support groups) have also been found to have negative consequences, such as increased depressive symptoms (Pariseau et al., 2019). For these reasons, it is important not to ignore a youth's gender questioning or delay consideration of the youth's gender-related

care needs. There is particular value in professionals recognizing youth need individualized approaches, support, and consideration of needs around gender expression, identity, and embodiment over time and across domains and relationships. Youth may need help coping with the tension of tolerating others' processing/adjusting to an adolescent's identity exploration and changes (e.g., Kuper, Lindley et al., 2019). It is important professionals collaborate with parents and others as they process their concerns and feelings and educate themselves about gender diversity because such processes may not necessarily reflect rejection or neutrality but may rather represent efforts to develop attitudes and gather information that foster acceptance (e.g., Katz-Wise et al., 2017).

Statement 6.5

We recommend against offering reparative and conversion therapy aimed at trying to change a person's gender and lived gender expression to become more congruent with the sex assigned at birth.

Some health care providers, secular or religious organizations, and rejecting families may undertake efforts to thwart an adolescent's expression of gender diversity or assertion of a gender identity other than the expression and behavior that conforms to the sex assigned at birth. Such efforts at blocking reversible social expression or transition may include choosing not to use the youth's identified name and pronouns or restricting self-expression in clothing and hairstyles (Craig et al., 2017; Green et al., 2020). These disaffirming behaviors typically aim to reinforce views that a young person's gender identity/expression must match the gender associated with the sex assigned at birth or expectations based on the sex assigned at birth. Activities and approaches (sometimes referred to as "treatments") aimed at trying to change a person's gender identity and expression to become more congruent with the sex assigned at birth have been attempted, but these approaches have not resulted in changes in gender identity (Craig et al., 2017; Green et al., 2020). We recommend against such efforts because they have been found to be ineffective and are associated with increases in mental illness and poorer psychological functioning (Craig et al., 2017; Green et al., 2020; Turban, Beckwith et al., 2020).

Much of the research evaluating "conversion therapy" and "reparative therapy" has investigated the impact of efforts to change gender expression (masculinity or femininity) and has conflated sexual orientation with gender identity (APA, 2009; Burnes et al., 2016; Craig et al., 2017). Some of these efforts have targeted both gender identity and expression (AACAP, 2018). Conversion/reparative therapy has been linked to increased anxiety, depression, suicidal ideation, suicide attempts, and health care avoidance (Craig et al., 2017; Green et al., 2020; Turban, Beckwith et al., 2020). Although some of these studies have been criticized for their methodologies and conclusions (e.g., D'Angelo et al., 2020), this should not detract from the importance of emphasizing efforts undertaken a priori to change a person's identity are clinically and ethically unsound. We recommend against any type of conversion or attempts to change a person's gender identity because 1) both secular and religion-based efforts to change gender identity/expression have been associated with negative psychological functioning that endures into adulthood (Turban, Beckwith et al., 2020); and 2) larger ethical reasons exist that should underscore respect for gender diverse identities.

It is important to note potential factors driving a young person's gender-related experience and report of gender incongruence, when carried out in the context of supporting an adolescent with self-discovery, is not considered reparative therapy as long as there is no a priori goal to change or promote one particular gender identity or expression (AACAP, 2018; see Statement 6.2). To ensure these explorations are therapeutic, we recommend employing affirmative consideration and supportive tone in discussing what steps have been tried, considered, and planned for a youth's gender expression. These discussion topics may include what felt helpful or affirming, what felt unhelpful or distressing and why. We recommend employing affirmative responses to these steps and discussions, such as those identified in SOC-8 Statement 6.4.

Statement 6.6

We suggest health care professionals provide transgender and gender diverse adolescents with health education on chest binding and genital tucking, including review of the benefits and risks.

TGD youth may experience distress related to chest and genital anatomy. Practices such as chest binding, chest padding, genital tucking, and genital packing are reversible, nonmedical interventions that may help alleviate this distress (Callen-Lorde, 2020a, 2020b; Deutsch, 2016a; Olson-Kennedy, Rosenthal et al., 2018; Transcare BC, 2020). It is important to assess the degree of distress related to physical development or anatomy, educate youth about potential nonmedical interventions to address this distress, and discuss the safe use of these interventions.

Chest binding involves compression of the breast tissue to create a flatter appearance of the chest. Studies suggest that up to 87% of trans masculine patients report a history of binding (Jones, 2015; Peitzmeier, 2017). Binding methods may include the use of commercial binders, sports bras, layering of shirts, layering of sports bras, or the use of elastics or other bandages (Peitzmeier, 2017). Currently, most youth report learning about binding practices from online communities composed of peers (Julian, 2019). Providers can play an important role in ensuring youth receive accurate and reliable information about the potential benefits and risks of chest binding. Additionally, providers can counsel patients about safe binding practices and monitor for potential negative health effects. While there are potential negative physical impacts of binding, youth who bind report many benefits, including increased comfort, improved safety, and lower rates of misgendering (Julian, 2019). Common negative health impacts of chest binding in youth include back/chest pain, shortness of breath, and overheating (Julian, 2019). More serious negative health impacts such as skin infections, respiratory infections, and rib fractures are uncommon and have been associated with chest binding in adults (Peitzmeier, 2017). If binding is employed, youth should be advised to use only those methods considered safe for binding—such as binders specifically designed for the gender diverse population—to reduce the risk of serious negative health effects. Methods that are considered unsafe for binding include the use of duct tape, ace wraps, and plastic wrap as these can restrict blood flow, damage skin, and restrict breathing. If youth report negative health impacts from chest binding, these should ideally be addressed by a gender-affirming medical provider with experience working with TGD youth.

Genital tucking is the practice of positioning the penis and testes to reduce the outward appearance of a genital bulge. Methods of tucking include tucking the penis and testes between the legs or tucking the testes inside the inguinal canal and pulling the penis back between the legs. Typically, genitals are held in place by underwear or a gaff, a garment that can be made or purchased. Limited studies are available on the specific risks and benefits of tucking in adults, and none have been carried out in youth. Previous studies have reported tight undergarments are associated with decreased sperm concentration and motility. In addition, elevated scrotal temperatures can be associated with poor sperm characteristics, and genital tucking could theoretically affect spermatogenesis and fertility (Marsh, 2019) although there are no definitive studies evaluating these adverse outcomes. Further research is needed to determine the specific benefits and risks of tucking in youth.

Statement 6.7

We recommend providers consider prescribing menstrual suppression agents for adolescents experiencing gender incongruence who may not desire testosterone therapy, who desire but have not yet begun testosterone therapy, or in conjunction with testosterone therapy for breakthrough bleeding.

When discussing the available options of menstrual-suppressing medications with gender diverse youth, providers should engage in shared decision-making, use gender-inclusive language (e.g., asking patients which terms they utilize to refer to their menses, reproductive organs, and genitalia) and perform physical exams in a sensitive, gender-affirmative manner (Bonnington et al., 2020; Krempasky et al., 2020). There is no formal research evaluating how menstrual

suppression may impact gender incongruence and/or dysphoria. However, the use of menstrual suppression can be an initial intervention that allows for further exploration of gender-related goals of care, prioritization of other mental health care, or both, especially for those who experience a worsening of gender dysphoria from unwanted uterine bleeding (see Statement 6.12d; Mehringer & Dowshen, 2019). When testosterone is not used, menstrual suppression can be achieved via a progestin. To exclude any underlying menstrual disorders, it is important to obtain a detailed menstrual history and evaluation prior to implementing menstrual-suppressing therapy (Carswell & Roberts, 2017). As part of the discussion about menstrual-suppressing medications, the need for contraception and information regarding the effectiveness of menstrual-suppressing medications as methods of contraception also need to be addressed (Bonnington et al., 2020). A variety of menstrual suppression options, such as combined estrogen-progestin medications, oral progestins, depot and subdermal progestin, and intrauterine devices (IUDs), should be offered to allow for individualized treatment plans while properly considering availability, cost and insurance coverage, as well as contraindications and side effects (Kanj et al., 2019).

Progestin-only hormonal medication are options, especially in trans masculine or nonbinary youth who are not interested in estrogen-containing medical therapies as well as those at risk for thromboembolic events or who have other contraindications to estrogen therapy (Carswell & Roberts, 2017). Progestin-only hormonal medications include oral progestins, depo-medroxyprogesterone injection, etonogestrel implant, and levonorgestrel IUD (Schwartz et al., 2019). Progestin-only hormonal options vary in terms of efficacy in achieving menstrual suppression and have lower rates of achieving amenorrhea than combined oral contraception (Pradhan & Gomez-Lobo, 2019). A more detailed description of the relevant clinical studies is presented in Chapter 12—Hormone Therapy. HCPs should not make assumptions regarding the individual's preferred method of administration as some trans masculine youth may prefer vaginal rings or IUD implants (Akgul et al., 2019). Although hormonal medications require monitoring for potential mood lability, depressive effects, or both, the benefits and risks of untreated menstrual suppression in the setting of gender dysphoria should be evaluated on an individual basis. Some patients may opt for combined oral contraception that includes different combinations of ethinyl estradiol, with ranging doses, and different generations of progestins (Pradhan & Gomez-Lobo, 2019). Lower dose ethinyl estradiol components of combined oral contraceptive pills are associated with increased breakthrough uterine bleeding. Continuous combined oral contraceptives may be used to allow for continuous menstrual suppression and can be delivered as transdermal or vaginal rings.

The use of gonadotropin releasing hormone (GnRH) analogues may also result in menstrual suppression. However, it is recommended gender diverse youth meet the eligibility criteria (as outlined in Statement 6.12) before this medication is considered solely for this purpose (Carswell & Roberts, 2017; Pradhan & Gomez-Lobo, 2019). Finally, menstrual-suppression medications may be indicated as an adjunctive therapy for breakthrough uterine bleeding that may occur while on exogenous testosterone or as a bridging medication while awaiting menstrual suppression with testosterone therapy. When exogenous testosterone is employed as a gender-affirming hormone, menstrual suppression is typically achieved in the first six months of therapy (Ahmad & Leinung, 2017). However, it is vital adolescents be counseled ovulation and pregnancy can still occur in the setting of amenorrhea (Gomez et al., 2020; Kanj et al., 2019).

Statement 6.8

We recommend health care professionals maintain an ongoing relationship with the gender diverse and transgender adolescent and any relevant caregivers to support the adolescent in their decision-making throughout the duration of puberty suppression treatment, hormonal treatment, and gender-related surgery until the transition is made to adult care.

HCPs with expertise in child and adolescent development, as described in Statement 6.1, play an important role in the continuity of care for

young people over the course of their gender-related treatment needs. Supporting adolescents and their families necessitates approaching care using a developmental lens through which understanding a young person's evolving emotional maturity and care needs can take place over time. As gender-affirming treatment pathways differ based on the needs and experiences of individual TGD adolescents, decision-making for these treatments (puberty suppression, estrogens/androgens, gender-affirmation surgeries) can occur at different points in time within a span of several years. Longitudinal research demonstrating the benefits of pubertal suppression and gender-affirming hormone treatment (GAHT) was carried out in a setting where an ongoing clinical relationship between the adolescents/families and the multidisciplinary team was maintained (de Vries et al., 2014).

Clinical settings that offer longer appointment times provide space for adolescents and caregivers to share important psychosocial aspects of emotional well-being (e.g., family dynamics, school, romantic, and sexual experiences) that contextualize individualized gender-affirming treatment needs and decisions as described elsewhere in the chapter. An ongoing clinical relationship can take place across settings, whether that be within a multidisciplinary team or with providers in different locations who collaborate with one another. Given the wide variability in the ability to obtain access to specialized gender care centers, particularly for marginalized groups who experience disparities with access, it is important for the HCP to appreciate the existence of any barriers to care while maintaining flexibility when defining how an ongoing clinical relationship can take place in that specific context.

An ongoing clinical relationship that increases resilience in the youth and provides support to parents/caregivers who may have their own treatment needs may ultimately lead to increased parental acceptance—when needed—which is associated with better mental health outcomes in youth (Ryan, Huebner et al., 2009).

Statement 6.9

We recommend health care professionals involve relevant disciplines, including mental health and medical professionals, to reach a decision about whether puberty suppression, hormone initiation, or gender-related surgery for gender diverse and transgender adolescents are appropriate and remain indicated throughout the course of treatment until the transition is made to adult care.

TGD adolescents with gender dysphoria/gender incongruence who seek gender-affirming medical and surgical treatments benefit from the involvement of health care professionals (HCPs) from different disciplines. Providing care to TGD adolescents includes addressing 1) diagnostic considerations (see Statements 6.3, 6.12a, and 6.12b) conducted by a specialized gender HCP (as defined in Statement 6.1) whenever possible and necessary; and 2) treatment considerations when prescribing, managing, and monitoring medications for gender-affirming medical and surgical care, requiring the training of the relevant medical/surgical professional. The list of key disciplines includes but is not limited to adolescent medicine/primary care, endocrinology, psychology, psychiatry, speech/language pathology, social work, support staff, and the surgical team.

The evolving evidence has shown a clinical benefit for transgender youth who receive their gender-affirming treatments in multidisciplinary gender clinics (de Vries et al., 2014; Kuper et al., 2020; Tollit et al., 2019). Finally, adolescents seeking gender-affirming care in multidisciplinary clinics are presenting with significant complexity necessitating close collaboration between mental health, medical, and/or surgical professionals (McCallion et al., 2021; Sorbara et al., 2020; Tishelman et al., 2015).

As not all patients and families are in the position or in a location to access multidisciplinary care, the lack of available disciplines should not preclude a young person from accessing needed care in a timely manner. When disciplines are available, particularly in centers with existing multidisciplinary teams, disciplines, or both, it is recommended efforts be made to include the relevant providers when developing a gender care team. However, this does not mean all disciplines are necessary to provide care to a particular youth and family.

If written documentation or a letter is required to recommend gender-affirming medical and surgical treatment (GAMST) for an adolescent, only one letter of assessment from a member of the multidisciplinary team is needed. This letter needs to reflect the assessment and opinion from the team that involves both medical HCPs and MHPs (American Psychological Association, 2015; Hembree et al., 2017; Telfer et al., 2018). Further assessment results and written opinions may be requested when there is a specific clinical need or when team members are in different locations or choose to write their own summaries. For further information see Chapter 5—Assessment for Adults, Statement 5.5.

Statement 6.10

We recommend health care professionals working with transgender and gender diverse adolescents requesting gender-affirming medical or surgical treatments inform them, prior to the initiation of treatment, of the reproductive effects, including the potential loss of fertility and available options to preserve fertility within the context of the youth's stage of pubertal development.

While assessing adolescents seeking gender-affirming medical or surgical treatments, HCPs should discuss the specific ways in which the required treatment may affect reproductive capacity. Fertility issues and the specific preservation options are more thoroughly discussed in Chapter 12—Hormone Therapy and Chapter 16—Reproductive Health.

It is important HCPs understand what fertility preservation options exist so they can relay the information to adolescents. Parents are advised to be involved in this process and should also understand the pros and cons of the different options. HCPs should acknowledge adolescents and parents may have different views around reproductive capacity and may therefore come to different decisions (Quain et al., 2020), which is why HCPs can be helpful in guiding this process.

HCPs should specifically pay attention to the developmental and psychological aspects of fertility preservation and decision-making competency for the individual adolescent. While adolescents may think they have made up their minds concerning their reproductive capacity, the possibility their opinions about having biologically related children in the future might change over time needs to be discussed with an HCP who has sufficient experience, is knowledgeable about adolescent development, and has experience working with parents.

Addressing the long-term consequences on fertility of gender-affirming medical treatments and ensuring transgender adolescents have realistic expectations concerning fertility preservation options or adoption cannot not be addressed with a one-time discussion but should be part of an ongoing conversation. This conversation should occur not only before initiating any medical intervention (puberty suppression, hormones, or surgeries), but also during further treatment and during transition.

Currently, there are only preliminary results from retrospective studies evaluating transgender adults and the decisions they made when they were young regarding the consequences of medical-affirming treatment on reproductive capacity. It is important not to make assumptions about what future adult goals an adolescent may have. Research in childhood cancer survivors found participants who acknowledged missed opportunities for fertility preservation reported distress and regret surrounding potential infertility (Armuand et al., 2014; Ellis et al., 2016; Lehmann et al., 2017). Furthermore, individuals with cancer who did not prioritize having biological children before treatment have reported "changing their minds" in survivorship (Armuand et al., 2014).

Given the complexities of the different fertility preservation options and the challenges HCPs may experience discussing fertility with the adolescent and the family (Tishelman et al., 2019), a fertility consultation is an important consideration for every transgender adolescent who pursues medical-affirming treatments unless the local situation is such that a fertility consultation is not covered by insurance or public health care plans, is not available locally, or the individual circumstances make this unpreferable.

Statement 6.11

We recommend when gender-affirming medical or surgical treatments are indicated for adolescents, health care professionals working with transgender and gender diverse adolescents

involve parent(s)/guardian(s) in the assessment and treatment process, unless their involvement is determined to be harmful to the adolescent or not feasible.

When there is an indication an adolescent might benefit from a gender-affirming medical or surgical treatment, involving the parent(s) or primary caregiver(s) in the assessment process is recommended in almost all situations (Edwards-Leeper & Spack, 2012; Rafferty et al., 2018). Exceptions to this might include situations in which an adolescent is in foster care, child protective services, or both, and custody and parent involvement would be impossible, inappropriate, or harmful. Parent and family support of TGD youth is a primary predictor of youth well-being and is protective of the mental health of TGD youth (Gower, Rider, Coleman et al., 2018; Grossman et al., 2019; Lefevor et al., 2019; McConnell et al., 2015; Pariseau et al., 2019; Ryan, 2009; Ryan et al., 2010; Simons et al., 2013; Wilson et al., 2016). Therefore, including parent(s)/caregiver(s) in the assessment process to encourage and facilitate increased parental understanding and support of the adolescent may be one of the most helpful practices available.

Parent(s)/caregiver(s) may provide key information for the clinical team, such as the young person's gender and overall developmental, medical, and mental health history as well as insights into the young person's level of current support, general functioning, and well-being. Concordance or divergence of reports given by the adolescent and their parent(s)/caregiver(s) may be important information for the assessment team and can aid in designing and shaping individualized youth and family supports (De Los Reyes et al., 2019; Katz-Wise et al., 2017). Knowledge of the family context, including resilience factors and challenges, can help providers know where special supports would be needed during the medical treatment process. Engagement of parent(s)/caregiver(s) is also important for educating families about various treatment approaches, ongoing follow-up and care needs, and potential treatment complications. Through psychoeducation regarding clinical gender care options and participation in the assessment process, which may unfold over time, parent(s)/caregiver(s) may better understand their adolescent child's gender-related experience and needs (Andrzejewski et al., 2020; Katz-Wise et al., 2017).

Parent/caregiver concerns or questions regarding the stability of gender-related needs over time and implications of various gender-affirming interventions are common and should not be dismissed. It is appropriate for parent(s)/caregiver(s) to ask these questions, and there are cases in which the parent(s)/caregiver(s)' questions or concerns are particularly helpful in informing treatment decisions and plans. For example, a parent/caregiver report may provide critical context in situations in which a young person experiences very recent or sudden self-awareness of gender diversity and a corresponding gender treatment request, or when there is concern for possible excessive peer and social media influence on a young person's current self-gender concept. Contextualization of the parent/caregiver report is also critical, as the report of a young person's gender history as provided by parent(s)/caregiver(s) may or may not align with the young person's self-report. Importantly, gender histories may be unknown to parent(s)/caregiver(s) because gender may be internal experience for youth, not known by others unless it is discussed. For this reason, an adolescent's report of their gender history and experience is central to the assessment process.

Some parents may present with unsupportive or antagonistic beliefs about TGD identities, clinical gender care, or both (Clark et al., 2020). Such unsupportive perspectives are an important therapeutic target for families. Although challenging parent perspectives may in some cases seem rigid, providers should not assume this is the case. There are many examples of parent(s)/caregiver(s) who, over time with support and psychoeducation, have become increasingly accepting of their TGD child's gender diversity and care needs.

Helping youth and parent(s)/caregiver(s) work together on important gender care decisions is a primary goal. However, in some cases, parent(s)/caregiver(s) may be too rejecting of their adolescent child and their child's gender needs to be part of the clinical evaluation process. In these situations, youth may require the engagement of larger systems of advocacy and support to move

forward with the necessary support and care (Dubin et al., 2020).

Statement 6.12

We recommend health care professionals assessing transgender and gender diverse adolescents only recommend gender-affirming medical or surgical treatments requested by the patient when:

Statement 6.12.a

The adolescent meets the diagnostic criteria of gender incongruence as per the ICD-11 in situations where a diagnosis is necessary to access health care. In countries that have not implemented the latest ICD, other taxonomies may be used although efforts should be undertaken to utilize the latest ICD as soon as practicable.

When working with TGD adolescents, HCPs should realize while a classification may give access to care, pathologizing transgender identities may be experienced as stigmatizing (Beek et al., 2016). Assessments related to gender health and gender diversity have been criticized, and controversies exist around diagnostic systems (Drescher, 2016).

HCPs should assess the overall gender-related history and gender care-related needs of youth. Through this assessment process, HCPs may provide a diagnosis when it is required to get access to transgender-related care.

Gender incongruence and gender dysphoria are the two diagnostic terms used in the World Health Organization's International Classification of Diseases (ICD) and the American Psychiatric Association's Diagnostic and Statistical Manual of Mental Disorders (DSM), respectively. Of these two widely used classification systems, the DSM is for psychiatric classifications only and the ICD contains all diseases and conditions related to physical as well as mental health. The most recent versions of these two systems, the DSM-5 and the ICD-11, reflect a long history of reconceptualizing and de-psychopathologizing gender-related diagnoses (American Psychiatric Association, 2013; World Health Organization, 2019a). Compared with the earlier version, the DSM-5 replaced gender identity disorder with gender dysphoria, acknowledging the distress experienced by some people stemming from the incongruence between experienced gender identity and the sex assigned at birth. In the most recent revision, the DSM-5-TR, no changes in the diagnostic criteria for gender dysphoria are made. However, terminology was adapted into the most appropriate current language (e.g., birth-assigned gender instead of natal-gender and gender-affirming treatment instead of gender reassignment (American Psychiatric Association, 2022). Compared with the ICD 10th edition, the gender incongruence classification was moved from the Mental Health chapter to the Conditions Related to Sexual Health chapter in the ICD-11. When compared with the DSM-5 classification of gender dysphoria, one important reconceptualization is distress is not a required indicator of the ICD-11 classification of gender incongruence (WHO, 2019a). After all, when growing up in a supporting and accepting environment, the distress and impairment criterion, an inherent part of every mental health condition, may not be applicable (Drescher, 2012). As such, the ICD-11 classification of gender incongruence may better capture the fullness of gender diversity experiences and related clinical gender needs.

Criteria for the ICD-11 classification gender incongruence of adolescence or adulthood require a marked and persistent incongruence between an individual´s experienced gender and the assigned sex, which often leads to a need to "transition" to live and be accepted as a person of the experienced gender. For some, this includes hormonal treatment, surgery, or other health care services to enable the individual´s body to align as much as required, and to the extent possible, with the person's experienced gender. Relevant for adolescents is the indicator that a classification cannot be assigned "prior to the onset of puberty." Finally, it is noted "that gender variant behaviour and preferences alone are not a basis for assigning the classification" (WHO, ICD-11, 2019a).

Criteria for the DSM-5 and DSM-5-TR classification of gender dysphoria in adolescence and adulthood denote "a marked incongruence between one's experienced/expressed gender and assigned gender, of at least 6 months' duration' (criterion A, fulfilled when 2 of 6 subcriteria are manifest; DSM-5, APA, 2013; DSM 5-TR, APA, 2022).

Of note, although a gender-related classification is one of the requirements for receiving medical gender-affirming care, such a classification alone does not indicate a person needs medical-affirming care. The range of youth experiences of gender incongruence necessitates professionals provide a range of treatments or interventions based on the individual's needs. Counseling, gender exploration, mental health assessment and, when needed, treatment with MHPs trained in gender development may all be indicated with or without the implementation of medical-affirming care.

Statement 6.12.b

The experience of gender diversity/incongruence is marked and sustained over time.

Identity exploration and consolidation are experienced by many adolescents (Klimstra et al., 2010; Topolewska-Siedzik & Cieciuch, 2018). Identity exploration during adolescence may include a process of self-discovery around gender and gender identity (Steensma, Kreukels et al., 2013). Little is known about how processes that underlie consolidation of gender identity during adolescence (e.g., the process of commitment to specific identities) may impact a young person's experience(s) or needs over time.

Therefore, the level of reversibility of a gender-affirming medical intervention should be considered along with the sustained duration of a young person's experience of gender incongruence when initiating treatment. Given potential shifts in gender-related experiences and needs during adolescence, it is important to establish the young person has experienced several years of persistent gender diversity/incongruence prior to initiating less reversible treatments such as gender-affirming hormones or surgeries. Puberty suppression treatment, which provides more time for younger adolescents to engage their decision-making capacities, also raises important considerations (see Statement 6.12f and Chapter 12—Hormone Therapy) suggesting the importance of a sustained experience of gender incongruence/diversity prior to initiation. However, in this age group of younger adolescents, several years is not always practical nor necessary given the premise of the treatment as a means to buy time while avoiding distress from irreversible pubertal changes. For youth who have experienced a shorter duration of gender incongruence, social transition-related and/or other medical supports (e.g., menstrual suppression/androgen blocking) may also provide some relief as well as furnishing additional information to the clinical team regarding a young person's broad gender care needs (see Statements 6.4, 6.6, and 6.7).

Establishing evidence of persistent gender diversity/incongruence typically requires careful assessment with the young person over time (see Statement 6.3). Whenever possible and when appropriate, the assessment and discernment process should also include the parent(s)/caregiver(s) (see Statement 6.11). Evidence demonstrating gender diversity/incongruence sustained over time can be provided via history obtained directly from the adolescent and parents/caregivers when this information is not documented in the medical records.

The research literature on continuity versus discontinuity of gender-affirming medical care needs/requests is complex and somewhat difficult to interpret. A series of studies conducted over the last several decades, including some with methodological challenges (as noted by Temple Newhook et al., 2018; Winters et al., 2018) suggest the experience of gender incongruence is not consistent for all children as they progress into adolescence. For example, a subset of youth who experienced gender incongruence or who socially transitioned prior to puberty over time can show a reduction in or even full discontinuation of gender incongruence (de Vries et al., 2010; Olson et al., 2022; Ristori & Steensma, 2016; Singh et al., 2021; Wagner et al., 2021). However, there has been less research focused on rates of continuity and discontinuity of gender incongruence and gender-related needs in pubertal and adolescent populations. The data available regarding broad unselected gender-referred pubertal/adolescent cohorts (from the Amsterdam transgender clinic) suggest that, following extended assessments over time, a subset of adolescents with gender incongruence presenting for gender care elect not to pursue gender-affirming medical care

(Arnoldussen et al., 2019; de Vries, Steensma et al., 2011). Importantly, findings from studies of gender incongruent pubertal/adolescent cohorts, in which participants who have undergone comprehensive gender evaluation over time, have shown persistent gender incongruence and gender-related need and have received referrals for medical gender care, suggest low levels of regret regarding gender-related medical care decisions (de Vries et al., 2014; Wiepjes et al., 2018). Critically, these findings of low regret can only currently be applied to youth who have demonstrated sustained gender incongruence and gender-related needs over time as established through a comprehensive and iterative assessment (see Statement 6.3).

Statement 6.12.c

The adolescent demonstrates the emotional and cognitive maturity required to provide informed consent/assent for the treatment.

The process of informed consent includes communication between a patient and their provider regarding the patient's understanding of a potential intervention as well as, ultimately, the patient's decision whether to receive the intervention. In most settings, for minors, the legal guardian is integral to the informed consent process: if a treatment is to be given, the legal guardian (often the parent[s]/caregiver[s]) provides the informed consent to do so. In most settings, assent is a somewhat parallel process in which the minor and the provider communicate about the intervention and the provider assesses the level of understanding and intention.

A necessary step in the informed consent/assent process for considering gender-affirming medical care is a careful discussion with qualified HCPs trained to assess the emotional and cognitive maturity of adolescents. The reversible and irreversible effects of the treatment, as well as fertility preservation options (when applicable), and all potential risks and benefits of the intervention are important components of the discussion. These discussions are required when obtaining informed consent/assent. Assessment of cognitive and emotional maturity is important because it helps the care team understand the adolescent's capacity to be informed.

The skills necessary to assent/consent to any medical intervention or treatment include the ability to 1) comprehend the nature of the treatment; 2) reason about treatment options, including the risks and benefits; 3) appreciate the nature of the decision, including the long-term consequences; and 4) communicate choice (Grootens-Wiegers et al., 2017). In the case of gender- affirming medical treatments, a young person should be well-informed about what the treatment may and may not accomplish, typical timelines for changes to appear (e.g., with gender-affirming hormones), and any implications of stopping the treatment. Gender-diverse youth should fully understand the reversible, partially reversible, and irreversible aspects of a treatment, as well as the limits of what is known about certain treatments (e.g., the impact of pubertal suppression on brain development (Chen and Loshak, 2020)). Gender-diverse youth should also understand, although many gender-diverse youth begin gender- affirming medical care and experience that care as a good fit for them long-term, there is a subset of individuals who over time discover this care is not a fit for them (Wiepjes et al., 2018). Youth should know such shifts are sometimes connected to a change in gender needs over time, and in some cases, a shift in gender identity itself. Given this information, gender diverse youth must be able to reason thoughtfully about treatment options, considering the implications of the choices at hand. Furthermore, as a foundation for providing assent, the gender-diverse young person needs to be able to communicate their choice.

The skills needed to accomplish the tasks required for assent/consent may not emerge at specific ages per se (Grootens-Wiegers et al., 2017). There may be variability in these capacities related to developmental differences and mental health presentations (Shumer & Tishelman, 2015) and dependent on the opportunities a young person has had to practice these skills (Alderson, 2007). Further, assessment of emotional and cognitive maturity must be conducted separately for each gender-related treatment decision (Vrouenraets et al., 2021).

The following questions may be useful to consider in assessing a young person's emotional and

cognitive readiness to assent or consent to a specific gender-affirming treatment:

- Can the young person think carefully into the future and consider the implications of a partially or fully irreversible intervention?
- Does the young person have sufficient self-reflective capacity to consider the possibility that gender-related needs and priorities can develop over time, and gender-related priorities at a certain point in time might change?
- Has the young person, to some extent, thought through the implications of what they might do if their priorities around gender do change in the future?
- Is the young person able to understand and manage the day-to-day short- and long-term aspects of a specific medical treatment (e.g., medication adherence, administration, and necessary medical follow-ups)?

Assessment of emotional and cognitive maturity may be accomplished over time as the care team continues to engage in conversations about the treatment options and affords the young person the opportunity to practice thinking into the future and flexibly consider options and implications. For youth with neurodevelopmental and/or some types of mental health differences, skills for future thinking, planning, big picture thinking, and self-reflection may be less-well developed (Dubbelink & Geurts, 2017). In these cases, a more careful approach to consent and assent may be required, and this may include additional time and structured opportunities for the young person to practice the skills necessary for medical decision-making (Strang, Powers et al., 2018).

For unique situations in which an adolescent minor is consenting for their own treatment without parental permission (see Statement 6.11), extra care must be taken to support the adolescent's informed decision-making. This will typically require greater levels of engagement of and collaboration between the HCPs working with the adolescent to provide the young person appropriate cognitive and emotional support to consider options, weigh benefits and potential challenges/costs, and develop a plan for any needed (and potentially ongoing) supports associated with the treatment.

Statement 6.12.d

The adolescent's mental health concerns (if any) that may interfere with diagnostic clarity, capacity to consent, and/or gender-affirming medical treatments have been addressed.

Evidence indicates TGD adolescents are at increased risk of mental health challenges, often related to family/caregiver rejection, non-affirming community environments, and neurodiversity-related factors (e.g., de Vries et al., 2016; Pariseau et al., 2019; Ryan et al., 2010; Weinhardt et al., 2017). A young person's mental health challenges may impact their conceptualization of their gender development history and gender identity-related needs, the adolescent's capacity to consent, and the ability of the young person to engage in or receive medical treatment. Additionally, like cisgender youth, TGD youth may experience mental health concerns irrespective of the presence of gender dysphoria or gender incongruence. In particular, depression and self-harm may be of specific concern; many studies reveal depression scores and emotional and behavioral problems comparable to those reported in populations referred to mental health clinics (Leibowitz & de Vries, 2016). Higher rates of suicidal ideation, suicide attempts, and self-harm have also been reported (de Graaf et al., 2020). In addition, eating disorders occur more frequently than expected in non-referred populations (Khatchadourian et al., 2013; Ristori et al., 2019; Spack et al., 2012). Importantly, TGD adolescents show high rates of autism spectrum disorder/characteristics (Øien et al., 2018; van der Miesen et al., 2016; see also Statement 6.1d). Other neurodevelopmental presentations and/or mental health challenges may also be present, (e.g., ADHD, intellectual disability, and psychotic disorders (de Vries, Doreleijers et al., 2011; Meijer et al., 2018; Parkes & Hall, 2006).

Of note, many transgender adolescents are well-functioning and experience few if any mental health concerns. For example, socially transitioned pubertal adolescents who receive medical

gender- affirming treatment at specialized gender clinics may experience mental health outcomes equivalent to those of their cisgender peers (e.g., de Vries et al., 2014; van der Miesen et al., 2020). A provider's key task is to assess the direction of the relationships that exist between any mental health challenges and the young person's self-understanding of gender care needs and then prioritize accordingly.

Mental health difficulties may challenge the assessment and treatment of gender-related needs of TGD adolescents in various ways:

1. First, when a TGD adolescent is experiencing acute suicidality, self-harm, eating disorders, or other mental health crises that threaten physical health, safety must be prioritized. According to the local context and existing guidelines, appropriate care should seek to mitigate the threat or crisis so there is sufficient time and stabilization for thoughtful gender-related assessment and decision-making. For example, an actively suicidal adolescent may not be emotionally able to make an informed decision regarding gender-affirming medical/surgical treatment. If indicated, safety-related interventions should not preclude starting gender-affirming care.
2. Second, mental health can also complicate the assessment of gender development and gender identity-related needs. For example, it is critical to differentiate gender incongruence from specific mental health presentations, such as obsessions and compulsions, special interests in autism, rigid thinking, broader identity problems, parent/child interaction difficulties, severe developmental anxieties (e.g., fear of growing up and pubertal changes unrelated to gender identity), trauma, or psychotic thoughts. Mental health challenges that interfere with the clarity of identity development and gender-related decision-making should be prioritized and addressed.
3. Third, decision-making regarding gender-affirming medical treatments that have life-long consequences requires thoughtful, future-oriented thinking by the adolescent, with support from the parents/caregivers, as indicated (see Statement 6.11). To be able to make such an informed decision, an adolescent should be able to understand the issues, express a choice, appreciate and give careful thought regarding the wish for medical-affirming treatment (see Statement 6.12c). Neurodevelopmental differences, such as autistic features or autism spectrum disorder (see Statement 6.1d, e.g., communication differences; a preference for concrete or rigid thinking; differences in self-awareness, future thinking and planning), may challenge the assessment and decision-making process; neurodivergent youth may require extra support, structure, psychoeducation, and time built into the assessment process (Strang, Powers et al., 2018). Other mental health presentations that involve reduced communication and self-advocacy, difficulty engaging in assessment, memory and concentration difficulties, hopelessness, and difficulty engaging in future-oriented thinking may complicate assessment and decision-making. In such cases, extended time is often necessary before any decisions regarding medical-affirming treatment can be made.
4. Finally, while addressing mental health concerns is important during the course of medical treatment, it does not mean all mental health challenges can or should be resolved completely. However, it is important any mental health concerns are addressed sufficiently so that gender-affirming medical treatment can be provided optimally (e.g., medication adherence, attending follow-up medical appointments, and self-care, particularly during a postoperative course).

Statement 6.12.e

The adolescent has been informed of the reproductive effects, including the potential loss of fertility, and available options to preserve fertility, and these have been discussed in the context of the adolescent's stage of pubertal development.

For guidelines regarding the clinical approach, the scientific background, and the rationale, see Chapter 12—Hormone Therapy and Chapter 16—Reproductive Health.

Statement 6.12.f

The adolescent has reached Tanner stage 2 of puberty for pubertal suppression to be initiated.

The onset of puberty is a pivotal point for many gender diverse youth. For some, it creates an intensification of their gender incongruence, and for others, pubertal onset may lead to gender fluidity (e.g., a transition from binary to nonbinary gender identity) or even attenuation of a previously affirmed gender identity (Drummond et al., 2008; Steensma et al., 2011, Steensma, Kreukels et al., 2013; Wallien & Cohen-Kettenis, 2008). The use of puberty-blocking medications, such as GnRH analogues, is not recommended until children have achieved a minimum of Tanner stage 2 of puberty because the experience of physical puberty may be critical for further gender identity development for some TGD adolescents (Steensma et al., 2011). Therefore, puberty blockers should not be implemented in prepubertal gender diverse youth (Waal & Cohen-Kettenis, 2006). For some youth, GnRH agonists may be appropriate in late stages or in the post-pubertal period (e.g., Tanner stage 4 or 5), and this should be highly individualized. See Chapter 12—Hormone Therapy for a more comprehensive review of the use of GnRH agonists.

Variations in the timing of pubertal onset is due to multiple factors (e.g., sex assigned at birth, genetics, nutrition, etc.). Tanner staging refers to five stages of pubertal development ranging from prepubertal (Tanner stage 1) to post-pubertal, and adult sexual maturity (Tanner stage 5) (Marshall & Tanner, 1969, 1970). For assigned females at birth, pubertal onset (e.g., gonadarche) is defined by the occurrence of breast budding (Tanner stage 2), and for birth-assigned males, the achievement of a testicular volume of greater than or equal to 4 mL (Roberts & Kaiser, 2020). An experienced medical provider should be relied on to differentiate the onset of puberty from physical changes such as pubic hair and apocrine body odor due to sex steroids produced by the adrenal gland (e.g., adrenarche) as adrenarche does not warrant the use of puberty-blocking medications (Roberts & Kaiser, 2020). Educating parents and families about the difference between adrenarche and gonadarche helps families understand the timing during which shared decision-making about gender-affirming medical therapies should be undertaken with their multidisciplinary team.

The importance of addressing other risks and benefits of pubertal suppression, both hypothetical and actual, cannot be overstated. Evidence supports the existence of surgical implications for transgender girls who proceed with pubertal suppression (van de Grift et al., 2020). Longitudinal data exists to demonstrate improvement in romantic and sexual satisfaction for adolescents receiving puberty suppression, hormone treatment and surgery (Bungener et al., 2020). A study on surgical outcomes of laparoscopic intestinal vaginoplasty (performed because of limited genital tissue after the use of puberty blockers) in transgender women revealed that the majority experienced orgasm after surgery (84%), although a specific correlation between sexual pleasure outcomes and the timing of pubertal suppression initiation was not discussed in the study (Bouman, van der Sluis et al., 2016), nor does the study apply to those who would prefer a different surgical procedure. This underscores the importance of engaging in discussions with families about the future unknowns related to surgical and sexual health outcomes.

Statement 6.12.g

The adolescent had at least 12 months of gender-affirming hormone therapy or longer, if required, to achieve the desired surgical result for gender-affirming procedures, including breast augmentation, orchiectomy, vaginoplasty, hysterectomy, phalloplasty, metoidioplasty, and facial surgery as part of gender-affirming treatment unless hormone therapy is either not desired or is medically contraindicated.

GAHT leads to anatomical, physiological, and psychological changes. The onset of the anatomic effects (e.g., clitoral growth, breast growth, vaginal mucosal atrophy) may begin early after the initiation of therapy, and the peak effect is expected at 1–2 years (T'Sjoen et al., 2019). To

ensure sufficient time for psychological adaptations to the physical change during an important developmental time for the adolescent, 12 months of hormone treatment is suggested. Depending upon the surgical result required, a period of hormone treatment may need to be longer (e.g., sufficient clitoral virilization prior to metoidioplasty/phalloplasty, breast growth and skin expansion prior to breast augmentation, softening of skin and changes in facial fat distribution prior to facial GAS) (de Blok et al., 2021).

For individuals who are not taking hormones prior to surgical interventions, it is important surgeons review the impact of hormone therapy on the proposed surgery. In addition, for individuals undergoing gonadectomy who are not taking hormones, a plan for hormone replacement can be developed with their prescribing professional prior to surgery.

Consideration of ages for gender-affirming medical and surgical treatment for adolescents

Age has a strong, albeit imperfect, correlation with cognitive and psychosocial development and may be a useful objective marker for determining the potential timing of interventions (Ferguson et al., 2021). Higher (i.e., more advanced) ages may be required for treatments with greater irreversibility, complexity, or both. This approach allows for continued cognitive/emotional maturation that may be required for the adolescent to fully consider and consent to increasingly complex treatments (see Statement 6.12c).

A growing body of evidence indicates providing gender-affirming treatment for gender diverse youth who meet criteria leads to positive outcomes (Achille et al., 2020; de Vries et al., 2014; Kuper et al., 2020). There is, however, limited data on the optimal timing of gender-affirming interventions as well as the long-term physical, psychological, and neurodevelopmental outcomes in youth (Chen et al., 2020; Chew et al., 2018; Olson-Kennedy et al., 2016). Currently, the only existing longitudinal studies evaluating gender diverse youth and adult outcomes are based on a specific model (i.e., the Dutch approach) that involved a comprehensive initial assessment with follow-up. In this approach, pubertal suppression was considered at age 12, GAHT at age 16, and surgical interventions after age 18 with exceptions in some cases. It is not clear if deviations from this approach would lead to the same or different outcomes. Longitudinal studies are currently underway to better define outcomes as well as the safety and efficacy of gender-affirming treatments in youth (Olson-Kennedy, Garofalo et al., 2019; Olson-Kennedy, Rosenthal et al., 2019). While the long-term effects of gender-affirming treatments initiated in adolescence are not fully known, the potential negative health consequences of delaying treatment should also be considered (de Vries et al., 2021). As the evidence base regarding outcomes of gender-affirming interventions in youth continues to grow, recommendations on the timing and readiness for these interventions may be updated.

Previous guidelines regarding gender-affirming treatment of adolescents recommended partially reversible GAHT could be initiated at approximately 16 years of age (Coleman et al., 2012; Hembree et al., 2009). More recent guidelines suggest there may be compelling reasons to initiate GAHT prior to the age of 16, although there are limited studies on youth who have initiated hormones prior to 14 years of age (Hembree et al., 2017). A compelling reason for earlier initiation of GAHT, for example, might be to avoid prolonged pubertal suppression, given potential bone health concerns and the psychosocial implications of delaying puberty as described in more detail in Chapter 12—Hormone Therapy (Klink, Caris et al., 2015; Schagen et al., 2020; Vlot et al., 2017; Zhu & Chan, 2017). Puberty is a time of significant brain and cognitive development. The potential neurodevelopmental impact of extended pubertal suppression in gender diverse youth has been specifically identified as an area in need of continued study (Chen et al., 2020). While GnRH analogs have been shown to be safe when used for the treatment of precocious puberty, there are concerns delaying exposure to sex hormones (endogenous or exogenous) at a time of peak bone mineralization may lead to decreased bone mineral density. The potential decrease in bone mineral density as well as the clinical significance of any decrease requires continued study (Klink, Caris et al., 2015; Lee, Finlayson et al.,

2020; Schagen et al., 2020). The potential negative psychosocial implications of not initiating puberty with peers may place additional stress on gender diverse youth, although this has not been explicitly studied. When considering the timing of initiation of gender-affirming hormones, providers should compare the potential physical and psychological benefits and risks of starting treatment with the potential risks and benefits of delaying treatment. This process can also help identify compelling factors that may warrant an individualized approach.

Studies carried out with trans masculine youth have demonstrated chest dysphoria is associated with higher rates of anxiety, depression, and distress and can lead to functional limitations, such as avoiding exercising or bathing (Mehringer et al., 2021; Olson-Kennedy, Warus et al., 2018; Sood et al., 2021). Testosterone unfortunately does little to alleviate this distress, although chest masculinization is an option for some individuals to address this distress long-term. Studies with youth who sought chest masculinization surgery to alleviate chest dysphoria demonstrated good surgical outcomes, satisfaction with results, and minimal regret during the study monitoring period (Marinkovic & Newfield, 2017; Olson-Kennedy, Warus et al., 2018). Chest masculinization surgery can be considered in minors when clinically and developmentally appropriate as determined by a multidisciplinary team experienced in adolescent and gender development (see relevant statements in this chapter). The duration or current use of testosterone therapy should not preclude surgery if otherwise indicated. The needs of some TGD youth may be met by chest masculinization surgery alone. Breast augmentation may be needed by trans feminine youth, although there is less data about this procedure in youth, possibly due to fewer individuals requesting this procedure (Boskey et al., 2019; James, 2016). GAHT, specifically estrogen, can help with development of breast tissue, and it is recommended youth have a minimum of 12 months of hormone therapy, or longer as is surgically indicated, prior to breast augmentation unless hormone therapy is not clinically indicated or is medically contraindicated.

Data are limited on the optimal timing for initiating other gender-affirming surgical treatments in adolescents. This is partly due to the limited access to these treatments, which varies in different geographical locations (Mahfouda et al., 2019). Data indicate rates of gender-affirming surgeries have increased since 2000, and there has been an increase in the number of TGD youth seeking vaginoplasty (Mahfouda et al., 2019; Milrod & Karasic, 2017). A 2017 study of 20 WPATH-affiliated surgeons in the US reported slightly more than half had performed vaginoplasty in minors (Milrod & Karasic, 2017). Limited data are available on the outcomes for youth undergoing vaginoplasty. Small studies have reported improved psychosocial functioning and decreased gender dysphoria in adolescents who have undergone vaginoplasty (Becker et al., 2018; Cohen-Kettenis & van Goozen, 1997; Smith et al.,2001). While the sample sizes are small, these studies suggest there may be a benefit for some adolescents to having these procedures performed before the age of 18. Factors that may support pursuing these procedures for youth under 18 years of age include the increased availability of support from family members, greater ease of managing postoperative care prior to transitioning to tasks of early adulthood (e.g., entering university or the workforce), and safety concerns in public spaces (i.e., to reduce transphobic violence) (Boskey et al., 2018; Boskey et al., 2019; Mahfouda et al., 2019). Given the complexity and irreversibility of these procedures, an assessment of the adolescent's ability to adhere to postsurgical care recommendations and to comprehend the long-term impacts of these procedures on reproductive and sexual function is crucial (Boskey et al., 2019). Given the complexity of phalloplasty, and current high rates of complications in comparison to other gender-affirming surgical treatments, it is not recommended this surgery be considered in youth under 18 at this time (see Chapter 13—Surgery and Postoperative Care).

Additional key factors that should be taken into consideration when discussing the timing of interventions with youth and families are addressed in detail in statements 6.12a-f. For a summary of the criteria/recommendations for medically necessary gender-affirming medical treatment in adolescents, see Appendix D.

CHAPTER 7 Children

These Standards of Care pertain to prepubescent gender diverse children and are based on research, ethical principles, and accumulated expert knowledge. The principles underlying these standards include the following 1) childhood gender diversity is an expected aspect of general human development (Endocrine Society and Pediatric Endocrine Society, 2020; Telfer et al., 2018); 2) childhood gender diversity is not a pathology or mental health disorder (Endocrine Society and Pediatric Endocrine Society, 2020; Oliphant et al., 2018; Telfer et al., 2018); 3) diverse gender expressions in children cannot always be assumed to reflect a transgender identity or gender incongruence (Ehrensaft, 2016; Ehrensaft, 2018; Rael et al., 2019); 4) guidance from mental health professionals (MHPs) with expertise in gender care for children can be helpful in supporting positive adaptation as well as discernment of gender-related needs over time (APA, 2015; Ehrensaft, 2018; Telfer et al., 2018); 5) conversion therapies for gender diversity in children (i.e., any "therapeutic" attempts to compel a gender diverse child through words, actions, or both to identify with, or behave in accordance with, the gender associated with the sex assigned at birth are harmful and we repudiate their use (APA, 2021; Ashley, 2019b, Paré, 2020; SAMHSA, 2015; Telfer et al., 2018; UN Human Rights Council, 2020).

Throughout the text, the term "health care professional" (HCP) is used broadly to refer to professionals working with gender diverse children. Unlike pubescent youth and adults, prepubescent gender diverse children are not eligible to access medical intervention (Pediatric Endocrine Society, 2020); therefore, when professional input is sought, it is most likely to be from an HCP specialized in psychosocial supports and gender development. Thus, this chapter is uniquely focused on developmentally appropriate psychosocial practices, although other HCPs, such as pediatricians and family practice HCPs may also find these standards useful as they engage in professional work with gender diverse children and their families.

This chapter employs the term "gender diverse" given that gender trajectories in prepubescent children cannot be predicted and may evolve over time (Steensma, Kreukels et al., 2013). At the same time, this chapter recognizes some children will remain stable in a gender identity they articulate early in life that is discrepant from the sex assigned at birth (Olson et al., 2022). The term, "gender diverse" includes transgender binary and nonbinary children, as well as gender diverse children who will ultimately not identify as transgender later in life. Terminology is inherently culturally bound and evolves over time. Thus, it is possible terms used here may become outdated and we will find better descriptors.

This chapter describes aspects of medical necessary care intended to promote the well-being and gender-related needs of children (see medically necessary statement in the Global Applicability chapter, Statement 2.1). This chapter advocates everyone employs these standards, to the extent possible. There may be situations or locations in which the recommended resources are not fully available. HCPs/teams lacking resources need to work toward meeting these standards. However, if unavoidable limitations preclude components of these recommendations, this should not hinder providing the best services currently available. In those locations where some but not all recommended services exist, choosing not to implement potentially beneficial care services risks harm to a child (Murchison et al., 2016; Telfer et al., 2018; Riggs et al., 2020). Overall, it is imperative to prioritize a child's best interests.

A vast empirical psychological literature indicates early childhood experiences frequently set the stage for lifelong patterns of risk and/or resilience and contribute to a trajectory of development more or less conducive to well-being and a positive quality of life (Anda et al., 2010; Masten & Cicchetti, 2010; Shonkoff & Garner, 2012). The available research indicates, in general, gender diverse youth are at greater risk for experiencing psychological difficulties (Ristori & Steensma, 2016) than age- matched cisgender peers as a result of encountering destructive experiences, including trauma and maltreatment stemming from gender diversity-related rejection and other harsh, non-accepting interactions (Barrow & Apostle, 2018; Giovanardi et al., 2018; Gower, Rider, Brown et al., 2018; Grossman & D'Augelli, 2006; Hendricks & Testa, 2012; Reisner, Greytak

et al., 2015; Roberts et al., 2014; Tishelman & Neumann-Mascis, 2018). Further, literature indicates prepubescent children who are well accepted in their gender diverse identities are generally well-adjusted (Malpas et al., 2018; Olson et al., 2016). Assessment and treatment of children typically emphasizes an *ecological* approach, recognizing children need to be safe and nurtured in each setting they frequent (Belsky, 1993; Bronfenbrenner, 1979; Kaufman & Tishelman, 2018; Lynch & Cicchetti, 1998; Tishelman et al., 2010; Zielinski & Bradshaw, 2006). Thus, the perspective of this chapter draws on basic psychological literature and knowledge of the unique risks to gender diverse children and emphasizes the integration of an ecological approach to understanding their needs and to facilitating positive mental health in all gender care. This perspective prioritizes fostering well-being and quality of life for a child throughout their development. Additionally, this chapter also embraces the viewpoint, supported by the substantial psychological research cited above, that psychosocial gender-affirming care (Hidalgo et al., 2013) for prepubescent children offers a window of opportunity to promote a trajectory of well-being that will sustain them over time and during the transition to adolescence. This approach potentially can mitigate some of the common mental health risks faced by transgender and gender diverse (TGD) teens, as frequently described in literature (Chen et al., 2021; Edwards-Leeper et al., 2017; Haas et al., 2011; Leibowitz & de Vries, 2016; Reisner, Bradford et al., 2015; Reisner, Greytak et al., 2015).

Developmental research has focused on understanding various aspects of gender development in the earliest years of childhood based on a general population of prepubescent children. This research has typically relied on the assumption that child research participants are cisgender (Olezeski et al., 2020) and has reported gender identity stability is established in the preschool years for the general population of children, most of whom are likely not gender diverse (Kohlberg, 1966; Steensma, Kreukels et al., 2013). Recently, developmental research has demonstrated gender diversity can be observed and identified in young prepubescent children (Fast & Olson, 2018; Olson & Gülgöz, 2018; Robles et al., 2016). Nonetheless, empirical study in this area is limited, and at this time there are no psychometrically sound assessment measures capable of reliably and/or fully ascertaining a prepubescent child's self-understanding of their own gender and/or gender-related needs and preferences (Bloom et al., 2021). Therefore, this chapter emphasizes the importance of a nuanced and individualized clinical approach to gender assessment, consistent with the recommendations from various guidelines and literature (Berg & Edwards-Leeper, 2018; de Vries & Cohen-Kettenis, 2012; Ehrensaft, 2018; Steensma & Wensing-Kruger, 2019). Research and clinical experience have indicated gender diversity in prepubescent children may, for some, be fluid; there are no reliable means of predicting an individual child's gender evolution (Edwards-Leeper et al., 2016; Ehrensaft, 2018; Steensma, Kreukels et al., 2013), and the gender-related needs for a particular child may vary over the course of their childhood.

It is important to understand the meaning of the term "assessment" (sometimes used synonymously with the term "evaluation"). There are multiple contexts for assessment (Krishnamurthy et al., 2004) including rapid assessments that take place during an immediate crisis (e.g., safety assessment when a child may be suicidal) and focused assessments when a family may have a circumscribed question, often in the context of a relatively brief consultation (Berg & Edwards-Leeper, 2018). The term assessment is also often used in reference to "diagnostic assessment," which can also be called an "intake" and is for the purpose of determining whether there is an issue that is diagnosable and/or could benefit from a therapeutic process. This chapter focus on comprehensive assessments, useful for understanding a child and family's needs and goals (APA, 2015; de Vries & Cohen-Kettenis, 2012; Srinath et al., 2019; Steensma & Wensing-Kruger, 2019). This type of psychosocial assessment is not necessary for all gender diverse children, but may be requested for a number of reasons. Assessments may present a useful opportunity to start a process of support for a gender diverse child and their family, with the understanding that gender diverse children benefit when their family dynamics include

Statements of Recommendations

7.1- We recommend health care professionals working with gender diverse children receive training and have expertise in gender development and gender diversity in children and possess a general knowledge of gender diversity across the life span.
7.2- We recommend health care professionals working with gender diverse children receive theoretical and evidenced-based training and develop expertise in general child and family mental health across the developmental spectrum.
7.3- We recommend health care professionals working with gender diverse children receive training and develop expertise in autism spectrum disorders and other neurodiversity or collaborate with an expert with relevant expertise when working with autistic/neurodivergent, gender diverse children.
7.4- We recommend health care professionals working with gender diverse children engage in continuing education related to gender diverse children and families.
7.5- We recommend health care professionals conducting an assessment with gender diverse children access and integrate information from multiple sources as part of the assessment.
7.6- We recommend health care professionals conducting an assessment with gender diverse children consider relevant developmental factors, neurocognitive functioning, and language skills.
7.7- We recommend health care professionals conducting an assessment with gender diverse children consider factors that may constrain accurate reporting of gender identity/gender expression by the child and/or family/caregiver(s).
7.8- We recommend health care professionals consider consultation, psychotherapy, or both for a gender diverse child and family/caregivers when families and health care professionals believe this would benefit the well-being and development of a child and/or family.
7.9- We recommend health care professionals offering consultation, psychotherapy, or both to gender diverse children and families/caregivers work with other settings and individuals important to the child to promote the child's resilience and emotional well-being.
7.10- We recommend health care professionals offering consultation, psychotherapy, or both to gender diverse children and families/caregivers provide both parties with age-appropriate psychoeducation about gender development.
7.11- We recommend that health care professionals provide information to gender diverse children and their families/caregivers as the child approaches puberty about potential gender affirming medical interventions, the effects of these treatments on future fertility, and options for fertility preservation.
7.12- We recommend parents/caregivers and health care professionals respond supportively to children who desire to be acknowledged as the gender that matches their internal sense of gender identity.
7.13- We recommend health care professionals and parents/caregivers support children to continue to explore their gender throughout the pre-pubescent years, regardless of social transition.
7.14- We recommend the health care professionals discuss the potential benefits and risks of a social transition with families who are considering it.
7.15- We suggest health care professionals consider working collaboratively with other professionals and organizations to promote the well-being of gender diverse children and minimize the adversities they may face.

acceptance of their gender diversity and parenting guidance when requested. Comprehensive assessments are appropriate when solicited by a family requesting a full understanding of the child's gender and mental health needs in the context of gender diversity.

In these circumstances, family member mental health issues, family dynamics, and social and cultural contexts, all of which impact a gender diverse child, should be taken into consideration (Barrow & Apostle, 2018; Brown & Mar, 2018; Cohen-Kettenis et al., 2003; Hendricks & Testa, 2012; Kaufman & Tishelman, 2018; Ristori & Steensma, 2016; Tishelman & Neumann-Mascis, 2018). This is further elaborated upon in the text below.

It is important HCPs working with gender diverse children strive to understand the child and the family's various aspects of identity and experience: racial, ethnic, immigrant/refugee status, religious, geographic, and socio-economic, for example, and be respectful and sensitive to cultural context in clinical interactions (Telfer et al., 2018). Many factors may be relevant to culture and gender, including religious beliefs, gender-related expectations, and the degree to which gender diversity is accepted (Oliphant et al., 2018). Intersections between gender diversity, sociocultural diversity, and minority statuses can be sources of strength, social stress, or both (Brown & Mar, 2018; Oliphant et al., 2018; Riggs & Treharne, 2016).

Each child, family member, and family dynamic is unique and potentially encompasses multiple cultures and belief patterns. Thus, HCPs of all disciplines should avoid stereotyping based on preconceived ideas that may be incorrect or biased (e.g., that a family who belongs to a religious organization that is opposed to appreciating gender diversity will necessarily be unsupportive of their child's gender diversity) (Brown & Mar, 2018). Instead, it is essential to approach each family openly and understand each family member and family pattern as distinct.

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 7.1

We recommend the health care professionals working with gender diverse children receive training and have expertise in gender development and gender diversity in children and possess general knowledge of gender diversity across the life span.

HCPs working with gender diverse children should acquire and maintain the necessary training and credentials relevant to the scope of their role as professionals. This includes licensure, certification, or both by appropriate national and/or regional accrediting bodies. We recognize the specifics of credentialing and regulation of professionals vary globally. Importantly, basic licensure, certification, or both may be insufficient in and of itself to ensure competency working with gender diverse children, as HCPs specifically require in-depth training and supervised experience in childhood gender development and gender diversity to provide appropriate care.

Statement 7. 2

We recommend health care professionals working with gender diverse children receive theoretical and evidenced-based training and develop expertise in general child and family mental health across the developmental spectrum.

HCPs should receive training and supervised expertise in general child and family mental health across the developmental spectrum from toddlerhood through adolescence, including evidence-based assessment and intervention approaches. Gender diversity is not a mental health disorder; however, as cited above, we know mental health can be adversely impacted for gender diverse children (e.g., through gender minority stress) (Hendricks & Testa, 2012) that may benefit from exploration and support; therefore, mental health expertise is highly recommended. Working with children is a complex endeavor, involving an understanding of a child's developmental needs at various ages, the ability to comprehend the forces impacting a child's well-being both inside and outside the family (Kaufman & Tishelman, 2018), and an ability to fully assess when a child is unhappy or experiencing significant mental health difficulties, related or unrelated to gender. Research has indicated high levels of adverse experiences and trauma in the gender diverse community of children, including susceptibility to rejection or even maltreatment (APA, 2015; Barrow & Apostle, 2018; Giovanardi et al., 2018; Reisner, Greytak et al., 2015; Roberts et al., 2012; Tishelman & Neumann-Mascis, 2018). HCPs need to be cognizant of the potential for adverse experiences and be able to initiate effective interventions to prevent harm and promote positive well-being.

Statement 7.3

We recommend health care professionals working with gender diverse children receive training and develop expertise in autism spectrum disorders and other neurodiversity or collaborate with an expert with relevant expertise when working with autistic/neurodivergent, gender diverse children.

The experience of gender diversity in autistic children as well as in children with other forms of neurodivergence may present extra clinical complexities (de Vries et al., 2010; Strang, Meagher et al., 2018). For example, autistic children may find it difficult to self-advocate for their gender-related needs and may communicate in highly individualistic ways (Kuvalanka et al., 2018; Strang, Powers et al., 2018). They may have varied interpretations of gender-related experiences given common differences in communication and thinking style. Because of the unique needs of gender diverse neurodivergent children, they may be at high risk for being misunderstood (i.e., for their communications to be misinterpreted). Therefore, professionals providing support to these children can best serve them by receiving training and developing expertise in autism and related neurodevelopmental presentations and/or collaborating with autism specialists (Strang, Meagher et al., 2018). Such training is especially relevant as research has documented

higher rates of autism among gender diverse youth than in the general population (de Vries et al., 2010; Hisle-Gorman et al., 2019; Shumer et al., 2015).

Statement 7.4

We recommend health care professionals working with gender diverse children engage in continuing education related to gender diverse children and families.

Continuing professional development regarding gender diverse children and families may be acquired through various means, including through readings (journal articles, books, websites associated with gender knowledgeable organizations), attending on-line and in person trainings, and joining peer supervision/consultation groups (Bartholomaeus et al., 2021).

Continuing education includes 1) maintaining up-to-date knowledge of available and relevant research on gender development and gender diversity in prepubescent children and gender diversity across the life span; 2) maintaining current knowledge regarding best practices for assessment, support, and treatment approaches with gender diverse children and families. This is a relatively new area of practice and health care professionals need to adapt as new information emerges through research and other avenues (Bartholomaeus et al., 2021).

Statement 7.5

We recommend health care professionals conducting an assessment with gender diverse children access and integrate information from multiple sources as part of the assessment.

A comprehensive assessment, when requested by a family and/or an HCP can be useful for developing intervention recommendations, as needed, to benefit the well-being of the child and other family members. Such an assessment can be beneficial in a variety of situations when a child and/or their family/guardians, in coordination with providers, feel some type of intervention would be helpful. Neither assessments nor interventions should ever be used as a means of covertly or overtly discouraging a child's gender diverse expressions or identity. Instead, with appropriately trained providers, assessment can be an effective means of better understanding how to support a child and their family without privileging any particular gender identity or expression. An assessment can be especially important for some children and their families by collaborating to promote a child's gender health, well-being, and self-fulfillment.

A comprehensive assessment can facilitate the formation of an individualized plan to assist a gender diverse prepubescent children and family members (de Vries & Cohen-Kettenis, 2012; Malpas et al., 2018; Steensma & Wensing-Kruger, 2019; Telfer et al., 2018; Tishelman & Kaufman, 2018). In such an assessment, integrating information from multiple sources is important to 1) best understand the child's gender needs and make recommendations; and 2) identify areas of child, family/caregiver, and community strengths and supports specific to the child's gender status and development as well as risks and concerns for the child, their family/caregivers and environment. Multiple informants for both evaluation and support/intervention planning purposes may include the child, parents/caregivers, extended family members, siblings, school personnel, HCPs, the community, broader cultural and legal contexts and other sources as indicated (Berg & Edwards-Leeper, 2018; Srinath, 2019).

An HCP conducting an assessment of gender diverse children needs to explore gender-related issues but must also take a broad view of the child and the environment, consistent with the ecological model described above (Bronfenbrenner, 1979) to fully understand the factors impacting a child's well-being and areas of gender support and risk (Berg & Edwards-Leeper, 2018; Hendricks & Testa, 2012; Kaufman & Tishelman, 2018; Tishelman & Neumann-Mascis, 2018). This includes understanding the strengths and challenges experienced by the child/family and that are present in the environment. We advise HCPs conducting an assessment with gender diverse children to consider incorporating multiple assessment domains, depending on the child and the family's needs and circumstances. Although some of the latter listed domains below do not directly address the child's gender (see items 7–12 below), they need to be accounted for in a gender assessment, as indicated by clinical judgment, to understand the complex web of factors

that may be affecting the child's well-being in an integrated fashion, including gender health, consistent with evaluation best practices a (APA, 2015; Berg & Edwards-Leeper, 2018; Malpas et al., 2018) and develop a multi-pronged intervention when needed.

Summarizing from relevant research and clinical expertise, assessment domains often include 1) a child's asserted gender identity and gender expression, currently and historically; 2) evidence of dysphoria, gender incongruence, or both; 3) strengths and challenges related to the child, family, peer and others' beliefs and attitudes about gender diversity, acceptance and support for child; 4) child and family experiences of gender minority stress and rejection, hostility, or both due to the child's gender diversity; 5) level of support related to gender diversity in social contexts (e.g., school, faith community, extended family); 6) evaluation of conflict regarding the child's gender and/or parental/caregiver/sibling concerning behavior related to the child's gender diversity; 7) child mental health, communication and/or cognitive strengths and challenges, neurodivergence, and/or behavioral challenges causing significant functional difficulty; 8) relevant medical and developmental history; 9) areas that may pose risks (e.g., exposure to domestic and/or community violence, any form of child maltreatment; history of trauma; safety and/or victimization with peers or in any other setting; suicidality); 10) co-occurring significant family stressors, such as chronic or terminal illness, homelessness or poverty; 11) parent/caregiver and/or sibling mental health and/or behavioral challenges causing significant functional difficulty; and 12) child's and family's strengths and challenges.

A thorough assessment incorporating multiple forms of information gathering is helpful for understanding the needs, strengths, protective factors, and risks for a specific child and family across environments (e.g., home/school). Methods of information gathering often include 1) interviews with the child, family members and others (e.g., teachers), structured and unstructured; 2) caregiver and child completed standardized measures related to gender; general child well-being; child cognitive and communication skills and developmental disorders/disabilities; support and acceptance by parent/caregiver, sibling, extended family and peers; parental stress; history of childhood adversities; and/or other issues as appropriate (APA, 2020; Berg & Edwards-Leeper, 2018; Kaufman & Tishelman, 2018; Srinath, 2019).

Depending on the family characteristics, the developmental profile of the child, or both, methods of information gathering also may also benefit from including the following 1) child and/or family observation, structured and unstructured; and 2) structured and visually supported assessment techniques (worksheets; self-portraits; family drawings, etc.) (Berg & Edwards-Leeper, 2018).

Statement 7.6

We recommend that health care professionals conducting an assessment with gender diverse children consider relevant developmental factors, neurocognitive functioning and language skills.

Given the complexities of assessing young children who, unlike adults, are in the process of development across a range of domains (cognitive, social, emotional, physiological), it is important to consider the developmental status of a child and gear assessment modalities and interactions to the individualized abilities of the child. This includes tailoring the assessment to a child's developmental stage and abilities (preschoolers, school age, early puberty prior to adolescence), including using language and assessment approaches that prioritize a child's comfort, language skills, and means of self-expression (Berg & Edwards-Leeper, 2018; Srinath, 2019). For example, relevant developmental factors, such as neurocognitive differences (e.g., autism spectrum conditions), and receptive and expressive language skills should be considered in conducting the assessment. Health care professionals may need to consult with specialists for guidance in cases in which they do not possess the specialized skills themselves (Strang et al., 2021).

Statement 7.7

We recommend health care professionals conducting an assessment with gender diverse children consider factors that may constrain accurate reporting of gender identity/gender expression by the child and/or family/caregiver(s).

HCPs conducting an assessment with gender diverse children and families need to account for developmental, emotional, and environmental factors that may constrain a child's, caregiver's, sibling or other's report or influence their belief systems related to gender (Riggs & Bartholomaeus, 2018). As with all child psychological assessments, environmental and family/caregiver reactions (e.g., punishment), and/or cognitive and social factors may influence a child's comfort and/or ability to directly discuss certain factors, including gender identity and related issues (Srinath, 2019). Similarly, family members may feel constrained in freely expressing their concerns and ideas depending on family conflicts or dynamics and/or other influences (e.g., cultural/religious; extended family pressure) (Riggs & Bartholomaeus, 2018).

Statement 7.8

We recommend health care professionals consider consultation, psychotherapy, or both for a gender diverse child and family/caregivers when families and health care professionals believe this would benefit the well-being and development of a child and/or family.

The goal of psychotherapy should never be aimed at modifying a child's gender identity (APA, 2021; Ashley, 2019b; Paré, 2020; SAMHSA, 2015; UN Human Rights Council, 2020), either covertly or overtly. Not all gender diverse children or their families need input from MHPs as gender diversity is not a mental health disorder (Pediatric Endocrine Society, 2020; Telfer et al., 2018). Nevertheless, it is often appropriate and helpful to seek psychotherapy when there is distress or concerns are expressed by parents to improve psychosocial health and prevent further distress (APA, 2015). Some of the common reasons for considering psychotherapy for a gender diverse child and family include the following 1) A child is demonstrating significant conflicts, confusion, stress or distress about their gender identity or needs a protected space to explore their gender (Ehrensaft, 2018; Spivey and Edwards-Leeper, 2019); 2) A child is experiencing external pressure to express their gender in a way that conflicts with their self-knowledge, desires, and beliefs (APA, 2015); 3) A child is struggling with mental health concerns, related to or independent of their gender (Barrow & Apostle, 2018); 4) A child would benefit from strengthening their resilience in the face of negative environmental responses to their gender identity or presentation (Craig & Auston, 2018; Malpas et al., 2018); 5) A child may be experiencing mental health and/or environmental concerns, including family system problems that can be misinterpreted as gender congruence or incongruence (Berg & Edwards-Leeper, 2018); and 6) A child expresses a desire to meet with an MHP to get gender-related support. In these situations, the psychotherapy will focus on supporting the child with the understanding that the child's parent(s)/caregiver(s) and potentially other family members will be included as necessary (APA, 2015; Ehrensaft, 2018; McLaughlin & Sharp, 2018). Unless contraindicated, it is extremely helpful for parents/guardians to participate in some capacity in the psychotherapy process involving prepubescent children as family factors are often central to a child's well-being. Although relatively unexplored in research involving gender diverse children, it may be important to attend to the relationship between siblings and the gender diverse child (Pariseau et al., 2019; Parker & Davis-McCabe, 2021).

HCPs should employ interventions tailor-made to the individual needs of the child that are designed to 1) foster protective social and emotional coping skills to promote resilience in the face of potential negative reactions to the child's gender identity, expressions, or both (Craig & Austin, 2016; Malpas et al., 2018; Spencer, Berg et al., 2021); 2) collaboratively problem-solve social challenges to reduce gender minority stress (Barrow & Apostle, 2018; Tishelman & Neumann-Mascis, 2018); 3) strengthen environmental supports for the child and/or members of the immediate and extended family (Kaufman & Tishelman, 2018); and 4) provide the child an opportunity to further understand their internal gender experiences (APA, 2015; Barrow& Apostle, 2018; Ehrensaft, 2018; Malpas et al., 2018; McLaughlin & Sharp, 2018). It is helpful for HCPs to develop a relationship with a gender diverse child and family that can endure over time as needed. This enables the child/family to establish a long-term trusting relationship throughout childhood whereby the HCP can offer support and guidance as a child matures and as potentially

different challenges or needs emerge for the child/family (Spencer, Berg et al., 2021; Murchison et al., 2016). In addition to the above and within the limits of available resources, when a child is neurodivergent, an HCP who has the skill set to address both neurodevelopmental differences and gender is most appropriate (Strang et al., 2021).

As outlined in the literature, there are numerous reasons parents/caregivers, siblings, and extended family members of a prepubescent child may find it useful to seek psychotherapy for themselves (Ehrensaft, 2018; Malpas et al., 2018; McLaughlin & Sharp, 2018). As summarized below, some of these common catalysts for seeking such treatment occur when one or more *family members* 1) desire education around gender development (Spivey & Edwards-Leeper, 2019); 2) are experiencing significant confusion or stress about the child's gender identity, expression, or both (Ashley, 2019c; Ehrensaft, 2018); 3) need guidance related to emotional and behavioral concerns regarding the gender diverse child (Barrow & Apostle, 2018; 4) need support to promote affirming environments outside of the home (e.g., school, sports, camps) (Kaufman & Tishelman, 2018); 5) are seeking assistance to make informed decisions about social transition, including how to do so in a way that is optimal for a child's gender development and health (Lev & Wolf-Gould, 2018); 6) are seeking guidance for dealing with condemnation from others, including political entities and accompanying legislation, regarding their support for their gender diverse child (negative reactions directed toward parents/caregivers can sometimes include rejection and/or harassment/abuse from the social environment arising from affirming decisions (Hidalgo & Chen, 2019); 7) are seeking to process their own emotional reactions and needs about their child's gender identity, including grief about their child's gender diversity and/or potential fears or anxieties for their child's current and future well-being (Pullen Sansfaçon et al., 2019); and 8) are emotionally distressed and/or in conflict with other family members regarding the child's gender diversity (as needed, HCPs can provide separate sessions for parents/caregivers, siblings and extended family members for support, guidance, and/or psychoeducation) (McLaughlin & Sharp, 2018; Pullen Sansfaçon et al., 2019; Spivey & Edwards-Leeper, 2019).

Statement 7.9

We recommend health care professionals offering consultation, psychotherapy, or both to gender diverse children and families/caregivers work with other settings and individuals important to the child to promote the child's resilience and emotional well-being.

Consistent with the ecological model described above and, as appropriate, based on individual/family circumstances, it can be extremely helpful for HCPs to prioritize coordination with important others (e.g., teachers, coaches, religious leaders) in a child's life to promote emotional and physical safety across settings (e.g., school settings, sports and other recreational activities, faith-based involvement) (Kaufman & Tishelman, 2018). Therapeutic and/or support groups are often recommended as a valuable resource for families/caregivers and/or gender diverse children themselves (Coolhart, 2018; Horton et al., 2021; Malpas et al., 2018; Murchison et al., 2016).

Statement 7.10

We recommend HCPs offering consultation, psychotherapy, or both to gender diverse children and families/caregivers provide both parties with age appropriate psycho-education about gender development.

Parents/caregivers and their gender diverse child should have the opportunity to develop knowledge regarding ways in which families/caregivers can best support their child to maximize resilience, self-awareness, and functioning (APA, 2015; Ehrensaft, 2018; Malpas, 2018; Spivey & Edwards-Leeper, 2019). It is neither possible nor is it the role of the HCP to predict with certainty the child's ultimate gender identity; instead, the HCP's task is to provide a safe space for the child's identity to develop and evolve over time without attempts to prioritize any particular developmental trajectory with regard to gender (APA, 2015; Spivey & Edwards-Leeper, 2019). Gender diverse children and early adolescents have different needs and experiences than older adolescents, socially and physiologically, and those differences should be reflected in the individualized approach HCPs

provide to each child/family (Keo-Meir & Ehrensaft, 2018; Spencer, Berg et al., 2021).

Parents/caregivers and their children should also have the opportunity to develop knowledge about gender development and gender literacy through age-appropriate psychoeducation (Berg & Edwards-Leeper, 2018; Rider, Vencill et al., 2019; Spencer, Berg et al., 2021). Gender literacy involves understanding the distinctions between sex designated at birth, gender identity, and gender expression, including the ways in which these three factors uniquely come together for a child (Berg & Edwards-Leeper, 2018; Rider, Vencill et al., 2019; Spencer, Berg et al., 2021). As a child gains gender literacy, they begin to understand their body parts do not necessarily define their gender identity and/or their gender expression (Berg & Edwards-Leeper, 2018; Rider, Vencill et al., 2019; Spencer, Berg et al., 2021). Gender literacy also involves learning to identify messages and experiences related to gender within society. As a child gains gender literacy, they may view their developing gender identity and gender expression more positively, promoting resilience and self-esteem, and diminishing risk of shame in the face of negative messages from the environment. Gaining gender literacy through psychoeducation may also be important for siblings and/or extended family members who are important to the child (Rider, Vencill et al., 2019; Spencer, Berg et al., 2021).

Statement 7.11

We recommend health care professionals provide information to gender diverse children and their families/caregivers as the child approaches puberty about potential gender-affirming medical interventions, the effects of these treatments on future fertility, and options for fertility preservation.

As a child matures and approaches puberty, HCPs should prioritize working with children and their parents/caregivers to integrate psychoeducation about puberty, engage in shared decision-making about potential gender-affirming medical interventions, and discuss fertility-related and other reproductive health implications of medical treatments (Nahata, Quinn et al., 2018; Spencer, Berg et al., 2021). Although only limited empirical research exists to evaluate such interventions, expert consensus and developmental psychological literature generally support the notion that open communication with children about their bodies and preparation for physiological changes of puberty, combined with gender-affirming acceptance, will promote resilience and help to foster positive sexuality as a child matures into adolescence (Spencer, Berg et al., 2019). All these discussions may be extended (e.g., starting earlier) to include neurodivergent children, to ensure there is enough time for reflection and understanding, especially as choices regarding future gender- affirming medical care potentially arise (Strang, Jarin et al., 2018). These discussions could include the following topics:

- Review of body parts and their different functions;
- The ways in which a child's body may change over time with and without medical intervention;
- The impact of medical interventions on later sexual functioning and fertility;
- The impact of puberty suppression on potential later medical interventions;
- Acknowledgment of the current lack of clinical data in certain areas related to the impacts of puberty suppression;
- The importance of appropriate sex education prior to puberty.

These discussions should employ developmentally appropriate language and teaching styles, and be geared to the specific needs of each individual child (Spencer, Berg et al., 2021).

Statement 7.12

We recommend parents/caregivers and health care professionals respond supportively to children who desire to be acknowledged as the gender that matches their internal sense of gender identity.

Gender social transition refers to a process by which a child is acknowledged by others and has the opportunity to live publicly, either in all situations or in certain situations, in the gender identity they affirm and has no singular set of parameters or actions (Ehrensaft et al., 2018).

Gender social transition has often been conceived in the past as binary—a girl transitions to a boy, a boy to a girl. The concept has expanded to include children who shift to a nonbinary or individually shaped iteration of gender identity (Chew et al., 2020; Clark et al., 2018). Newer research indicates the social transition process may serve a protective function for some prepubescent children and serve to foster positive mental health and well-being (Durwood et al., 2017; Gibson et al., 2021; Olson et al., 2016). Thus, recognition that a child's gender may be fluid and develop over time (Edwards-Leeper et al., 2016; Ehrensaft, 2018; Steensma, Kreukels et al., 2013) is not sufficient justification to negate or deter social transition for a prepubescent child when it would be beneficial. Gender identity evolution may continue even after a partial or complete social transition process has taken place (Ashley, 2019e; Edwards-Leeper et al., 2018; Ehrensaft, 2020; Ehrensaft et al., 2018; Spivey & Edwards-Leeper, 2019). Although empirical data remains limited, existing research has indicated children who are most assertive about their gender diversity are most likely to persist in a diverse gender identity across time, including children who socially transition prior to puberty (Olson et al., 2022; Rae et al., 2019; Steensma, McGuire et al., 2013). Thus, when considering a social transition, we suggest parents/caregivers and HCPs pay particular attention to children who consistently and often persistently articulate a gender identity that does not match the sex designated at birth. This includes those children who may explicitly request or desire a social acknowledgement of the gender that better matches the child's articulated gender identity and/or children who exhibit distress when their gender as they know it is experienced as incongruent with the sex designated at birth (Rae et al., 2019; Steensma, Kreukels et al., 2013).

Although there is a dearth of empirical literature regarding best practices related to the social transition process, clinical literature and expertise provides the following guidance that prioritizes a child's best interests (Ashley, 2019e; Ehrensaft, 2018; Ehrensaft et al, 2018; Murchison et al., 2016; Telfer et al., 2018): 1) social transition should originate from the child and reflect the child's wishes in the process of making the decision to initiate a social transition process; 2) an HCP may assist exploring the advantages/benefits, plus potential challenges of social transition; 3) social transition may best occur in all or in specific contexts/settings only (e.g., school, home); and 4) a child may or may not choose to disclose to others that they have socially transitioned, or may designate, typically with the help of their parents/caregivers, a select group of people with whom they share the information.

In summary, social transition, when it takes place, is likely to best serve a child's well-being when it takes place thoughtfully and individually for each child. A child's social transition (and gender as well) may evolve over time and is not necessarily static, but best reflects the cross-section of the child's established self-knowledge of their present gender identity and desired actions to express that identity (Ehrensaft et al., 2018).

A social transition process can include one or more of a number of different actions consistent with a child's affirmed gender (Ehrensaft et al., 2018), including:

- Name change;
- Pronoun change;
- Change in sex/gender markers (e.g., birth certificate; identification cards; passport; school and medical documentation; etc.);
- Participation in gender-segregated programs (e.g., sports teams; recreational clubs and camps; schools; etc.);
- Bathroom and locker room use;
- Personal expression (e.g., hair style; clothing choice; etc.);
- Communication of affirmed gender to others (e.g., social media; classroom or school announcements; letters to extended families or social contacts; etc.).

Statement 7.13

We recommend health care professionals and parents/caregivers support children to continue to explore their gender throughout the pre-pubescent years, regardless of social transition.

It is important children who have engaged in social transition be afforded the same opportunities as other children to continue considering

meanings and expressions of gender throughout their childhood years (Ashley 2019e; Spencer, Berg et al., 2021). Some research has found children may experience gender fluidity or even detransition after an initial social transition. Research has not been conclusive about when in the life span such detransition is most likely to occur, or what percentage of youth will eventually experience gender fluidity and/or a desire to detransition—due to gender evolution, or potentially other reasons (e.g., safety concerns; gender minority stress) (Olson et al., 2022; Steensma, Kreukels et al., 2013). A recent research report indicates in the US, detransition occurs with only a small percentage of youth five years after a binary social transition (Olson et al., 2022); further follow-up of these young people would be helpful. Replication of these findings is important as well since this study was conducted with a limited and self-selected participant pool in the US and thus may not be applicable to all gender diverse children. In summary, we have limited ability to know in advance the ways in which a child's gender identity and expressions may evolve over time and whether or why detransition may take place for some. In addition, not all gender diverse children wish to explore their gender (Telfer et al., 2018). Cisgender children are not expected to undertake this exploration, and therefore attempts to force this with a gender diverse child, if not indicated or welcomed, can be experienced as pathologizing, intrusive and/or cisnormative (Ansara & Hegarty, 2012; Bartholomaeus et al., 2021; Oliphant et al., 2018).

Statement 7.14

We recommend health care professionals discuss the potential benefits and risks of a social transition with families who are considering it.

Social transition in prepubescent children consists of a variety of choices, can occur as a process over time, is individualized based on both a child's wishes and other psychosocial considerations (Ehrensaft, 2018), and is a decision for which possible benefits and challenges should be weighted and discussed.

A social transition may have potential benefits as outlined in clinical literature (e.g., Ehrensaft et al., 2018) and supported by research (Fast & Olson, 2018; Rae et al., 2019). These include facilitating gender congruence while reducing gender dysphoria and enhancing psychosocial adjustment and well-being (Ehrensaft et al., 2018). Studies have indicated socially transitioned gender diverse children largely mirror the mental health characteristics of age matched cisgender siblings and peers (Durwood et al., 2017). These findings differ markedly from the mental health challenges consistently noted in prior research with gender diverse children and adolescents (Barrow & Apostle, 2018) and suggest the impact of social transition may be positive. Additionally, social transition for children typically can only take place with the support and acceptance of parents/caregivers, which has also been demonstrated to facilitate well-being in gender diverse children (Durwood et al., 2021; Malpas et al., 2018; Pariseau et al., 2019), although other forms of support, such as school-based support, have also been identified as important (Durwood et al., 2021; Turban, King et al., 2021). HCPs should discuss the potential benefits of a social transition with children and families in situations in which 1) there is a consistent, stable articulation of a gender identity that is incongruent with the sex assigned at birth (Fast & Olson, 2018). This should be differentiated from gender diverse expressions/behaviors/interests (e.g., playing with toys, expressing oneself through clothing or appearance choices, and/or engaging in activities socially defined and typically associated with the other gender in a binary model of gender) (Ehrensaft, 2018; Ehrensaft et al., 2018); 2) the child is expressing a strong desire or need to transition to the gender they have articulated as being their authentic gender (Ehrensaft et al., 2018; Fast & Olson, 2018; Rae et al., 2019); and 3) the child will be emotionally and physically safe during and following transition (Brown & Mar, 2018). Prejudice and discrimination should be considerations, especially in localities where acceptance of gender diversity is limited or prohibited (Brown & Mar, 2018; Hendricks & Testa, 2012; Turban, King et al., 2021). Of note, there can also be possible risks to a gender diverse child who does not socially transition, including 1) being ostracized or bullied for being perceived as not conforming to prescribed community

gender roles and/or socially expected patterns of behavior; and 2) living with the internal stress or distress that the gender they know themselves to be is incongruent with the gender they are being asked to present to the world.

To promote gender health, the HCP should discuss the potential challenges of a social transition. One concern often expressed relates to fear that a child will preclude considering the possible evolution of their gender identity as they mature or be reluctant to initiate another gender transition even if they no longer feel their social transition matches their current gender identity (Edwards-Leeper et al., 2016; Ristori & Steensma, 2016). Although limited, recent research has found some parents/caregivers of children who have socially transitioned may discuss with their children the option of new gender iterations (for example, reverting to an earlier expression of gender) and are comfortable about this possibility (Olson et al., 2019). Another often identified social transition concern is that a child may suffer negative sequelae if they revert to the former gender identity that matches their sex designated at birth (Chen et al., 2018; Edwards-Leeper et al., 2019; Steensma & Cohen-Kettenis, 2011). From this point of view, parents/caregivers should be aware of the potential developmental effect of a social transition on a child.

HCPs should provide guidance to parents/caregivers and supports to a child when a social gender transition is being considered or taking place by 1) providing consultation, assessment, and gender supports when needed and sought by the parents/caregivers; 2) aiding family members, as needed, to understand the child's desires for a social transition and the family members' own feelings about the child's expressed desires; 3) exploring with, and learning from, the parents/caregivers whether and how they believe a social transition would benefit their child both now and in their ongoing development; 4) providing guidance when parents/caregivers are not in agreement about a social transition and offering the opportunity to work together toward a consistent understanding of their child's gender status and needs; 5) providing guidance about safe and supportive ways to disclose their child's social transition to others and to facilitate their child transitioning in their various social environments (e.g., schools, extended family); 6) facilitating communication, when desired by the child, with peers about gender and social transition as well as fortifying positive peer relationships; 7) providing guidance when social transition may not be socially accepted or safe, either everywhere or in specific situations, or when a child has reservations about initiating a transition despite their wish to do so; there may be multiple reasons for reservations, including fears and anxieties; 8) working collaboratively with family members and MHPs to facilitate a social transition in a way that is optimal for the child's unfolding gender development, overall well-being, and physical and emotional safety; and 9) providing psychoeducation about the many different trajectories the child's gender may take over time, leaving pathways open to future iterations of gender for the child, and emphasizing there is no need to predict an individual child's gender identity in the future (Malpas et al., 2018).

All of these tasks incorporate enhancing the quality of communication between the child and family members and providing an opportunity for the child to be heard and listened to by all family members involved. These relational processes in turn facilitate the parents/caregivers' success in making informed decisions about the advisability and/or parameters of a social transition for their child (Malpas et al., 2018).

One role of HCPs is to provide guidance and support in situations in which children and parents/caregivers wish to proceed with a social transition but conclude that the social environment would not be accepting of those choices, by 1) helping parents/caregivers define and extend safe spaces in which the child can express their authentic gender freely; 2) discussing with parents/caregivers ways to advocate that increase the likelihood of the social environment being supportive in the future, if this is a realistic goal; 3) intervening as needed to help the child/family with any associated distress and/or shame brought about by the continued suppression of authentic gender identity and the need for secrecy; and 4) building both the child's and the family's resilience, instilling the understanding that if the social environment is having difficulty accepting a child's social transition and affirmed gender identity, it is not because of some shortcoming in the child but because of

insufficient gender literacy in the social environment (Ehrensaft et al., 2018).

Statement 7.15

We suggest health care professionals consider working collaboratively with other professionals and organizations to promote the well-being of gender diverse children and minimize the adversities they may face.

All children have the right to be supported and respected in their gender identities (Human Rights Campaign, 2018; Paré, 2020; SAMHSA, 2015). As noted above, gender diverse children are a particularly vulnerable group (Barrow & Apostle, 2018; Cohen-Kettenis et al., 2003; Giovanardi et al., 2018; Gower, Rider, Coleman et al., 2018; Grossman & D'Augelli, 2007; Hendricks & Testa, 2012; Reisner, Greytak et al., 2015; Ristori & Steensma, 2016; Roberts et al., 2012; Tishelman & Neumann-Mascis, 2018). The responsibilities of HCPs as advocates encompass acknowledging social determinants of health are critical for marginalized minorities (Barrow & Mar, 2018; Hendricks & Testa, 2012). Advocacy is taken up by all HCPs in the form of child and family support (APA, 2015; Malpas et al., 2018). Some HCPs may be called on to move beyond their individual offices or programs to advocate for gender diverse children in the larger community, often in partnership with stakeholders, including parents/caregivers, allies, and youth (Kaufman & Tishelman, 2018; Lopez et al., 2017; Vanderburgh, 2009). These efforts may be instrumental in enhancing children's gender health and promoting their civil rights (Lopez et al., 2017).

HCP's voices may be essential in schools, in parliamentary bodies, in courts of law, and in the media (Kuvalanka et al., 2019; Lopez et al., 2017; Whyatt-Sames, 2017; Vanderburgh, 2009). In addition, HCPs may have a more generalized advocacy role in acknowledging and addressing the frequent intentional or unintentional negating of the experience of gender diverse children that may be transmitted or communicated by adults, peers, and in media (Rafferty et al., 2018). Professionals who possess the skill sets and find themselves in appropriate situations can provide clear de-pathologizing statements on the needs and rights of gender diverse children and on the damage caused by discriminatory and transphobic rules, laws, and norms (Rafferty et al., 2018).

CHAPTER 8 Nonbinary

Nonbinary is used as an umbrella term referring to individuals who experience their gender as outside of the gender binary. The term nonbinary is predominantly but not exclusively associated with global north contexts and may sometimes be used to describe indigenous and non-Western genders. The term nonbinary includes people whose genders are comprised of more than one gender identity simultaneously or at different times (e.g., bigender), who do not have a gender identity or have a neutral gender identity (e.g., agender or neutrois), have gender identities that encompass or blend elements of other genders (e.g., polygender, demiboy, demigirl), and/or who have a gender that changes over time (e.g., genderfluid) (Kuper et al., 2014; Richards et al., 2016; Richards et al., 2017; Vincent, 2019). Nonbinary people may identify to varying degrees with binary-associated genders, e.g., nonbinary man/woman, or with multiple gender terms, e.g., nonbinary and genderfluid (James et al., 2016; Kuper et al., 2012). Nonbinary also functions as a gender identity in its own right (Vincent, 2020). It is important to acknowledge this is not an exhaustive list, the same identities can have different meanings for different people, and the use of terms can vary over time and by location.

Genderqueer, first used in the 1990s, is an identity category somewhat older than nonbinary—which first emerged in approximately the late 2000s (Nestle et al., 2002; Wilchins, 1995). Genderqueer may sometimes be used synonymously with nonbinary or may communicate a specific consciously politicized dimension to a person's gender. While transgender is used in many cultural contexts as an umbrella term inclusive of nonbinary people, not all nonbinary people consider themselves to be transgender for a range of reasons, including because they consider being transgender to be exclusively within the gender binary or because they do not feel "trans enough" to describe themselves as transgender (Garrison, 2018). Some nonbinary people are unsure or ambivalent about whether they would describe themselves as transgender (Darwin, 2020; Vincent, 2019).

In the context of the English language, nonbinary people may use the pronouns they/them/theirs, or neopronouns which include e/em/eir, ze/zir/hir, er/ers/erself among others (Moser & Devereux, 2019; Vincent, 2018). Some nonbinary people use a combination of pronouns (either deliberately mixing usage, allowing free choice, or changing with social context), or prefer to avoid gendered pronouns entirely, instead using their name. Additionally, some nonbinary people use she/her/hers, or he/him/his, sometimes or exclusively, whilst in some regions in the world descriptive language for nonbinary people does not (yet) exist. In contexts outside of English, a wide range of culturally specific linguistic adaptations and evolutions can be observed (Attig, 2022; Kirey-Sitnikova, 2021; Zimman, 2020). Also of note, some languages use one pronoun that is not associated with sex or gender while others gender all nouns. These variations in language are likely to influence nonbinary people's experience of gender and how they interact with others.

Recent studies suggest nonbinary people comprise roughly 25% to over 50% of the larger transgender population, with samples of youth reporting the highest percentage of nonbinary people (Burgwal et al., 2019; James et al., 2016; Watson, 2020). In recent studies of transgender adults, nonbinary people tend to be younger than transgender men and transgender women and in studies of both youth and adults, nonbinary people are more likely to have been assigned female at birth (AFAB). However, these findings should be interpreted with caution as there are likely a number of complex, sociocultural factors influencing the quality, representativeness, and accuracy of this data (Burgwal et al., 2019; James et al., 2016; Watson, 2020; Wilson & Meyer, 2021) (see also Chapter 3—Population Estimates).

Understanding gender identities and gender expressions as a non-linear spectrum

Nonbinary genders have long been recognized historically and cross-culturally (Herdt, 1994; McNabb, 2017; Vincent & Manzano, 2017). Many gender identity categories are culturally specific and cannot be easily translated from their context, either linguistically or in relation to the Western paradigm of gender. Historical settler colonial interactions with indigenous people with

non-Western genders remain highly relevant as cultural erasure and the intersections of racism and cisnormativity may detrimentally inform the social determinants of health of indigenous gender diverse people. From the 1950s, gender was used to reference the socially constructed categorization of behaviors, activities, appearance, etc. in relation to a binary model of male/man/masculine, and female/woman/feminine within contemporary Western contexts. However, gender now has a wider range of possible meanings, appreciating interrelated yet distinguishable concepts, including gendered biology (sex), gender roles, gender expression, and gender identity (Vincent, 2020). Aspects of gender expression that might traditionally be understood culturally as "masculine", "feminine", or "androgynous" may be legitimately expressed among people of any and all gender identities, whether nonbinary or not. For example, a nonbinary individual presenting in a feminine manner cannot be taken to imply they will necessarily later identify as a woman or access interventions associated with transgender women, such as vaginoplasty. A person's gender nonconformity in relation to cultural expectations should neither be viewed as a cause for concern nor assumed to be indicative of clinical complexity—for example, a nonbinary person assigned male at birth (AMAB) wearing feminine-coded clothing, using she/her pronouns, but keeping a masculine-coded first name.

Modeling gender as a spectrum offers greater nuance than a binary model. However, there remain significant limitations in a linear spectrum model that can lead to uncritical generalizations about gender. For example, while it is intuitive to position the "binary options" (man/male, woman/female) at either end of such a continuum, doing so situates masculinity as oppositional to femininity, failing to accommodate gender neutrality, the expression of masculinity and femininity simultaneously, and genderqueer or non-Western concepts of gender. It is essential HCPs do not view nonbinary genders as "partial" articulations of transgender manhood (in nonbinary people AFAB) or transgender womanhood (in nonbinary people AMAB), or definitively as "somewhere along the spectrum of masculinity/femininity"; some nonbinary individuals consider themselves outside male/female dichotomization altogether. A *non-linear* spectrum indicates differences of gender expression, identity, or needs around gender affirmation between clients should not be compared for the purposes of situating them along a linear spectrum. Additionally, the interpretation of gender expression is subjective and culturally defined, and what may be experienced or viewed as highly feminine by one person may not be viewed as such by another (Vincent, 2020). HCPs benefit from avoiding assumptions about how each client conceptualizes their gender and by being prepared to be led by a given client's personal understanding of gender as it relates to the client's gender identity, expression, and any need for medical care.

The gender development process experienced by all transgender and gender diverse (TGD) people regardless of their relationship to a gender binary appear to share similar themes (e.g., awareness, exploration, meaning making, integration), but the timing, progression, and personal experiences associated with each of these processes vary both within and across groups of transgender and nonbinary people (Kuper, Wright et al., 2018; Kuper, Lindley et al., 2019; Tatum et al., 2020). Sociocultural and intersectional perspectives can be helpful at contextualizing gender development and social transition, including how individual experiences are shaped by the social and cultural context and how they interact with additional domains of identity and personal experience.

The need for access to gender-affirming care

Some nonbinary people seek gender-affirming care to alleviate gender dysphoria or incongruence and increase body satisfaction through medically necessary interventions (see medically necessary statement in Chapter 2—Global Applicability, Statement 2.1). Some nonbinary people may feel a certain treatment is necessary for them—see also Chapter 5—Assessment of Adults (Beek et al., 2015; Jones et al., 2019; Köhler et al., 2018), whilst others do not (Burgwal & Motmans, 2021; Nieder, Eyssel et al., 2020), and the proportion of nonbinary people who seek gender-affirming care and the specific goals of

that care, remains unclear. It is the role of the health care professional to provide information about existing medical options (and their availability) that might help alleviate gender dysphoria or incongruence and increase body satisfaction without making assumptions about which treatment options may best fit each individual person.

Motivations for accessing (or not accessing) gender-affirming medical interventions, including hormone treatment, surgeries, or both are heterogeneous and potentially complex (Burgwal & Motmans, 2021; Vincent, 2019, 2020) and should be explored collaboratively before making decisions about physical interventions. The need of an individual to access gender-affirming medical procedures cannot be predicted by their gender role, expression, or identity. For example, some transgender women have no need of vaginoplasty, while some nonbinary individuals AMAB may need and benefit from that same intervention. Further, nonbinary people seeking gender-affirming care associated closely with a transition pathway from their assigned sex/gender to the other binarily-recognized category (i.e., estrogen therapy and vaginoplasty for someone AMAB) does not undermine the validity of their nonbinary identity.

While barriers to care remain widespread for many transgender people, nonbinary people appear to experience particularly high rates of difficulty accessing both mental health and gender-affirming medical care (Clark et al., 2018; James, 2016). Many nonbinary people report having experiences with health care professionals who were not affirming of their nonbinary gender, including experiences where health care professionals convey beliefs that their gender is not valid, or they are fundamentally more difficult to provide care for (Valentine, 2016; Vincent, 2020). Nonbinary people may face provider assumptions that they do not need or want gender-affirming treatment (Kcomt et al., 2020; Vincent, 2020) and have described experiencing pressure to present themselves as transgender men or transgender women (within a binary framework of gender) in order to access treatment (Bradford et al., 2019; Taylor et al., 2019). At times, nonbinary people find themselves educating the provider from whom they are seeking services despite the inappropriateness of providers relying primarily on their patients for education (Kcomt et al., 2020). In comparison to transgender men and transgender women, Burgwal and Motmans (2021) found that nonbinary people experienced more fear of prejudice from health care providers, less confidence in the services provided, and greater difficulty knowing where to go to for care. Studies in both Europe and US have shown that nonbinary individuals tend to delay care more often than binary transgender men or transgender women, with fear of insensitive or incompetent treatment being the most cited reason (Burgwal & Motmans, 2021; Grant et al., 2011). Nonbinary people also appear less likely to disclose their gender identity to their health care providers than other transgender people (Kcomt et al., 2020).

The need for an appropriate level of support

Providing gender-affirming care to nonbinary people goes beyond the provision of specific gender-affirming interventions such as hormone therapy or surgery and involves supporting the overall health and development of nonbinary people. Minority stress models have been adapted to conceptualize how the gender-related stressors experienced by transgender people are associated with physical and mental health disparities (Delozier et al., 2020; Testa et al., 2017). Nonbinary people appear to experience minority stressors that are both similar to and unique from those experienced by transgender men and transgender women. Johnson (2020) reported that experiences of invalidation are particularly high among nonbinary people, e.g., statements or actions conveying a belief that nonbinary identities are not "real" or are the result of a "fad" or "phase," and nonbinary people appear less likely than transgender men and transgender women to have their correct pronouns used by others. Similarly, nonbinary people have described feeling "invisible" to others (Conlin, 2019; Taylor, 2018) and one study found that nonbinary youth reported lower levels of self-esteem in comparison to young transgender men and transgender women (Thorne, Witcomb et al., 2019).

While many TGD people report experiences of discrimination, victimization, and interpersonal rejection (James, 2016) including bullying within

samples of youth (Human Rights Campaign, 2018; Witcomb et al., 2019), the prevalence of these experiences may vary across groups and appears influenced by additional intersecting characteristics. For example, Newcomb (2020) found transgender women and nonbinary youth AMAB experienced higher levels of victimization than transgender men and nonbinary youth AFAB, with nonbinary youth AMAB reporting the highest levels of traumatic stress. In a second study, Poquiz (2021) found transgender men and transgender women experienced higher levels of discrimination than nonbinary people. This intersectional complexity is also likely contributing to the variability in findings from studies comparing the physical and mental health of nonbinary and transgender men and transgender women, with some studies indicating more physical and mental health concerns among nonbinary people, some reporting less concerns, and some reporting no difference between groups (Scandurra, 2019).

Given nonbinary identity narratives may be less widely available than more binary-oriented identity narratives, nonbinary people may have less resources available to explore and articulate their gender-related sense of self. For example, this might include access to community spaces and interpersonal relationships where nonbinary identity can be explored, or access to language and concepts that allow more nuanced consideration of nonbinary experiences (Bradford et al., 2018; Fiani & Han, 2019; Galupo et al., 2019). Clinical guidance is now developing to assist providers in adapting gender-affirming therapeutic care to meet these unique experiences of nonbinary people (Matsuno, 2019; Rider, Vencill et al., 2019).

Gender-affirming medical interventions for nonbinary people

In contexts where a particular medical intervention does not have established precedent, it is important that before the intervention is considered, the individual is provided with an overview of the available information, including recognition of potential knowledge limits. It is equally important to undertake and document a comprehensive discussion of the physical changes needed and the potential limitations in achieving those attributes, as well as the implication that any given intervention may or may not enhance an individual's ability to express their gender.

With regards to estrogen therapy for nonbinary people AMAB, it is important to note the possibility of breast growth cannot be avoided (Seal, 2017). Although the extent of growth is highly variable, this should be made clear if a nonbinary person seeks some of the other changes associated with estrogen therapy (such as softening of skin and reduction in facial hair growth) but does not want or is ambivalent about breast growth. Likewise, for nonbinary people AFAB who may wish to access testosterone to acquire some changes but not others, it should be recognized that if facial hair development is needed, genital growth is inevitable (Seal, 2017). The time frame for taking testosterone means these changes are likely also to be accompanied by an irreversible vocal pitch drop, although the extent of each is individual (Vincent, 2019; Ziegler et al., 2018). A vocal pitch drop without the development of body hair is another such challenge. For some nonbinary people, hair removal is a very important part of their gender affirmation (Cocchetti, Ristori, Romani et al., 2020).

If hormonal therapy is discontinued and gonads are retained, many physical changes will revert to pre-hormone therapy status as gonadal hormones once again take effect, including reversal of amenorrhea and body hair development in nonbinary people AFAB and reduction in muscular definition and erectile dysfunction in nonbinary people AMAB. Other changes will be permanent such as "male-pattern" baldness, genital growth, and facial hair growth in nonbinary people AFAB or breast development in nonbinary people AMAB (Hembree et al., 2017). These will require further interventions to reverse, such as electrolysis or mastectomy and are sometimes described as "partially reversible" (Coleman et al., 2012). As the implications of using low-dose hormone therapy are not documented in this patient population, it is important to consider monitoring for cardiovascular risk and bone health if low-dose hormone therapy is used. For more detailed information see Chapter 12—Hormone Therapy.

If neither testosterone nor estrogen expression is needed, inhibition of estrogen and/or testosterone

Statements of Recommendations

8.1- We recommend health care professionals provide nonbinary people with individualized assessment and treatment that affirms their experience of gender.
8.2- We recommend health care professionals consider gender-affirming medical interventions (hormonal treatment or surgery) for nonbinary people in the absence of "social gender transition."
8.3- We recommend health care professionals consider gender-affirming surgical interventions in the absence of hormonal treatment, unless hormone therapy is required to achieve the desired surgical result.
8.4- We recommend health care professionals provide information to nonbinary people about the effects of hormonal therapies/surgery on future fertility and discuss the options for fertility preservation prior to starting hormonal treatment or undergoing surgery.

production is possible. The implications of this with regards to increased cardiovascular risk, reduced bone mineralization, and risk of depression should be discussed and measures taken to mitigate risk (Brett et al., 2007; Vale et al., 2010; Wassersug & Johnson, 2007). For more information see also Chapter 9—Eunuchs and Chapter 12—Hormone Therapy. Exploration of medical and/or social transition independently of each other and options to explore hormones, surgery, or both independently of each other should be available to everyone, whether the person is a transgender man, transgender woman, or a nonbinary person.

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 8.1

We recommend health care professionals provide nonbinary people with individualized assessment and treatment that affirms their nonbinary experiences of gender.

An individualized assessment with a nonbinary person starts with an understanding of how they experience their own gender and how this impacts their goals for the care they are seeking. How individuals conceptualize their gender-related experiences are likely to vary across groups and cultures and may incorporate experiences associated with other intersecting aspects of identity (e.g., age, sexuality, race, ethnicity, socioeconomic status, disability status) (Kuper et al., 2014; Subramanian et al., 2016).

HCPs should avoid making a priori assumptions about any client's gender identity, expression, or needs for care. They should also be mindful that a client's nonbinary experience of gender may or may not be relevant to the assessment and treatment-related goals. The extent to which the client's gender is relevant to their treatment goals should determine the level of detail at which their gender identity is explored. For example, when seeking care for a presenting concern wholly unrelated to gender, simply determining the correct name and pronouns may be sufficient (Knutson et al., 2019). When addressing a concern for which current or past hormonal or surgical status is relevant, more detail may be needed, even if the concern is not specifically gender-related.

Clinical settings need to be welcoming, reflective of the diversity of genders, and affirm the experiences of gender of nonbinary people to be culturally competent. Ensuring clinic and provider information (e.g., websites), forms (e.g., intake surveys), and other materials are inclusive of nonbinary identities and experiences conveys that nonbinary people are welcome and recognized (Hagen & Galupo, 2014). Using free text fields for gender identity and pronouns is more inclusive than using a list of response options. Ensuring privacy at the reception desk, setting up alternatives for listing legal names in digital databases (in cultural contexts where this is necessary), installing gender-neutral toilets, and setting up alternatives to calling out the legal name in the waiting room are additional examples of transgender and gender diverse (TGD) cultural competency (Burgwal et al., 2021). In care settings, it is important preferences for names, pronouns, and other gender-related terms are asked and used both initially and on a regular basis as they may vary over time and circumstance.

HCPs are encouraged to adopt an approach that focuses on strengths and resilience.

Increasingly, critiques are emerging regarding HCPs over-focus on gender-related distress as it is also important to consider experiences of increased comfort, joy, and self-fulfilment that can result from self-affirmation and access to care (Ashley, 2019a; Benestad, 2010). In addition to utilizing diagnoses when/where required to facilitate access to care, HCPs are encouraged to collaboratively explore with clients this broader range of potential gender-related experiences and how they may fit with treatment options (Motmans et al., 2019). For all TGD people, resiliency factors such as supportive relationships, participation in communities that include similar others, and identity pride are essential to consider as they are associated with a range of positive health outcomes (Bowling et al., 2019; Budge, 2015; Johns et al., 2018).

Awareness of the limitations that exist in the tools providers have historically used to assess transgender people's experience of dysphoria is important as they may be particularly pronounced for many nonbinary people. Most gender-related measures assume clients experience their gender in a binary way, among other concerns (e.g., Recalled Gender Identity Scale, Utrecht Gender Dysphoria Scale). While several newer measures have been developed in an attempt to better capture the experiences of nonbinary people (McGuire et al., 2018; McGuire et al., 2020), open-ended discussion is likely to provide a deeper and more accurate understanding of each individual's unique experiences of dysphoria and their associated care needs. Similarly, while more recent iterations of diagnostic categories (i.e., "gender dysphoria" in the DSM 5 and "gender incongruence" in ICD-11) were intended to be inclusive of people with nonbinary experiences of gender, they may not adequately capture the full diversity and scope of experiences of gender-related distress, particularly for nonbinary people. In addition to distress associated with aspects of one's physical body and presentation (including features that may be existing or absent), distress may arise from how one experiences their own gender, how one's gender is perceived within social situations, and from experiences of minority stress associated with one's gender (Winters & Ehrbar, 2010). Nonbinary peoples' experiences in each of these areas may or may not be similar to those of transgender men or women.

A person-centered approach for affirming care includes specific discussion of how different interventions may or may not shift the client's comfort with their own experience of gender, and how their gender is perceived by others. Nonbinary people can face challenges in reconciling their personal identities with the limits of the medical treatments available and can also encounter confusion and intolerance from society regarding their gender presentations (Taylor et al., 2019). Emerging research suggests the medical treatment needs of nonbinary people are particularly diverse, with some reporting needs for treatments that have typically been associated with transition trajectories historically associated with transgender men and women and some reporting alternative approaches (e.g., low dose hormone therapy, surgery without hormone therapy), some reporting a lack of interest in medical treatment, and some reporting feeling unsure about their needs (Burgwal & Motmans, 2021; James et al., 2016). Conceptualizing assessment as an ongoing process is particularly important given gender-related experiences and associated needs may shift throughout the lifespan. Given the ongoing evolution in treatment options and knowledge of treatment effects, particularly for nonbinary people, clients will benefit from providers who regularly seek up-to-date knowledge and convey these updates to their clients.

Statement 8.2

We recommend health care professionals consider medical interventions (hormonal treatment or surgery) for nonbinary people in the absence of "social gender transition."

Previous requirements for accessing hormonal treatment and surgery, such as "living in a gender role that is congruent with one's gender identity," do not reflect the lived experiences of many TGD people (Coleman et al., 2012). Due to the entrenched nature of the gender binary in most contemporary Western cultures, one can typically only be understood by others as a man or woman within most settings (Butler, 1993). Hence, the visibility and understanding of nonbinary embodiments and expressions is limited. This is due to gendered cues

being almost always understood in reference to a gender binary (Butler, 1993). Presently, it can be difficult for nonbinary people to be reliably recognized as their gender via visual cues associated with their gender expression (e.g., clothing, hair). However, androgyny or gender nonconformity may be communicated by the mixing or combining of cultural markers with traditionally masculine or feminine connotations. Because there is no commonly recognized "nonbinary category" within most contemporary Western, global north cultural contexts, nonbinary visibility often necessitates explicit sharing of one's gender with others or the use of cues that may be interpreted as gender nonconformity (but not necessarily nonbinary).

For these reasons, framing access to medical care in the context of someone experiencing a "social gender transition" where they are "living in a gender role that is congruent with one's gender identity" is not in line with the way many TGD people understand themselves and their personal transition process. For some, "living in a gender role that is congruent with one's gender identity" does not involve changes in name, pronouns, or gender expression even as medical intervention may be necessary. Even if a person is able to live in ways that are congruent with their gender identity, it may be difficult for an outside observer to assess this without learning directly from that person how they understand their own experience in this regard. Expectation of "social gender transition" may be unhelpful when considering eligibility for gender- affirming care, such as hormones and surgery, and rigid expectations of what a "social gender role transition" "should" look like can be a barrier to care for nonbinary people. There is no logical requirement gender-affirming medical interventions can only be done once a person legally changes their name, changes the gender marker on their identity documents, or wears or refrains from wearing particular items of clothing. Nonbinary people may struggle to access recognition of their genders on formal documentation, which may negatively affect their mental health or well-being (Goetz & Arcomano, 2021). TGD people may benefit from specific support in accessing (or retaining) their gender marker of preference. A requirement that someone disclose their gender identity in all circles of their lives (family, work, school, etc.) in order to access medical care may not be consistent with their goals and can place them at risk if it is not safe to do so.

Statement 8.3

We recommend health care professionals consider gender-affirming surgical interventions in the absence of hormonal treatment unless hormone therapy is required to achieve the desired surgical result.

The trajectory of "hormones before surgery" is an option across a range of surgical interventions. Some nonbinary people will seek gender-affirming surgical treatment to alleviate gender incongruence and increase body satisfaction (Beek et al., 2015; Burgwal & Motmans, 2021; Jones et al., 2019; Koehler et al., 2018), but do not want hormonal treatment or are unable to undergo hormonal therapy due to other medical reasons (Nieder, Eyssel et al., 2020). Currently, it is unknown for which proportion of nonbinary people these options apply.

Perhaps the surgery which has some specific association with nonbinary people (rather than sought by transgender men or undergone by some cisgender women) is mastectomy in nonbinary people AFAB who have not taken testosterone—although testosterone is not a requirement for this type of surgery—and some nonbinary people AFAB may need breast reduction (McTernan et al., 2020). An example of a surgery for which at least a period of hormone therapy may be necessary is metoidioplasty that enhances the enlarged clitoris produced by testosterone therapy. See Chapter 13—Surgery and Postoperative Care for more detail on whether hormone therapy is necessary for various surgeries. Procedures addressing the internal reproductive system include hysterectomy, unilateral or bilateral salpingo-oophorectomy, and vaginectomy. Hormone therapy is not required for any of these procedures, but hormone replacement therapy (either with estrogens, testosterone, or both) is advisable in those individuals undergoing a total gonadectomy to prevent adverse effects on their cardiovascular and musculoskeletal systems (Hembree et al., 2017; Seal, 2017). For phalloplasty, while there is no surgical requirement per se for a minimum period of testosterone

treatment, virilization (or the absence of virilization) of the clitoris and labia minora may impact the choice of surgical technique and influence surgical options. For more information see Chapter 13—Surgery and Postoperative Care.

Nonbinary AMAB clients should be informed commencing estrogen therapy post-surgically with no prior history of estrogen therapy may influence (perhaps adversely) the surgical result (Kanhai, Hage, Asscheman et al., 1999; Kanhai, Hage, Karim et al., 1999). Nonbinary people AMAB requesting a bilateral orchiedectomy do not require estrogen therapy to achieve a better outcome (Hembree et al., 2017). In these contexts, it is good practice to inform clients of the risks and benefits of hormone replacement therapy (estrogens, testosterone, or both) in preventing adverse effects on the cardiovascular and musculoskeletal system as well as alternative treatment options, such as calcium plus vitamin D supplementation to prevent osteoporosis (Hembree et al., 2017; Seal, 2017; Weaver et al., 2016). See also Chapter 9—Eunuchs for those who choose to forgo hormone replacement therapy. In the case of vaginoplasty, individuals should be advised lack of testosterone-blocking therapy may cause postoperative hair growth in the vagina when hair-bearing skin graft and flaps have been used (Giltay & Gooren, 2000).

Additional surgical requests for nonbinary people AMAB include penile-preserving vaginoplasty, vaginoplasty with preservation of the testicle(s), and procedures resulting in an absence of external primary sexual characteristics (i.e., penectomy, scrotectomy, orchiectomy, etc.). The surgeon and individual seeking treatment are advised to engage in discussions so as to understand the individual's goals and expectations as well as the benefits and limitations of the intended (or requested) procedure, to make decisions on an individualized basis and collaborate with other health care providers who are involved (if any).

Statement 8.4.

We recommend health care professionals provide information to nonbinary people about the effects of hormonal therapies/surgery on future fertility and discuss the options for fertility preservation prior to starting hormonal treatment or undergoing surgery.

All nonbinary individuals who seek gender-affirming hormonal therapies should be offered information and guidance about fertility options (Hembree et al., 2017; De Roo et al., 2016; Defreyne, Elaut et al., 2020; Defreyne, van Schuvlenbergh et al., 2020; Nahata et al., 2017; Quinn et al., 2021). It is important to discuss the potential impact of hormone therapy on fertility prior to initiation. This discussion should include fertility preservation options, the extent to which fertility may or may not be regained if hormone therapy is ceased, and the fact that hormone therapy per se is not birth control. For more information see Chapter 16—Reproductive Health.

Recent studies suggest that nonbinary individuals are less likely to access care and make their needs for potential interventions heard (Beek et al., 2015; Taylor et al., 2019). As such, it stands to reason that any gender diverse individual should be offered information on current options and techniques for fertility preservation, ideally prior to commencing hormonal treatment as the quality of the sperm or eggs may be impacted by exposure to hormones (Hamada et al., 2015; Payer et al., 1979). However, this should in no way preclude making inquiries and seeking more information at a later time, as there is evidence that fertility is still possible for individuals taking estrogen and testosterone (Light et al., 2014). A decision by a nonbinary or gender diverse person that fertility preservation or counseling is not needed should not be used as a basis for denying or delaying access to hormonal treatment.

CHAPTER 12 Hormone Therapy

Transgender and gender diverse (TGD) persons may require medically necessary gender-affirming hormone therapy (GAHT) to achieve changes consistent with their embodiment goals, gender identity, or both (see medically necessary statement in Chapter 2—Global Applicability, Statement 2.1). This chapter describes hormone therapy recommendations for TGD adults and adolescents. Please refer to Chapter 5—Assessment of Adults and Chapter 6—Adolescents for the assessment criteria related to initiation of hormone therapy for adults and adolescents, respectively. A summary of the recommendations and assessment criteria can be found in Appendix D.

Ever since the first World Professional Association for Transgender Health (WPATH) Standards of Care (SOC) was published in 1979 and in subsequent updates of the SOC, including SOC version 7, GAHT has been accepted as medically necessary (Coleman et al., 2012). WPATH endorsed the Endocrine Society's guidelines for GAHT for TGD persons in 2009 and 2017 (Hembree et al., 2009; Hembree et al., 2017). The European Society for Sexual Medicine has also published a position statement on hormone management in adolescent and adult TGD people (T'Sjoen et al., 2020). When provided under medical supervision, GAHT in adults is safe (Tangpricha & den Heijer, 2017; Safer & Tangpricha, 2019). However, there are some potential long-term risks, and careful monitoring and screening are required to reduce adverse events (Hembree et al., 2017; Rosenthal, 2021).

In general, the goal is to target serum levels of the sex steroids to match the levels associated with the individual's gender identity, although optimal target ranges have not been established (Hembree et al., 2017). Health care professionals (HCPs) can use serum testosterone and/or estradiol levels to monitor most sex steroid treatments. However, conjugated estrogens or synthetic estrogen use cannot be monitored. The assumption that the estrone/estradiol ratio should be monitored was not supported in a recent cohort study as there was no relationship between estrone concentration and change in body fat or breast development seen in a European cohort of 212 adult transgender women during a 1-year follow-up of hormone treatment (Tebbens et al., 2021). This study demonstrated higher estrone concentrations or higher estrone/estradiol ratios are not associated with antagonistic effects on feminization (fat percentage and breast development) (Tebbens et al., 2021). Thus, monitoring of the estrone to estradiol ratio is not supported by the current published evidence. Previously used conjugated estrogens have been abandoned in favor of bioidentical estrogens. Even if several studies have shown a significantly greater risk of thromboembolic and cardiovascular complications with the use of oral conjugated estrogens compared with oral estradiol in postmenopausal women, no randomized controlled trials have taken place, either in postmenopausal women or in transgender people undergoing estrogen treatment (Smith et al., 2014).

The approach to GAHT differs and depends on the developmental stage of the individual at the time of initiation of hormone therapy as well as their treatment goals. Hormone therapy is not recommended for children who have not begun endogenous puberty. In eligible youth (as per Chapter 6—Adolescents) who have reached the early stages of puberty, the focus is usually to delay further pubertal progression with gonadotropin releasing hormone agonists (GnRHas) until an appropriate time when GAHT can be introduced. In these cases, pubertal suppression is considered medically necessary. Eligible adults may initiate GAHT if they fulfill the criteria as per Chapter 5—Assessment for Adults. In addition, health care providers should discuss fertility goals and fertility preservation procedures prior to initiating GAHT. See Chapter 16—Reproductive Health.

GAHT with feminine embodiment goals typically consists of estrogen and an androgen-lowering medication (Hembree et al., 2017). Although there are anecdotal reports of progesterone use for breast development and mood management, there is currently insufficient evidence the potential benefits of progesterone administration outweigh the potential risks (Iwamoto, T'Sjoen et al., 2019). Masculinizing GAHT typically consists of testosterone. Both WPATH and the Endocrine Society recommend monitoring levels of sex

hormones. While GAHT is customized to meet the individual needs of the TGD person, typically hormone levels are maintained at a concentration sufficient to support good bone health and are not supraphysiologic (Hembree et al., 2017; Rosen et al., 2019).

Statements of Recommendations

12.1- We recommend health care professionals begin pubertal hormone suppression in eligible* transgender and gender diverse adolescents after they first exhibit physical changes of puberty (Tanner stage 2).
12.2- We recommend health care professionals use gonadotropin releasing hormone (GnRH) agonists to suppress endogenous sex hormones in eligible* transgender and gender diverse people for whom puberty blocking is indicated.
12.3- We suggest health care professionals prescribe progestins (oral or injectable depot) for pubertal suspension in eligible* transgender and gender diverse youth when GnRH agonists are either not available or are cost prohibitive.
12.4- We suggest health care professionals prescribe GnRH agonists for suppression of sex steroids without concomitant sex steroid hormone replacement in eligible* transgender and gender diverse adolescents seeking such intervention and who are well into or have completed pubertal development (past Tanner stage 3) but are either unsure about or do not want to begin sex steroid hormone therapy.
12.5- We recommend health care professionals prescribe sex hormone treatment regimens as part of gender-affirming treatment for eligible* transgender and gender diverse adolescents who are at least Tanner stage 2, with parental/guardian involvement unless their involvement is determined to be harmful or unnecessary to the adolescent.
12.6- We recommend health care professionals measure hormone levels during gender-affirming treatment to ensure endogenous sex steroids are lowered and administered sex steroids are maintained at levels appropriate for the treatment goals of transgender and gender diverse people according to the Tanner stage.
12.7- We recommend health care professionals prescribe progestogens or a GnRH agonist for eligible* transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.
12.8- We recommend health care providers involve professionals from multiple disciplines who are experts in transgender health and in the management of the care required for transgender and gender diverse adolescents.
12.9- We recommend health care professionals institute regular clinical evaluations for physical changes and potential adverse reactions to sex steroid hormones, including laboratory monitoring of sex steroid hormones every 3 months during the first year of hormone therapy or with dose changes until stable adult dosing is reached followed by clinical and laboratory testing once or twice a year once an adult maintenance dose is attained.
12.10- We recommend health care professionals inform and counsel all individuals seeking gender-affirming medical treatment about the options available for fertility preservation prior to initiating puberty suppression and prior to treating with hormone therapy.
12.11- We recommend health care professionals evaluate and address medical conditions that can be exacerbated by lowered endogenous sex hormone concentrations and treatment with exogenous sex hormones before beginning treatment for transgender and gender diverse people.
12.12- We recommend health care professionals educate transgender and gender diverse people undergoing gender-affirming treatment about the onset and time course of the physical changes induced by sex hormonal treatment.
12.13- We recommend health care professionals not prescribe ethinyl estradiol for transgender and gender diverse people as part of a gender-affirming hormonal treatment.
12.14- We suggest health care professionals prescribe transdermal estrogen for eligible* transgender and gender diverse people at higher risk of developing venous thromboembolism based on age > 45 years or a previous history of venous thromboembolism, when gender-affirming estrogen treatment is recommended.
12.15- We suggest health care professionals not prescribe conjugated estrogens in transgender and gender diverse people when estradiol is available as a component of gender-affirming hormonal treatment.
12.16- We recommend health care professionals prescribe testosterone-lowering medications (either cyproterone acetate, spironolactone, or GnRH agonists) for eligible* transgender and gender diverse people with testes who are taking estrogen as part of a hormonal treatment plan if the individual's goal is to approximate circulating sex hormone concentrations in cisgender women.
12.17- We recommend health care professionals monitor hematocrit (or hemoglobin) in transgender and gender diverse people treated with testosterone.
12.18- We suggest health care professionals collaborate with surgeons regarding hormone use before and after gender-affirmation surgery.
12.19- We suggest health care professionals counsel transgender and gender diverse people about the various options available for gender-affirmation surgery unless surgery is not indicated or is medically contraindicated.
12.20- We recommend health care professionals initiate and continue gender-affirming hormone therapy for eligible* transgender and gender diverse people who require this treatment due to demonstrated improvement in psychosocial functioning and quality of life.
12.21- We recommend health care professionals maintain existing hormone therapy if the transgender and gender diverse individual's mental health deteriorates and assess the reason for the deterioration, unless contraindicated.

** For eligibility criteria for adolescents and adults, please refer to Chapter 5—Assessment for Adults and Chapter 6—Adolescents and Appendix D.*

In most cases, GAHT is maintained throughout life. It is not known if doses of GAHT should be reduced in older TGD people. Discontinuation of hormone therapy may result in bone loss in TGD individuals and will definitely do so in individuals whose gonads have been removed (Wiepjes et al., 2020). Routine primary care should also be performed (see Chapter 15—Primary Care). Epidemiology studies have reported an increased incidence of cardiovascular disease and venous thromboembolism (VTE) in TGD people receiving estrogen, most notably in older people and with different preparations of GAHT (Irwig, 2018; Maraka et al., 2017). TGD individuals treated with testosterone may also have increased adverse cardiovascular risks and events, such as increased myocardial infarction, blood pressure, decreased HDL-cholesterol, and excess weight (Alzahrani et al., 2019; Irwig, 2018; Kyinn et al., 2021). Health care professionals (HCPs) should discuss lifestyle and pharmacologic therapy with patients who are at the highest risk of developing cardiovascular disease (see Chapter 15—Primary Care). Polycythemia is another disorder that may present in TGD people taking testosterone (Antun et al., 2020). Therefore, it is important to continuously monitor for the development of conditions that can be exacerbated by GAHT throughout life (Hembree et al., 2017).

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Gender-Affirming Hormone Therapy in Youth

The following sections will discuss hormone therapy in TGD youth. Depending on the developmental stage of the youth, this hormone therapy generally comprises two phases, namely pubertal suppression followed by the addition of GAHT. During the first phase, pubertal development is halted to allow the youth to explore their gender identity and embodiment goals to prepare for the next phase, which may include GAHT. This section will discuss the recommendations for the use of gonadotropin releasing hormone agonists (GnRHas) as well as alternate approaches to pubertal suppression and will be followed by recommendations for GAHT. Sections that are applicable to youth and adults will follow in the next section.

Statement 12.1

We recommend health care professionals begin pubertal hormone suppression in eligible* transgender and gender diverse adolescents only after they first exhibit physical changes of puberty (Tanner stage 2).

In general, the goal of GnRHa administration in TGD adolescents is to prevent further development of the endogenous secondary sex characteristics corresponding to the sex designated at birth. Since this treatment is fully reversible, it is regarded as an extended time for adolescents to explore their gender identity by means of an early social transition (Ashley, 2019e). Treatment with GnRHas also has therapeutic benefit since it often results in a vast reduction in the level of distress stemming from physical changes that occur when endogenous puberty begins (Rosenthal, 2014; Turban, King et al., 2020).

For those prepubertal TGD children who have been persistent in their gender identity, any amount of permanent development of secondary sex characteristics could result in significant distress. While one might consider use of a GnRHa to prevent initiation of puberty in such individuals who remain at Tanner Stage 1, this use of GnRHa has not been recommended (Hembree et al., 2017). When a child reaches an age where pubertal development would normally begin (typically from 7-8 to 13 years for those with ovaries and from 9 to 14 years for those with testes), it would be appropriate to screen the child more frequently, perhaps at 4-month intervals, for signs of pubertal development (breast budding or testicular volume > 4 cc). Given the typical tempo of pubertal development (3.5–4 years for completion), it would be very unlikely for permanent pubertal changes to develop if one is only in puberty for 4 months or less. Thus, with frequent follow-up, the initiation of puberty can easily be detected before there are irreversible physical changes, and GnRHa can be started at that time with great efficacy. Of note, following initiation of a GnRHa, there is typically

a regression of one Tanner stage. Thus, if there is only Tanner stage 2 breast development, it typically fully regresses to the prepubertal Tanner stage 1; the same is typically true with Tanner stage 2 testes (often not even discernable to the patient and is not associated with development of secondary sex characteristics).

Given GnRHas work through GnRH receptor desensitization, if there's no uptick in endogenous GnRH stimulation of the pituitary (the first biochemical sign of puberty), there's no need for GnRH receptor desensitization. In addition, because of the wide variability in the timing of the start of puberty (as noted above), it is hard to justify using a GnRHa that might have some unknown risk if there's no physiological benefit before pubertal onset. Using a GnRHa with a child at Tanner stage 1 would only be indicated in cases of constitutional delay in growth and puberty, likely alongside the start of GAHT.

However, the use of a GnRHa could be considered in a child who, due to a constitutional delay in growth and puberty, starts GAHT while still in Tanner Stage 1. Initiating GAHT may activate the hypothalamic-pituitary gonadal axis in the beginning but may also mask the effects on the body of this activation. To avoid body changes with the potential to exacerbate an individual's gender incongruence, the GnRHa can be started as an adjunctive therapy to the GAHT shortly after the initiation of the GAHT to provide for pubertal development of the identified phenotype.

In addition, the suppression of the development of secondary sex characteristics is most effective when sex hormonal treatment is initiated in early to mid-puberty when compared with the initiation of sex hormonal treatment after puberty is completed (Bangalore-Krisha et al., 2019). Correspondingly, for adolescents who have already completed endogenous puberty and are considering starting GAHT, GnRHas can be used to inhibit physical functions, such as menses or erections, and can serve as a bridge until the adolescent, guardian(s) (if the adolescent is not able to consent independently), and treatment team reach a decision (Bangalore-Krishna et al., 2019; Rosenthal, 2021).

The onset of puberty occurs through reactivation of the hypothalamic-pituitary-gonadal axis. Clinical assessment of the stages of puberty is based on physical features that reflect that reactivation. In individuals with functioning ovaries, Tanner stage 2 is characterized by the budding of the mammary gland. The development of the mammary gland occurs from exposure to estrogen produced by the ovaries. In individuals with functioning testes, Tanner stage 2 is characterized by an increase in testicular volume (typically greater than 4 ml). The growth of the testes is mediated through the gonadotropins luteinizing hormone (LH) and follicle stimulating hormone (FSH). In the later stages, the testes produce enough testosterone to induce masculinization of the body.

Statement 12.2

We recommend health care professionals use GnRH agonists to suppress endogenous sex hormones in eligible* transgender and gender diverse people for whom puberty blocking is indicated. For supporting text, see Statement 12.4.

Statement 12.3

We suggest health care professionals prescribe progestins (oral or injectable depot) for pubertal suspension in eligible* transgender and gender diverse youth when GnRH agonists are not available or are cost prohibitive. For supporting text, see Statement 12.4.

Statement 12.4.

We suggest health care professionals prescribe GnRH agonists to suppress sex steroids without concomitant sex steroid hormone replacement in eligible transgender and gender diverse adolescents seeking such intervention who are well into or have completed pubertal development (past Tanner stage 3) but are unsure about or do not wish to begin sex steroid hormone therapy.

GnRHas reduce gonadotrophin and sex steroid concentrations in TGD adolescents and thus halt the further development of secondary sex characteristics (Schagen et al., 2016). Their use is generally safe with the development of hypertension being the only short-term adverse event reported in the literature (Delemarre-van de Waal & Cohen-Kettenis, 2006; Klink, Bokenkamp et al., 2015). GnRHas prevent the pituitary gland from

secreting LH and FSH (Gava et al., 2020). When the gonadotropins decrease, the gonad is no longer stimulated to produce sex hormones (estrogens or androgens), and the sex hormone levels in the blood decrease to prepubertal levels. GnRHa treatment leads to partial regression of the initial stages of the already developed secondary sex characteristics (Bangalore et al., 2019). TGD adolescents with functioning ovaries will experience diminished growth of breast tissue, and if treatment is started at Tanner stage 2, the breast tissue may disappear completely (Shumer et al., 2016). Menarche can be prevented or discontinued following the administration of GnRHas in adolescents with a uterus. In TGD adolescents with functioning testes, testicular volume will regress to a lower volume.

When GnRHa treatment is started in adolescents at the later phases of pubertal development, some physical changes of pubertal development, such as late-stage breast development in TGD adolescents with functioning ovaries and a lower voice and growth of facial hair in TGD adolescents with functioning testes, will not regress completely, although any further progression will be stopped (Delemarre-van de Waal & Cohen-Kettenis, 2006). GnRHas have been used since 1981 for the treatment of central precocious puberty (Comite et al., 1981; Laron et al., 1981), and their benefits are well established (please also see the statements in Chapter 6—Adolescents). The use of GnRHas in individuals with central precocious puberty is regarded as both safe and effective, with no known long-term adverse effects (Carel et al., 2009). However, the use of GnRHas in TGD adolescents is considered off-label because they were not initially developed for this purpose. Nonetheless, data from adolescents prescribed GnRHas in a similar dose and fashion demonstrate effectiveness in delaying the onset of puberty although the long-term effects on bone mass have not been well established (Klink, Caris et al., 2015). Although long-term data are more limited in TGD adolescents than in adolescents with precocious puberty, data collection specifically in this population are ongoing (Klaver et al., 2020; Lee, Finlayson et al., 2020; Millington et al., 2020; Olson-Kennedy, Garofalo et al., 2019).

We recognize even though GnRHas are a medically necessary treatment, they may not be available for eligible adolescents because it is not covered by health insurance plans in some countries or may be cost-prohibitive. Therefore, other approaches should be considered in these cases, such as oral or injectable progestin formulations. In addition, for adolescents older than 14 years, there are currently no data to inform HCPs whether GnRHas can be administered as monotherapy (and for what duration) without posing a significant risk to skeletal health. This is because the skeleton will not have any exposure to adequate levels of sex steroid hormones (Rosenthal, 2021).

A prolonged hypogonadal state in adolescence, whether due to medical conditions such as hypergonadotropic hypogonadism, iatrogenic causes such as GnRHa monotherapy or physiological conditions such as conditional delay of growth and development, is often associated with an increased risk of poor bone health later in life (Bertelloni et al., 1998; Finkelstein et al., 1996). However, bone mass accrual is a multifactorial process that involves a complex interplay between endocrine, genetic, and lifestyle factors (Anai et al., 2001). When deciding on the duration of GnRHa monotherapy, all contributing factors should be considered, including factors such as pretreatment bone mass, bone age, and pubertal stage from an endocrine perspective and height gain, as well as psychosocial factors such as mental maturity and developmental stage relative to one's adolescent cohort and the adolescent's individual treatment goals (Rosenthal, 2021). For these reasons, a multidisciplinary team and an ongoing clinical relationship with the adolescent and the family should be maintained when initiating GnRHa treatment (see Statements 6.8, 6.9, and 6.12 in Chapter 6—Adolescents). The clinical course of the treatment, e.g., the development of bone mass during GnRHa treatment and the adolescent's response to treatment, can help to determine the length of GnRHa monotherapy.

Statement 12.5

We recommend health care professionals prescribe sex hormone treatment regimens as part of gender-affirming treatment in eligible*

transgender and gender diverse adolescents who are at least Tanner stage 2, with parental/guardian involvement unless their involvement is determined to be harmful or unnecessary to the adolescent. For supporting text, see Statement 12.6.

Statement 12.6

We recommend health care professionals measure hormone levels during gender-affirming treatment to ensure endogenous sex steroids are lowered and administered sex steroids are maintained at a level appropriate for the treatment goals of transgender and gender diverse people according to the Tanner stage.

Sex steroid hormone therapy generally comprises two treatment regimens, depending on the timing of the GnRHa treatment. When GnRHa treatment is started in the early stages of endogenous pubertal development, puberty corresponding with gender identity or embodiment goals is induced with doses of sex steroid hormones similar to those used in peripubertal hypogonadal adolescents. In this context, adult doses of sex steroid hormones are typically reached over approximately a 2-year period (Chantrapanichkul et al., 2021). When GnRHa treatment is started in late- or postpubertal transgender adolescents, sex steroid hormones can be given at a higher starting dose and increased more rapidly until a maintenance dose is achieved, resembling treatment protocols used in transgender adults (Hembree et al., 2017). An additional advantage of GnRHa treatment is sex steroid hormones do not have to be administered in supraphysiological doses, which would otherwise be needed to suppress endogenous sex steroid production (Safer & Tangpricha, 2019). For TGD individuals with functioning testes, GnRHa treatment (or another testosterone-blocking medication) should be continued until such time as the TGD adolescent/young adult ultimately undergoes gonadectomy, if this surgical procedure is pursued as a medically necessary part of their gender-affirming care. Once adult levels of testosterone are reached in TGD individuals with functioning ovaries who have been initially suppressed with GnRHa's, testosterone alone at physiological doses is typically sufficient to lower ovarian estrogen secretion, and GnRHas can be discontinued as discussed below (Hembree et al., 2017). For TGD adolescents with functioning ovaries who are new to care, GAHT can be accomplished with physiological doses of testosterone alone without the need for concomitant GnRHa administration (Hembree et al., 2017).

Gender-affirming sex steroid hormone therapy induces the development of secondary sex characteristics of the gender identity. Also, the rate of bone mineralization, which decreases during treatment with GnRHa's, rapidly recovers (Klink, Caris et al., 2015). During GnRHa treatment in early-pubertal TGD adolescents, the bone epiphyseal plates are still unfused (Kvist et al., 2020; Schagen et al., 2020). Following the initiation of sex steroid hormone treatment, a growth spurt can occur, and bone maturation continues (Vlot et al., 2017). In postpubertal TGD adolescents, sex steroid hormone treatment will not affect height since the epiphyseal plates have fused, and bone maturation is complete (Vlot et al., 2017).

In TGD adolescents with functioning testes, the use of 17-ß-estradiol for pubertal induction is preferred over that of synthetic estrogens, such as the more thrombogenic ethinyl estradiol (see Appendix D (Asscheman et al., 2015). It is still necessary to either continue GnRHa's to suppress endogenous testosterone production or transition to another medication that suppresses endogenous testosterone production (Rosenthal et al., 2016). Breast development and a female-typical fat distribution are among a number of physical changes that occur in response to estrogen treatment. See Appendix C—Table 1.

For TGD adolescents seeking masculinizing treatment, androgens are available as injectable preparations, transdermal formulations, and subcutaneous pellets. For pubertal induction, the use of testosterone-ester injection is generally recommended by most experts initially because of cost, availability, and experience (Shumer et al., 2016). It is advised to continue GnRHas at least until a maintenance level of testosterone is reached. In response to androgen treatment, virilization of the body occurs, including a lowering of the voice, more muscular development particularly in the upper body, growth of facial and body hair, and clitoral enlargement (Rosenthal et al., 2016). See Appendix C—Table 1.

In almost all situations, parental/caregiver consent should be obtained. Exceptions to this recommendation, in particular when caregiver or parental involvement is determined to be harmful to the adolescent, are described in more detail in Chapter 6—Adolescents (see Statement 6.11) where the rationale for involving parents/caregivers in the consent process is also described.

Statement 12.7

We recommend health care professionals prescribe progestogens or a GnRH agonist for eligible* transgender and gender diverse adolescents with a uterus to reduce dysphoria caused by their menstrual cycle when gender-affirming testosterone use is not yet indicated.

Menstrual suppression is a treatment option commonly needed by TGD individuals who experience distress related to menses or the anticipation of menarche. Statement 6.7 in Chapter 6—Adolescents describes this in more detail. To achieve amenorrhea, menstrual suppression can be initiated as a solo option before initiating testosterone or alongside testosterone therapy (Carswell & Roberts, 2017). Some youth, who are not ready for testosterone therapy or are not yet at an appropriate pubertal/developmental stage to begin such treatment, will benefit from the induction of amenorrhea (Olson-Kennedy, Rosenthal et al., 2018). Adolescents who experience an exacerbation of dysphoria related to the onset of puberty may elect to be treated with GnRHas for pubertal suppression (also see the Adolescents chapter).

Progestogens may be effective in adolescents whose goal is solely menstrual suppression. Continuous administration of progestin-only oral pills (including the contraceptive and noncontraceptive options), medroxyprogesterone injections, or levonorgestrel intrauterine device can be used for induction of amenorrhea (Pradhan & Gomez-Lobo, 2019). TGD individuals with functioning ovaries who start testosterone therapy may have 1–5 menstrual cycles before amenorrhea is achieved (Taub et al., 2020). Once amenorrhea is achieved, some TGD individuals with functioning ovaries may also choose to continue progestin treatment for birth control if relevant to their sexual practices.

TGD individuals with functioning ovaries and a uterus should be counseled about the potential for breakthrough menstrual bleeding in the first few months after initiating menstrual suppression. With GnRHa therapy, breakthrough bleeding may occur 2–3 weeks after initiation of the medication. For individuals seeking contraception or for those who continue to experience menstrual bleeding on progestin therapy, an estrogen combination with progestin may be considered for the maintenance of amenorrhea, yet they should be counseled on the possible side effect of breast development (Schwartz et al., 2019).

Statement 12.8

We recommend health care providers involve professionals from multiple disciplines who are experts in transgender health and in the management of the care of transgender and gender diverse adolescents.

As with the care of adolescents, we suggest where possible a multidisciplinary expert team of medical and mental health professionals (MHPs) be assembled to manage this treatment. In adolescents who pursue GAHT (given this is a partly irreversible treatment), we suggest initiating treatment using a schedule of gradually increasing doses after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and has established the individual possesses the mental capacity to give informed consent (Hembree et al., 2017). Specific aspects concerning the assessment of adolescents and the involvement of their caregivers and a multidisciplinary team are described in more detail in Chapter 6—Adolescents.

If possible, TGD adolescents should have access to experts in pediatric transgender health from multiple disciplines including primary care, endocrinology, fertility, mental health, voice, social work, spiritual support, and surgery (Chen, Hidalgo et al., 2016; Eisenberg et al., 2020; Keo-Meier & Ehrensaft, 2018). Individual providers are encouraged to form collaborative working relationships with providers from other disciplines to facilitate referrals as needed for the individual youth and their family (Tishelman et al., 2015). However, the lack of available

experts and resources should not constitute a barrier to care (Rider, McMorris et al., 2019). Helpful support for adolescents includes access to accurate, culturally informed information related to gender and sexual identities, transition options, the impact of family support, and connections to others with similar experiences and with TGD adults through online and in person support groups for adolescents and their family members (Rider, McMorris et al., 2019).

Many TGD adolescents have been found to experience mental health disparities and initial mental health screening (e.g., PHQ-2, GAD) can be employed as indicated (Rider, McMorris et al., 2019). Providers should keep in mind being transgender or questioning one's gender does not constitute pathology or a disorder. Therefore, individuals should not be referred for mental health treatment exclusively on the basis of a transgender identity. HCPs and MHPs who treat these youths and make referrals should, at a minimum, be familiar with the impact of trauma, gender dysphoria, and gender minority stressors on any potential mental health symptomatology, such as disordered eating, suicidal ideation, social anxiety. These health care providers should also be knowledgeable about the level of readiness of inpatient mental health services in their region to provide competent, gender-affirming care to TGD youth (Barrow & Apostle, 2018; Kuper, Wright et al., 2018; Kuper, Mathews et al., 2019; Tishelman & Neumann-Mascis, 2018). Statements 6.3, 6.4, and 6.12d in Chapter 6—Adolescents address this in more detail. Because parents of these youth commonly experience high levels of anxiety immediately after learning their youth is TGD, and their response to their child predicts that child's long-term physical and mental health outcomes, appropriate referrals for mental health support of the parents can be of great utility (Coolhart et al., 2017; Pullen Sansfaçon et al., 2015; Taliaferro et al., 2019).

Statement 12.9

We recommend health care professionals organize regular clinical evaluations for physical changes and potential adverse reactions to sex steroid hormones, including laboratory monitoring of sex steroid hormones every 3 months during the first year of hormone therapy or with dose changes until a stable adult dosing is reached followed by clinical and laboratory testing once or twice a year once an adult maintenance dose is attained.

Sex steroid hormone therapy is associated with a broad array of physical and psychological changes (Irwig, 2017; Tangpricha & den Heijer, 2017) (see Appendix C—Table 1). After sex steroid hormone therapy has been initiated, the HCP should regularly assess the progress and response of the individual to the treatment (also see Chapter 6—Adolescents). This evaluation should assess the presence of any physical changes as well as the impact of treatment on gender dysphoria (if present) and psychological well-being (see Appendix C—Table 1). Clinical visits provide important opportunities for HCPs to educate patients about the typical time course required for physical changes to manifest and encourage realistic expectations. During the first year of hormone therapy, sex steroid hormone doses are often increased. A major factor guiding the dose is the serum level of the corresponding sex steroid hormone. In general, the goal is to target serum levels of the sex steroids to match the levels associated with the individual's gender identity, although optimal target ranges have not been established (Hembree et al., 2017).

In addition to assessing the positive changes associated with sex steroid hormone therapy, the HCP should regularly assess whether the treatment has caused any adverse effects (see Appendix C—Table 2). Examples of adverse signs and symptoms include androgenic acne or bothersome sexual dysfunction (Braun et al., 2021; Kerckhof et al., 2019). GAHT also has the potential to adversely influence several laboratory tests. For example, spironolactone may cause hyperkalemia, although it is an uncommon and transient phenomenon (Millington et al., 2019). Testosterone increases the red blood cell count (hematocrit), which may occasionally cause erythrocytosis (Antun et al., 2020) (see Statement 12.17) (Hembree et al., 2017). Both estrogen and testosterone can alter lipid parameters, such as high-density protein lipoprotein (HDL) cholesterol and triglycerides (Maraka et al., 2017). See Appendix C—Tables 3 and 4.

The frequency of clinical evaluations should be individualized and guided by the individual's response to treatment. We suggest clinical assessments be performed approximately every 3 months during the first year of hormone therapy in patients who are stable and are not experiencing significant adverse effects (Appendix C—Table 5). We suggest rather than recommend testing be carried out every 3 months in the first year to allow some flexibility on the timing of these tests as there is no strong evidence or evidence from published studies supporting specific testing intervals. If an individual does experience an adverse effect, more frequent laboratory testing and/or clinical visits are often needed. Given the potential harm associated with sex hormone levels that exceed expected ranges in humans, we strongly recommend regular testing be performed as a standard practice when initiating GAHT in TGD individuals. Once a person has reached a stable adult dose of sex steroid hormone with no significant adverse effects, the frequency of clinic visits can be reduced to one to two per year (Hembree et al., 2017).

Statement 12.10

We recommend health care professionals inform and counsel all individuals seeking gender-affirming medical treatment about options for fertility preservation prior to initiating puberty suppression and prior to administering hormone therapy.

Pubertal suppression and hormone treatment with sex steroid hormones may have potential adverse effects on a person's future fertility (Cheng et al., 2019) (see also Chapter 6—Adolescents and Chapter 16—Reproductive Health). Although some TGD people may not have given much thought to their future reproductive potential at the time of their initial assessment to begin medical therapy, the potential implications of the treatment and fertility preservation options should be reviewed by the hormone prescriber and discussed with the person seeking these therapies (Ethics Committee of the American Society for Reproductive Medicine et al., 2015; De Roo et al., 2016).

Individuals with testes should be advised prolonged treatment with estrogen often causes testicular atrophy and a reduction in sperm count and other semen parameters (Adeleye et al., 2018). Nonetheless, there are major gaps in knowledge, and findings regarding the fertility of trans feminine people who take estrogen and antiandrogens are inconsistent (Cheng et al., 2019). In one study, heterogeneity in testicular histology was evident whether patients discontinued or continued therapy prior to orchiectomies (Schneider et al., 2015). For example, the discontinuation of estrogen and antiandrogens for six weeks resulted in complete spermatogenesis in 45% of individuals with the remainder showing meiotic arrest or spermatogonial arrest (Schneider et al., 2015). However, serum testosterone levels confirmed to be within female reference ranges leads to complete suppression of spermatogenesis in most transgender women (Vereecke et al., 2020). The principal fertility preservation option for patients with functioning testes is sperm cryopreservation, also known as sperm banking (Mattawanon et al., 2018). For prepubertal patients, suppression of puberty with GnRHs pauses the maturation of sperm (Finlayson et al., 2016).

Individuals with functioning ovaries should be advised testosterone therapy usually results in the cessation of menses and ovulation, often within a few months of initiation (Taub et al., 2020). There are also major gaps in knowledge regarding the potential effects of testosterone on oocytes and subsequent fertility of TGD patients (Eisenberg et al., 2020; Stuyver et al., 2020). One study found testosterone treatment may be associated with polycystic ovarian morphology, whereas other studies reported no metabolic (Chan et al., 2018) or histologic (De Roo et al., 2017; Grynberg et al., 2010) evidence of polycystic ovary syndrome (PCOS) following treatment with testosterone, and some studies have found a pre-existing higher prevalence of PCOS in transgender patients with ovaries (Baba, 2007; Gezer et al., 2021). TGD patients with an intact uterus and ovaries often regain their fertility potential if testosterone therapy is discontinued (Light et al., 2014). Indeed, a live birth after assisted reproductive technology has been reported following hormone-stimulated egg retrieval from a TGD

individual who did not discontinue testosterone therapy (Greenwald et al., 2021; Safer and Tangpricha, 2019). Other fertility preservation options for TGD patients with ovaries are oocyte cryopreservation and embryo cryopreservation with sperm from a partner or donor. The above options require hormonal stimulation for egg retrieval and the use of assisted reproductive technology.

For early pubertal transgender youth, suppression of puberty with GnRHa's pauses the maturation of germ cells, although a recent report noted ovarian stimulation of a TGD adolescent treated with a GnRHa's in early puberty (and continued during ovarian stimulation) resulted in a small number of mature oocytes that were cryopreserved (Rothenberg et al., 2019). Treating an TGD adolescent with functioning testes in the early stages of puberty with a GnRHa not only pauses maturation of germ cells but will also maintains the penis in a prepubertal size. This will likely impact surgical considerations if that person eventually undergoes a penile-inversion vaginoplasty as there will be less penile tissue to work with. In these cases, there is an increased likelihood a vaginoplasty will require a more complex surgical procedure, e.g., intestinal vaginoplasty (Dy et al., 2021; van de Grift et al., 2020). Such considerations should be included in any discussions with patients and families considering use of pubertal blockers in early pubertal adolescents with functioning testes.

Statement 12.11

We recommend health care professionals evaluate and address medical conditions that can be exacerbated by lowered endogenous sex hormone concentrations and treatment with exogenous sex hormones before beginning treatment in transgender and gender diverse people.

TGD people seeking masculinization must be informed about the possibilities, consequences, limitations, and risks associated with testosterone treatment. Testosterone therapy is contraindicated during pregnancy or while attempting to become pregnant given its potential iatrogenic effects on the fetus. Relative contraindications to testosterone therapy include severe hypertension, sleep apnea, and polycythemia since these conditions can be exacerbated by testosterone. Monitoring blood pressure and lipid profiles should be performed before and after the onset of testosterone therapy. The increase in blood pressure typically occurs within 2 to 4 months following the initiation of testosterone therapy (Banks et al., 2021). Patients who develop hypercholesterolemia and/or hypertriglyceridemia may require treatment with dietary modifications, medication, or both.

TGD people seeking feminizing treatment with a history of thromboembolic events, such as deep vein thrombosis and pulmonary embolism, should undergo evaluation and treatment prior to the initiation of hormone therapy. This is because estrogen therapy is strongly associated with an increased risk of thromboembolism, a potentially life-threatening complication. In addition, risk factors that can increase the risk of thromboembolic conditions, such as smoking, obesity, and sedentary lifestyle, should be modified. In patients with nonmodifiable risk factors, such as a known history of thrombophilia, a past history of thrombosis, or a strong family history of thromboembolism, treatment with transdermal estrogen concomitant with anticoagulants may decrease the risk of thromboembolism. However, there are limited data to guide treatment decisions. The presence of a disease at baseline such as a hormone sensitive cancer, coronary artery disease, cerebrovascular disease, hyperprolactinemia, hypertriglyceridemia, and cholelithiasis should be evaluated prior to the initiation of gender-affirming hormone therapy as relative risks may be shifted in association with exogenous hormone treatment (Hembree et al., 2017).

Statement 12.12

We recommend health care professionals educate transgender and gender diverse people undergoing gender-affirming treatment about the onset and time course of physical changes induced by sex hormone treatment.

The effects of testosterone treatment are multiple and may include the appearance of increased body and facial hair, male pattern baldness, increased muscle mass and strength, decreased fat mass, deepening of the voice, interruption of

menses (if still present), increased prevalence and severity of acne, clitoral enlargement, and increased sexual desire (Defreyne, Elaut et al., 2020; Fisher, Castellini et al., 2016; Giltay & Gooren, 2000; T'Sjoen et al., 2019; Yeung et al., 2020). Other testosterone-associated changes include increased lean body mass, skin oiliness, (de Blok et al., 2020; Hembree et al., 2017; Kuper, Mathews et al., 2019; Taliaferro et al., 2019; Tishelman & Neumann-Mascis, 2018) (see Appendix C—Table 1).

Estrogen treatment induces breast development. However, fewer than 20% of individuals reach Tanner breast stages 4–5 after 2 years of treatment (de Blok et al., 2021). Additional changes include decreases in testicular volume, lean body mass, skin oiliness, sexual desire, spontaneous erections, facial hair, and body hair along with increased subcutaneous body fat) (see Appendix C—Table 1). In adult patients, estrogen does not alter a person's voice or height (Iwamoto, Defreyne et al., 2019; Wiepjes et al., 2019).

The time course and extent of physical changes vary among individuals and are related to factors such as genetics, age of initiation, and overall state of health (Deutsch, Bhakri et al., 2015; van Dijk et al., 2019). Knowledge of the extent and timing of sex hormone–induced changes, if available, may prevent the potential harm and expense of unnecessary treatment changes, dosage increases, and premature surgical procedures (Dekker et al., 2016).

Statement 12.13

We recommend health care professionals not prescribe ethinyl estradiol for transgender and gender diverse people as part of a gender-affirming hormonal treatment. For supporting text, see Statement 12.15.

Statement 12.14

We suggest health care professionals prescribe transdermal estrogen for eligible* transgender and gender diverse people at higher risk of developing venous thromboembolism based on age >45 years or a previous history of venous thromboembolism, when gender-affirming estrogen treatment is recommended. For supporting text, see Statement 12.15).

Statement 12.15

We suggest health care professionals not prescribe conjugated estrogens in transgender and gender diverse people when estradiol is available as part of a gender- affirming hormonal treatment.

Determining the safest and most efficacious estrogen compound and route of administration for TGD people is an important topic. The recommended estrogen-based regimens are presented in Appendix C—Table 4. The Amsterdam Medical Center (AMC) first reported 45 events of VTE occurring in 816 transgender women, notably an expected incidence ratio of VTE 20-fold higher than that reported in a reference population (van Kesteren et al., 1997). Following this report, the AMC clinic recommended the use of transdermal estradiol for transgender women older than 40 years of age, which subsequently lowered the incidence of VTE (Nota et al., 2019; Toorians et al., 2003). Other studies suggested ethinyl estradiol is associated with a higher risk of blood clotting due to an increased resistance to the anticoagulating effects of activated protein C (APC) and elevated concentrations of the clotting factors protein C and protein S (Toorians et al., 2013). Other studies published within the past 15 years from other clinics reported transgender women taking other forms of estrogen had lower rates of VTE than transgender women taking ethinyl estradiol (Asscheman et al., 2013). Furthermore, a 2019 systematic review concluded ethinyl estradiol administration was associated with the highest risk of VTE in transgender women, while an association between progesterone use and VTE was also identified (Goldstein et al., 2019).

The 2017 Endocrine Society guidelines did not recommend conjugated equine estrogens (CEEs) as a treatment option because blood levels of conjugated estrogens cannot be measured in transgender women making it difficult to prevent supraphysiologic dosing of estrogen and thereby increasing the potential risk of VTE (Hembree et al., 2017). A retrospective study from the UK examined the risks of oral CEE versus oral estradiol valerate versus oral ethinyl estradiol and found up to a 7-fold increase in the percentage of transgender women in the oral CEE group

who developed VTE compared with transgender women using other forms of estrogen (Seal et al., 2012). In a nested, case-control study, over 80,000 cisgender women aged 40–79 who developed a VTE were matched to approximately 390,000 cisgender women without VTE; the results showed oral estradiol use had a lower risk of VTE than conjugated estrogens, and transdermal estrogen was not associated with an increased risk of VTE (Vinogradova et al., 2019).

A systematic review evaluated several formulations of estrogen and identified a retrospective and a cross-sectional study that made head-to-head comparisons of the risks associated with different formulations (Wierckx, Mueller et al., 2012; Wierckx et al., 2013). No identified studies evaluating the risk of different formulations of estrogen employed a prospective interventional design. The retrospective study examined 214 transgender women taking transdermal estradiol (17β-estradiol gel 1.5 mg/d or estradiol patch 50 mcg/d) or a daily intake of oral estrogens (estradiol 2 mg/d, estriol 2 mg/d, ethinyl estradiol 50 mcg/day, or ethinyl estradiol 30–50 mcg in an oral contraceptive) (Wierckx et al., 2013). Within a 10-year observation period, 5% of the cohort developed a VTE, 1.4% (3 of 214) experienced a myocardial infarction (MI), and 2.3% (5 of 214) a transient ischemic attack or cerebrovascular accident (TIA/CVA). The prevalence of VTE, MI and TIA/CVA was increased following the initiation of estrogen therapy. However, the authors did not report differences between regimens of estrogen in terms of these endpoints.

The same group of investigators conducted a cross-sectional study that examined 50 transgender women (mean age 43 ± 10) taking oral estrogen (estradiol valerate 2 mg/d, estriol 2 mg/d or ethinyl estradiol 50–120 mcg/day) or using transdermal estradiol (17β-estradiol 1.5 mg/day or estradiol 50 mcg/day) over a follow-up duration of 9.2 years (Wierckx, Mueller et al., 2012). Twelve percent (n = 6) developed either a VTE, MI, or a TIA/CVA. Two of the participants were taking conjugated estrogen 0.625 mg/d (one person in combination with cyproterone acetate), 2 participants were taking ethinyl estradiol 20–50 mcg/d, 1 was taking cyproterone acetate 50 mg/d, while the estrogen regimen used by the sixth participant was not defined. None of the subjects taking oral estradiol or transdermal estradiol developed a VTE, MI, or TIA/CVA.

One prospective study examined the route of estrogen administration in 53 transgender women in a multicenter study carried out throughout Europe. Transgender women younger than 45 years of age (n = 40) received estradiol valerate 4 mg/d in combination with cyproterone acetate (CPA) 50 mg/d and transgender women older than 45 years of age (n = 13) received transdermal 17β-estradiol, also with CPA. No VTE, MI, or TIA/CVA was reported after a 1-year follow-up in either the oral or transdermal estrogen group. An additional retrospective study from Vienna found no occurrences of VTE among 162 transgender women using transdermal estradiol who were followed for a mean of 5 years (Ott et al., 2010).

We are strongly confident in our recommendation against the use of ethinyl estradiol based on historical data from the Amsterdam clinic demonstrating a reduction in the incidence of VTE after discontinuing the use of ethinyl estradiol and the recent systematic review demonstrating an increased risk of VTE in transgender women taking ethinyl estradiol (Weinand & Safer, 2015). We are confident in our recommendation against the use of CEE based on the 2012 study by Seal et al. demonstrating an increased risk of VTE in transgender women taking CEE compared with other formulations of estrogen and with data from cisgender women on hormone replacement therapy (Canonico et al., 2007; Seal et al., 2012). Prospective and retrospective studies in transgender women have reported occurrences of VTE/MI/CVA only in those taking CEE or ethinyl estradiol. Since estradiol is inexpensive, more widely available, and appears safer than CEE in limited studies, the committee recommends against using CEE when estradiol is an available treatment option. The quality of studies may be limited to prospective, cohort or cross-sectional study designs; however, the stronger level of recommendation is based on the consistent evidence supporting the association between the use of ethinyl estradiol and CEE and a greater risk of VTE/MI/CVA in transgender women.

We are also confident in our recommendation for the administration of transdermal preparations of estrogen in older transgender women

(age > 45 years) or those with a previous history of VTE. The confidence in our recommendation is based on the decreased incidence of VTE reported from the Amsterdam clinic when transgender women are switched to using transdermal preparations after age 40 (van Kesteren et al., 1997). Furthermore, the prospective, multicenter cohort study ENIGI found no incidence of VTE/MI/CVA in transgender women who are routinely switched to transdermal estrogen at age 45 (Dekker et al., 2016). In addition, a study by Ott et al. demonstrated no incidence of VTE in 162 transgender women treated with estradiol patches (Ott et al., 2010).

With the exception of cyproterone acetate (note this is not approved for use in the US because of concerns of potential hepatotoxicity), the use of progestins in hormone therapy regimens remains controversial. To date, there have been no quality studies evaluating the role of progesterones in hormone therapy for transgender patients.

We are aware some practitioners who prescribe progestins, including micronized progesterone, are under the impression there may be improvements in breast and/or areolar development, mood, libido, and overall shape for those seeking it along with other benefits yet to be demonstrated (Deutsch, 2016a; Wierckx, van Caenegem et al., 2014). However, these improvements remain anecdotal, and there are no quality data to support such progestin use. An attempted systematic review we commissioned for this version of the SOC failed to identify enough data to make a recommendation in favor of any progestins. Instead, existing data suggest harm is associated with extended progestin exposure (Safer, 2021).

For cisgender women who have a uterus, progestins in combination with estrogens are necessary to avoid the endometrial cancer risk associated with the administration of unopposed estrogen. For cisgender women who do not have a uterus, progestins are not used. The best data for the concerns related to progestin use come from comparisons between the above two cisgender populations, which we acknowledge is not necessarily generalizable to this population. Although not definitive of a class effect for all progestins, medroxyprogesterone added to combined equine estrogens is associated with greater breast cancer and cardiac risks (Chlebowski 2020; Manson, 2013). It is important to note data from the Women's Health Initiative (WHI) studies may not be generalizable to transgender populations. Compared with the cisgender women in the studies, transgender populations seeking hormone therapy tend to be younger, do not use equine estrogen, and hormone therapy in these cases address current mental health and quality of life and not solely risk prevention (Deutsch, 2016a).

Potential adverse effects of progestins include weight gain, depression, and lipid changes. Micronized progesterone may be better tolerated and may have a more favorable impact on the lipid profile than medroxyprogesterone (Fitzpatrick et al., 2000). When paired with estrogens for transgender women, the progestin cyproterone acetate is associated with elevated prolactin, decreased HDL cholesterol, and rare meningiomas—none of which are seen when estrogens are paired with GnRH agonists or spironolactone (Bisson, 2018; Borghei-Razavi, 2014; Defreyne, Nota et al., 2017; Sofer et al., 2020).

Thus, data to date do not include quality evidence supporting a benefit of progestin therapy for transgender women. However, the literature does suggest a potential harm of some progestins, at least in the setting of multi-year exposure. If, after a discussion of the risks and benefits of progesterone treatment, there is a collaborative decision to begin a trial of progesterone therapy, the prescriber should evaluate the patient within a year to review the patient's response to this treatment.

Statement 12.16

We recommend health care professionals prescribe testosterone-lowering medications (either cyproterone acetate, spironolactone, or GnRH agonists) for eligible* transgender and gendered diverse people with testes taking estrogen as part of a hormonal treatment plan if their individual goal is to approximate levels of circulating sex hormone in cisgender women.

Most gender clinics in the US and Europe prescribe estrogen combined with a testosterone-lowering medication (Mamoojee et al., 2017) (see Appendix C—Table 5). In the

US, spironolactone is the most commonly prescribed testosterone-lowering medication, while GnRHas are commonly used in the UK, and cyproterone acetate are most often prescribed in the rest of Europe (Angus et al., 2021; Kuijpers et al., 2021). The rationale for adding a testosterone-lowering medication is two-fold 1) to lower testosterone levels to within the reference range of cisgender women; and 2) to reduce the amount of estrogen needed to achieve adequate physical effects. Each testosterone-lowering medication has a different side effect profile. Spironolactone is an antihypertensive and potassium-sparing diuretic, and thus may lead to hyperkalemia, increased frequency of urination, and a reduction in blood pressure (Lin et al., 2021). Cyproterone acetate has been associated with the development of meningioma and hyperprolactinemia (Nota et al., 2018). GnRHa's, while very effective in lowering testosterone levels, can result in osteoporosis if doses of estrogen given concurrently are insufficient (Klink, Caris et al., 2015).

One systematic review identified one study that reported findings from a head-to-head comparison of the testosterone-lowering medications cyproterone acetate and leuprolide (Gava et al., 2016). Two studies compared a group of transgender women taking estrogen plus testosterone-lowering medications with a group who received only estrogen. The systematic review did not provide sufficient evidence to suggest any of the three testosterone-lowering medications had a better safety profile in terms of improved outcomes in bone health, testosterone levels, potassium levels, or in the incidence of hyperprolactinemia or meningiomas (Wilson et al., 2020). Therefore, no recommendation can be given. The review did report spironolactone-based regimens were associated with a 45% increase in prolactin levels, whereas cyproterone-based regimens increased prolactin levels by more than 100%. However, the clinical significance of elevated prolactin levels is not clear because the rates of prolactinomas were not significantly elevated in either the spironolactone- or CPA-treated groups (Wilson et al., 2020). One retrospective, cohort study from a single center in the US reported no clinically significant increases in prolactin levels in 100 transgender women treated with estrogen plus spironolactone (Bisson et al., 2018). A retrospective study from the Netherlands of 2,555 transgender women taking primarily CPA with various formulations of estrogen reported an increased standardized incidence ratio of meningiomas in patients who used cyproterone acetate after gonadectomy for many years when compared with the general Dutch population (Nota et al., 2018). Furthermore, in a shorter study in Belgium, 107 transgender women had transient elevations in prolactin levels following treatment with cyproterone acetate, which declined to normal after discontinuation (Defreyne, Nota et al., 2017). A recent publication, not included in the systematic review, examined 126 transgender women taking spironolactone, GnRHas, or cyproterone and concluded cyproterone was associated with higher prolactin levels and a worse lipid profile than spironolactone or GnRHas (Sofer et al., 2020). After balancing the costs and accessibility of measuring prolactin levels against the clinical significance of an elevated level, a decision was made not to make a recommendation for or against monitoring prolactin levels at this time. HCPs should therefore make individualized clinical decisions about the necessity to measure prolactin levels based on the type of hormone regimen and/or the presence of symptoms of hyperprolactinemia or a pituitary tumor (e.g., galactorrhea, visual field changes).

Cyproterone has also been linked to meningiomas. Nine cases of meningioma have been reported in the literature among transgender women primarily taking cyproterone acetate (Mancini et al., 2018). This increased risk has also been identified in cisgender populations. In 2020, the European Medicines Agency published a report recommending cyproterone products with daily doses of 10 mg or more should be restricted because of the risk of developing meningioma (European Medicines Agency, 2020). Most likely this association is a specific effect of cyproterone acetate and has not been extrapolated to include other testosterone-lowering drugs. In the US, where cyproterone acetate is not available, the North American Association of Central Cancer Registries (NAACCRs) database did not identify an increased risk of brain tumors (not specific to

meningiomas) among transgender women (Nash et al., 2018). Furthermore, there was not an increase in the hazard ratio of brain tumors in the Kaiser cohort of 2,791 transgender women compared with cisgender controls (Silverberg et al., 2017). No long-term studies have reported on the risk of meningiomas and prolactinomas in transgender women taking GnRHas.

Our strong recommendation for the use of testosterone-lowering medications as part of a hormone regimen for transgender individuals with testes is based on the global practice of using these medications in addition to estrogen therapies as well as the relatively minimal risk associated with these therapies. However, we are not able to make a recommendation favoring one testosterone-lowering medication over another at this time. The published data thus far raises some concerns about the risk of meningiomas with the prolonged use (>2 years) and higher doses (>10mg daily) of cyproterone acetate (Nota et al., 2018; Ter Wengel et al., 2016; Weill et al., 2021).

Bicalutamide is an antiandrogen that has been used in the treatment of prostate cancer. It competitively binds to the androgen receptor to block the binding of androgens. Data on the use of bicalutamide in trans feminine populations is very sparse and safety data is lacking. One small study looked at the use of bicalutamide 50 mg daily as a puberty blocker in 23 trans feminine adolescents who could not obtain treatment with a GnRH analogue (Neyman et al., 2019). All adolescents experienced breast development which is also commonly seen in men with prostate cancer who are treated with bicalutamide. Although rare, fulminant hepatotoxicity resulting in death has been described with bicalutamide (O'Bryant et al., 2008). Given that bicalutamide has not been adequately studied in trans feminine populations, we do not recommend its routine use.

The administration of 5α-reductase inhibitors block the conversion of testosterone to the more potent androgen dihydrotestosterone. The Food & Drug Administration (FDA) approved indications of finasteride administration include benign prostatic hypertrophy and androgenetic alopecia. Data on the use of 5α-reductase inhibitors in trans feminine populations is very sparse (Irwig, 2021). It is unclear whether this class of medication could have any clinical benefit in trans feminine individuals whose testosterone and dihydrotestosterone levels have already been lowered with estrogen and an antiandrogen. We therefore do not recommend their routine use in trans feminine populations. Finasteride may be an appropriate treatment option in trans masculine individuals experiencing bothersome alopecia resulting from higher dihydrotestosterone levels. Nonetheless, treatment with a 5α-reductase inhibitor may impair clitoral growth and the development of facial and body hair in trans masculine individuals. Studies are needed to assess the efficacy and safety of 5α-reductase inhibitors in transgender populations.

Statement 12.17

We recommend health care professionals monitor hematocrit (or hemoglobin) levels in transgender and gender diverse people treated with testosterone.

There are good quality data suggesting a rise in hematocrit (or hemoglobin) is associated with TGD persons treated with testosterone (Defreyne et al., 2018). The testosterone regimens in the systematic review included testosterone esters ranging from the equivalent of 25–250 mg SC/IM weekly, testosterone undecanoate 1000 mg every 12 weeks, or testosterone gel 50 mg applied daily to the skin (Defreyne et al., 2018; Gava et al., 2018; Giltay et al., 2000; Meriggiola et al., 2008; Pelusi et al., 2014; T'Sjoen et al., 2005; Wierckx, van Caenegem et al., 2014; Wierckx, van de Peer et al., 2014). The expected rise should be consistent with reference ranges in cisgender males.

Statement 12.18

We suggest health care professionals collaborate with surgeons regarding hormone use before and after gender-affirmation surgery. For supporting text, see Statement 12.19.

Statement 12.19

We suggest health care professionals counsel eligible* transgender and gender diverse people about the various options for gender-affirmation surgery unless surgery is either not indicated or is medically contraindicated.

Despite the absence of evidence, perioperative clinical standards for gender-affirmation surgeries have included cessation of hormone therapy for 1–4 weeks before and after surgery, most commonly genital surgeries (Hembree et al., 2009). Such practice was meant to mitigate the risk of VTE associated with exogenous estrogen administration (Hembree et al., 2009). Estrogen and testosterone could then be resumed at some point postoperatively.

After careful examination, investigators have found no perioperative increase in the rate of VTE among transgender individuals undergoing surgery, while being maintained on sex steroid treatment throughout when compared with that among patients whose sex steroid treatment was discontinued preoperatively (Gaither et al., 2018; Hembree et al., 2009; Kozato et al., 2021; Prince & Safer, 2020). Sex steroid treatment is especially important after gonadectomy to avoid the sequelae of hypogonadism, the risk of developing osteoporosis, and for the maintenance of mental health and quality of life (Fisher, Castellini et al., 2016; Rosen et al., 2019). Thus, hormone providers and surgeons should educate patients about the necessity for continuous exogenous hormone therapy after gonadectomy.

To be able to educate patients and serve as clinical advocates, HCPs should be knowledgeable about the risks and benefits of gender-affirmation surgeries and should also be cognizant of the performance measures and surgical outcomes of the surgeons to whom they might refer patients (Beek, Kreukels et al., 2015; Colebunders et al., 2017; Wiepjes et al., 2018). In general, most medically necessary surgeries can be thought of as involving three regions: the face, chest/breasts, and genitalia (internal and external). Additional medically necessary procedures include body contouring and voice surgery. See medical necessity statement in Chapter 2—Global Applicability, Statement 2.1).

Multiple procedures are available for facial gender-affirming surgeries including, but not limited to chondrolanryngoplasty, rhinoplasty, contouring or augmentation of the jaw, chin, and forehead, facelift, hair removal and hair transplantation (see Chapter 13—Surgery and Postoperative Care). Procedures available for chest/breast surgery include breast augmentation, double mastectomy with nipple grafts, periareolar mastectomy, and liposuction. The most common gender-affirmation surgery for TGD individuals with endogenous breast development is masculinizing chest surgery (mastectomy) (Horbach et al., 2015; Kailas et al., 2017).

Internal genital surgery procedures include but are not limited to orchiectomy, hysterectomy, salpingo-oophorectomy, vaginoplasty, and colpectomy/vaginectomy (Horbach et al., 2015; Jiang et al., 2018). The inner lining in vaginoplasty is typically constructed from penile skin, skin grafts, a combination of both, or a bowel segment. Removal of the uterus/ovaries can be performed individually or all at once (hysterectomy, salpingo-oophorectomy, and colpectomy). If colpectomy is performed, a hysterectomy must also be performed. The ovaries may remain in situ, upon patient request. A potential benefit of leaving one or both ovaries is fertility preservation, while the downside is the potential for the development of ovarian pathology, including cancer (De Roo et al., 2017).

External genital surgery procedures include but are not limited to vulvoplasty, metoidioplasty, and phalloplasty (Djordjevic et al., 2008; Frey et al., 2016). Hair removal is generally necessary before performing external genital procedures (Marks et al., 2019). Vulvoplasty can include the creation of the mons, labia, clitoris, and urethral opening. Urethral lengthening is an option for both metoidioplasty and phalloplasty, but is associated with a greatly increased complication rate (Schechter & Safa, 2018). Wound care and physical therapy are necessary for managing wounds resulting from the donor sites for phalloplasty (van Caenegem, Verhaeghe et al., 2013). Pelvic physical therapy can also be an important adjunct intervention after surgery for managing voiding and sexual function (Jiang et al., 2019). Dialogue, mutual understanding, and clear communication in a common language between patients, HCPs, and surgeons will contribute to well-considered decisions about the available surgical procedures.

Statement 12.20

We recommend health care professionals initiate and continue gender-affirming hormone

therapy for eligible* transgender and gender diverse people who wish this treatment due to demonstrated improvement in psychosocial functioning and quality of life. For supporting text, see Statement 12.21.

Statement 12.21

We recommend health care professionals maintain existing hormone therapy if the transgender and gender diverse individual's mental health deteriorates and assess the reason for the deterioration, unless contraindicated.

Several mental health disparities have been documented in the transgender population including depression, suicidality, anxiety, decreased self-esteem, and post-traumatic stress disorder (Arcelus et al., 2016; Becerra-Culqui et al, 2018; Bouman et al., 2017; Eisenberg et al., 2017; Heylens, Elaut et al., 2014; Witcomb et al., 2018). The gender minority stress model provides evidence of several mediators and moderators of these disparities (Hendricks & Testa, 2012; Meyer, 2003). Mediators and moderators of mental health disparities unique to transgender people include experiences of discrimination, victimization, misgendering, family rejection, and internalized transphobia (Hendricks & Testa, 2012). Factors that have a positive effect on mental health include family acceptance, supportive social and romantic relationships, transgender community connectedness, protection by affirming and inclusive policies, policies of affirmation and inclusion, possession of updated legal name/gender documentation, and achievement of physical gender transition based on individualized embodiment goals (Bauer et al., 2015; Bockting et al., 2013; Bouman et al., 2016; Davey et al., 2014; de Vries et al., 2014; Du Bois et al., 2018; Gower, Rider, Brown et al., 2018; Hendricks & Testa, 2012; Keo-Meier et al., 2015; Meier et al., 2013; Pflum et al., 2015; Ryan et al., 2010; Smith et al., 2018).

Hormone therapy has been found to positively impact the mental health and quality of life of TGD youth and adults who embark on this treatment (Aldridge et al., 2020; Allen et al., 2019; Bauer et al., 2015; Nobili et al., 2018; Russell et al., 2018; Ryan, 2009). In many cases, hormone therapy is considered a lifesaving intervention (Allen et al., 2019; Grossman & D'Augelli, 2006; Moody et al., 2015). Several studies have found associations between the initiation of hormone therapy and improved mental health in youth and adults (Aldridge et al., 2020; Costa et al., 2016; de Vries et al., 2014; Kuper et al., 2020; Nguyen et al., 2018; White Hughto & Reisner, 2016), including improvements in quality of life (Gorin-Lazard et al., 2012; Gorin-Lazard et al., 2013; Murad et al., 2010; Newfield et al., 2006; Nobili et al., 2018; White Hughto & Reisner, 2016), a reduction in anxiety and depression (Aldridge et al., 2020; Colizzi et al., 2014; Davis & Meier, 2014; de Vries, Steensma et al., 2011; Gómez-Gil et al., 2012; Rowniak et al., 2019), decreased stress, and decreased paranoia (Keo-Meier & Fitzgerald, 2017). A prospective, controlled trial using the Minnesota Multiphasic Personality Inventory-2 (MMPI-2) demonstrated significant improvement in multiple domains of psychological functioning in transgender men after only 3 months of testosterone treatment (Keo-Meier et al., 2015). Although there are higher rates of autism symptoms in the transgender population, these symptoms have not been found to increase after the initiation of hormone therapy (Nobili et al., 2020).

As a reduction in depressive symptoms may correlate with a decrease in the risk of suicide, withholding hormone therapy based on the presence of depression or suicidality may cause harm (Keo-Meier et al., 2015; Levy et al., 2003). Turban, King et al. (2020) found a decrease in the odds of lifetime suicidal ideation in adolescents who required pubertal suppression and had access to this treatment compared with those with a similar desire with no such access (Turban, King et al., 2020). A recent systematic review found pubertal suppression in TGD adolescents was associated with an improved social life, decreased suicidality in adulthood, improved psychological functioning and quality of life (Rew et al., 2020). Because evidence suggests hormone therapy is directly linked to decreased symptoms of depression and anxiety, the practice of withholding hormone therapy until these symptoms are treated with traditional psychiatry is considered to have iatrogenic effects

(Keo-Meier et al., 2015). If psychiatric treatment is indicated, it can be started or adjusted concurrently without discontinuing hormone therapy.

**For eligibility criteria for adolescents and adults, please refer to Chapter 5—Assessment for Adults and Chapter 6—Adolescents as well as Appendix D.*

CHAPTER 16 Reproductive Health

All humans, including transgender individuals, have the reproductive right to decide whether or not to have children (United Nations Population Fund, 2014). Medically necessary gender-affirming hormonal treatments (GAHTs) and surgical interventions (see medically necessary statement in Chapter 2—Global Applicability, Statement 2.1) that alter reproductive anatomy or function may limit future reproductive options to varying degrees (Hembree et al., 2017; Nahata et al., 2019). It is thus critical to discuss infertility risk and fertility preservation (FP) options with transgender individuals and their families prior to initiating any of these treatments and to continue these conversations on an ongoing basis thereafter (Hembree et al., 2017). Established FP options, such as embryo, oocyte, and sperm cryopreservation, may be available for postpubertal transgender individuals (Nahata et al., 2019). Research protocols for ovarian and testicular tissue cryopreservation have also been developed and studied (Borgström et al., 2020; Nahata et al., 2019; Rodriguez-Wallberg, et al., 2019). Whereas the use of embryos, mature oocytes, and sperm have all proven to be efficacious when employed within clinical treatments, cryopreserved gonadal tissues would require either future retransplantation aimed at obtaining fully functional gametes or the application of laboratory methods for culture, which are still under development in basic science research settings. Of note, recent American Society for Reproductive Medicine guidelines have lifted the experimental label on ovarian tissue cryopreservation, but evidence remains limited in prepubertal children (Practice Committee of the American Society for Reproductive Medicine, 2019).

Individualized care should be provided in the context of each person's parenthood goals. Some research suggests transgender and gender diverse (TGD) people may be less likely to desire genetically related children or children at all when compared with cisgender peers (Defreyne, van Schuylenbergh et al., 2020; Russell et al., 2016; von Doussa et al., 2015). Yet, several other studies have shown many TGD individuals 1) desire genetically related children; 2) regret missed opportunities for FP; and 3) are willing to delay or interrupt hormone therapy to preserve fertility and/or conceive (Armuand, Dhejne et al., 2017; Auer et al., 2018; De Sutter et al., 2002; Defreyne, van Schuylenbergh et al., 2020; Tornello & Bos, 2017).

Many barriers to FP have been reported, such as cost (which is exacerbated when insurance coverage is lacking), urgency to start treatment, inability to make future-oriented decisions, inadequate provider knowledge/provider biases that affect offering FP, and difficulties accessing FP (Baram et al., 2019; Defreyne, van Schuylenbergh et al., 2020). Additionally, transgender individuals may have worsening dysphoria due to various steps in the FP process that are inseparably connected with the gender assigned at birth (Armuand, Dhejne, et al., 2017; Baram et al., 2019). When available, a multidisciplinary team approach, where both medical and mental health providers collaborate with gender-affirming fertility specialists, can help overcome some of these barriers (Tishelman et al., 2019). TGD individuals should be educated about the distinction between fertility (utilizing one's own gametes/reproductive tissues) and pregnancy. In addition to fertility considerations, efforts to ensure equitable high-quality care for all forms of family planning and building throughout the full reproductive continuum must be maintained. This includes procreative options such as perinatal care, pregnancy, delivery, and postpartum care, as well as family planning and contraceptive options to prevent unplanned pregnancies, and pregnancy termination if sanctioned (Bonnington et al., 2020; Cipres et al., 2017; Krempasky et al., 2020; Light et al., 2018; Moseson, Fix et al., 2020). TGD people who wish to carry a pregnancy should undergo standard of care preconception care and prenatal counseling and should receive counseling about breast/chest feeding in environments supportive of people with diverse gender identities and experiences (MacDonald et al., 2016; Obedin-Maliver & Makadon, 2016).

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and

Statements of Recommendations

16.1- We recommend health care professionals who are treating transgender and gender diverse people and prescribing or referring patients for hormone therapies/surgeries advise their patients about:
16.1.a- Known effects of hormone therapies/surgery on future fertility;
16.1.b- Potential effects of therapies that are not well studied and are of unknown reversibility;
16.1.c- Fertility preservation (FP) options (both established and experimental);
16.1.d- Psychosocial implications of infertility.
16.2- We recommend health care professionals refer transgender and gender diverse people interested in fertility preservation to providers with expertise in fertility preservation for further discussion.
16.3- We recommend transgender care teams partner with local reproductive specialists and facilities to provide specific and timely information and fertility preservation services prior to offering medical and surgical interventions that may impact fertility.
16.4- We recommend health care professionals counsel pre- or early-pubertal transgender and gender diverse youth seeking gender-affirming therapy and their families that currently evidence-based/established fertility preservation options are limited.
16.5- We recommend transgender and gender diverse people with a uterus who wish to carry a pregnancy undergo preconception care, prenatal counseling regarding use and cessation of gender-affirming hormones, pregnancy care, labor and delivery, chest/breast feeding supportive services, and postpartum support according to local standards of care in a gender-affirming way.
16.6. We recommend medical providers discuss contraception methods with transgender and gender diverse people who engage in sexual activity that can result in pregnancy.
16.7. We recommend providers who offer pregnancy termination services ensure procedural options are gender-affirming and serve transgender people and those of diverse genders.

harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 16.1

We recommend health care professionals who are treating transgender and gender diverse people and prescribing or referring patients for hormone therapies/surgeries advise their patients about:

a. **Known effects of hormone therapies/surgeries on future fertility;**
b. **Potential effects of therapies that are not well studied and are of unknown reversibility;**
c. **Fertility preservation (FP) options (both established and experimental;**
d. **Psychosocial implications of infertility.**

TGD individuals assigned female at birth

GAHT may negatively impact future reproductive capacity (Hembree et al., 2017). Based on current evidence in transgender men and gender diverse people assigned female at birth, these risks are as follows:

Gonadotropin-releasing hormone agonists (GnRHas) may be used for pubertal suppression to prevent further pubertal progression until adolescents are ready for masculinizing treatment. GnRHas may also be used for menstrual suppression. GnRHas impact the maturation of gametes but do not cause permanent damage to gonadal function. Thus, if GnRHas are discontinued, oocyte maturation would be expected to resume.

There are few studies detailing the effects of testosterone therapy on reproductive function in transgender men (Moravek et al., 2020). Restoration of normal ovarian function with oocyte maturation after testosterone interruption has been demonstrated in transgender men who have achieved natural conception. A retrospective study on oocyte cryopreservation showed no differences in the total number of oocytes retrieved or in the number of mature oocytes between transgender men and age- and BMI-matched cisgender women (Adeleye et al., 2018, 2019). The first results have recently been published evaluating live birth rates after controlled ovarian stimulation in transgender men compared with cisgender women (Leung et al., 2019). Testosterone was discontinued prior to ovarian stimulation. Overall, the results concerning the influence of testosterone on reproductive organs and their function appear to be reassuring. However, there have been no prospective studies to date evaluating the effect of long-term hormone therapy on fertility (i.e., started in adolescence) or in those treated with GnRHas in early puberty followed by testosterone therapy. It is important to take into consideration that required medications and procedures for cryopreserving oocytes (a

pelvic examination, vaginal ultrasound monitoring, and oocyte retrievals) may lead to increasing gender dysphoria in transgender men (Armuand, Dhejne et al., 2017).

Surgical interventions among transgender men will have obvious implications for reproductive capacity. If patients desire a hysterectomy, the option should be offered of preserving the ovaries to retain the possibility of having a genetically related child. Alternatively, if the ovaries are removed either separately or concurrently with the hysterectomy, egg freezing should be offered prior to surgery and/or ovarian tissue cryopreservation can be done at the time of oophorectomy. Although this procedure is no longer considered experimental, many transgender men may desire *in vitro* maturation of primordial follicles, which is still investigational. Studies evaluating oocyte function have shown oocytes isolated from transgender men with testosterone exposure at the time of oophorectomy can be matured *in vitro* to develop normal metaphase II meiotic spindle structure (De Roo et al., 2017; Lierman et al., 2017).

TGD individuals assigned male at birth

Based on current evidence in transgender women and gender diverse people assigned male at birth (AMAB), the influence of medical treatment is as follows:

GnRHas inhibit spermatogenesis. Data suggest discontinuation of treatment results in a re-initiation of spermatogenesis, although this may take at least 3 months and most likely longer (Bertelloni et al., 2000). Furthermore, the psychological burden of re-exposure to testosterone should be considered.

Anti-androgens and estrogens result in an impaired sperm production (de Nie et al., 2020; Jindarak et al., 2018; Kent et al., 2018). Spermatogenesis might resume after discontinuation of prolonged treatment with anti-androgens and estrogens, but data are limited (Adeleye et al., 2019; Alford et al., 2020; Schneider et al., 2017). Testicular volumes diminish under the influence of gender-affirming hormone treatment (Matoso et al., 2018). Semen quality in transgender women may also be negatively affected by specific life-style factors, such as a low frequency of masturbation, wearing the genitals tight against the body (e.g., with use of tight undergarments for tucking) (Jung & Schuppe, 2007; Mieusset et al., 1985, 1987; Rodriguez-Wallberg, Häljestig et al., 2021).

Statement 16.2

We recommend health care professionals refer transgender and gender diverse people interested in fertility preservation to providers with expertise in fertility preservation for further discussion.

Research shows many transgender adults desire biological children (De Sutter et al., 2002; Defreyne, van Schuylenbergh et al., 2020; Wierckx, Van Caenegem et al., 2012), yet FP rates remain widely variable, particularly in youth (< 5%–40%) (Brik et al., 2019; Chen et al., 2017; Chiniara et al., 2019; Nahata et al., 2017; Segev-Becker et al., 2020). In a recent survey, many youth acknowledged their feelings about having a biological child might change in the future (Strang, Jarin et al., 2018). Non-elective sterilization is a violation of human rights (Ethics Committee of the American Society for Reproductive Medicine, 2015; Equality and Human Rights Commission, 2021; Meyer III et al., 2001) and due to advances in social attitudes, fertility medicine, and affirmative transgender health care, opportunities for biological parenthood during transition should be supported for transgender people. Due to the influence clinical opinion may have on transgender or nonbinary people's FP and on parenting decisions, FP options should be explored by health care providers alongside options such as fostering, adoption, coparenting, and other parenting alternatives (Bartholomaeus & Riggs, 2019). Transgender patients who have been offered this type of discussion and have been given the choice to undergo procedures for FP have reported the experience to be an overall positive one (Armuand, Dhejne et al., 2017; De Sutter et al., 2002; James-Abra et al., 2015).

In other patient populations, fertility referrals and formal fertility programs have been shown to increase FP rates and improve patient satisfaction (Kelvin et al., 2016; Klosky, Anderson et al., 2017; Klosky, Wang et al., 2017;

Shnorhavorian et al., 2012) Physician attitudes have been investigated, and recent studies indicate both an awareness and a desire to provide fertility-related information to children and their families (Armuand et al., 2020). However, barriers have also been identified, including lack of knowledge, comfort, and resources (Armuand, Nilsson et al., 2017; Frederick et al., 2018). Thus, the need for appropriate training of health care providers has been highlighted, with emphasis placed on fertility counseling and offering FP options to all at-risk individuals in an unbiased way (Armuand, Nilsson et al., 2017). Parents' recommendations have also been shown to significantly influence FP rates in adolescent and young adult males with cancer (Klosky, Flynn et al., 2017). While there are clear clinical differences in these populations, these findings can help inform best practices for fertility counseling and FP referrals for transgender individuals.

Statement 16.3

We recommend transgender care teams partner with local reproductive specialists and facilities to provide specific and timely information and fertility preservation services prior to offering medical and surgical interventions that may impact fertility.

Cryopreservation of sperm and oocytes are established FP techniques and can be offered to pubertal, late pubertal, and adult birth assigned males and birth assigned females, respectively, preferably prior to the initiation of GAHT (Hembree et al., 2017; Practice Committee of the American Society for Reproductive Medicine, 2019). Cryopreservation of embryos can be offered to adult (post-pubertal) TGD people who wish to have a child and have an available partner. The future use of cryopreserved gametes is also dependent on the gametes and reproductive organs of the future partner (Fischer, 2021; Maxwell et al., 2017)

Although semen parameters have been shown to be compromised when FP is performed after initiation of GAH medication (Adeleye et al., 2019), one small study showed when the treatment was discontinued, semen parameters were comparable to those in TGD patients who had never undergone GAH treatment. With regard to ovarian stimulation, oocyte vitrification yield and subsequent use of the oocytes in in-vitro fertilization (IVF), there is no reason to anticipate a different outcome in assisted reproductive technology (ART) treatments for TGD patients than that obtained in cisgender patients undergoing ART—other than individual confounding factors related to (in)fertility—when gametes are banked prior to any medical treatment (Adeleye et al., 2019). The use of oocytes in ART treatment resulted in similarly successful outcomes in TGD compared with controlled, matched cisgender patients (Adeleye et al., 2019; Leung et al., 2019; Maxwell et al., 2017).

Although these are established options, few pubertal, late pubertal or adult TGD people undergo FP (Nahata et al., 2017), and many experience challenges while undergoing FP interventions. Not only is access and cost of these methods a barrier (particularly in regions without insurance coverage), but these procedures are often physically and emotionally uncomfortable, and many express concerns about postponing the transitioning process (Chen et al., 2017; De Sutter et al., 2002; Nahata et al., 2017; Wierckx, Stuyver et al., 2012). Especially for the birth assigned females, the invasiveness of endovaginal ultrasound follow-up of the ovarian stimulation and oocyte retrieval procedures (and associated psychological distress) have been cited as a barrier (Armuand, Dhejne et al., 2017; Chen et al., 2017). There is also the concern young adults going through transitioning may not have a clear vision of parenting and are therefore likely to decline the opportunity to use FP at that time—while as adults, they may have different opinions about parenthood (Cauffman & Steinberg, 2000). The reduction of gender dysphoria during transitioning could also influence the decision-making process surrounding FP (Nahata et al., 2017). Based on research showing TGD youths' fertility perspectives may change over time (Nahata et al., 2019; Strang, Jarin et al., 2018), FP options should be discussed on an ongoing basis.

Statement 16.4

We recommend health care professionals counsel pre- or early-pubertal transgender and

gender diverse youth seeking gender-affirming therapy and their families that currently evidence-based/established fertility preservation options are limited.

For prepubertal and early-pubertal children, FP options are limited to the storage of gonadal tissue. Although this option is available for TGD children in the same way that it is available for cisgender prepubertal and early-pubertal oncological patients, there is no literature describing the utilization of this approach in the transgender population. Ovarian tissue autotransplantation has resulted in over 130 live births in cisgender women. Most of these patients conceived naturally without ART (Donnez & Dolmans, 2015; Jadoul et al., 2017), and the majority stored their ovarian tissue either as adults or during puberty. Although the recent American Society for Reproductive Medicine guideline has lifted the experimental label from ovarian tissue cryopreservation (Practice Committee of the American Society for Reproductive Medicine, 2019), there are very few case reports describing a successful pregnancy in a woman following the transplantation of ovarian tissue cryopreserved before puberty. Demeestere et al. (2015) and Rodriguez-Wallberg, Milenkovic et al. (2021) described cases of successful pregnancies following transplantation of tissue procured at the age of 14, and recently Matthews et al. (2018) described the case of a girl diagnosed with thalassemia who had ovarian tissue stored at the age of 9 and transplantation 14 years late. She subsequently conceived through IVF and delivered a healthy baby.

Currently, the only future clinical application for storing ovarian tissue is autotransplantation, which might be undesirable in a transgender man (due to the potentially undesirable effects of estrogen). A laboratory procedure that would make it possible to mature oocytes *in vitro* starting with ovarian tissue would be the ideal future application of stored ovarian tissue for transgender people, but this technique is currently only being investigated and optimized in basic science research settings (Ladanyi et al., 2017; Oktay et al., 2010).

Prepubertal procurement of testicular tissue has been documented as a low-risk procedure (Borgström et al., 2020; Ming et al., 2018). Some authors have also described this approach as a theoretical option in transgender people (De Roo et al., 2016; Martinez et al., 2017; Nahata, Curci et al., 2018). However, there are no reports in the literature describing the clinical or investigational utilization of this FP option for TGD patients. Moreover, the viability of the clinical application of autotransplantation of testicular tissue remains unknown in humans, and *in vitro* maturation techniques are still in the realm of basic science research. Thus, specialists currently consider this technique experimental (Picton et al., 2015). The possibility of storing gonadal tissue should be discussed prior to any genital surgery that would result in sterilization, although the probability of being able to use this tissue must be clearly addressed.

Statement 16.5

We recommend transgender and gender diverse people with a uterus who wish to carry a pregnancy undergo preconception care and prenatal counseling regarding the use and cessation of gender-affirming hormones, pregnancy care, labor and delivery, chest/breast feeding supportive services, and postpartum support according to local standards of care in a gender-affirming way.

Most transgender men and gender diverse people (AFAB) retain their uterus and ovaries and thus can conceive and carry a pregnancy even after long-term testosterone use (Light et al., 2014). Many transgender men desire children (Light et al., 2018; Wierckx, van Caenegem et al., 2012) and are willing to carry a pregnancy (Moseson, Fix, Hastings et al., 2021; Moseson, Fix, Ragosta et al., 2021). ART has expanded the opportunity for many transgender men to conceive and fulfill their family planning wishes (De Roo et al., 2017; Ellis et al., 2015; Maxwell et al., 2017). Some transgender men report psychological isolation, dysphoria related to the gravid uterus and chest changes, and depression (Charter, 2018; Ellis et al., 2015; Hoffkling et al., 2017; Obedin-Maliver & Makadon, 2016). Conversely, other studies have reported some positive experiences during pregnancy as well (Fischer, 2021; Light et al., 2014). Mental health providers should be involved to provide support, and counseling should be

provided addressing when to stop and when to resume gender-affirming hormones, what options are available for the mode of delivery and for chest/breast feeding (Hoffkling et al., 2017). Finally, system-level and interpersonal-level interventions should be implemented to ensure person-centered reproductive health care for all people (Hahn et al., 2019; Hoffkling et al., 2017; Moseson, Zazanis et al., 2020; Snowden et al., 2018).

Given the potential harmful effects of testosterone on the developing embryo, discontinuing testosterone or masculinizing hormone therapy prior to conception and during the entire pregnancy is recommended. However, the optimal time for both the discontinuation of testosterone prior to pregnancy and its resumption after pregnancy is unknown. Since stopping gender-affirming hormones may cause distress and exacerbate dysphoria in transgender men, when and how to stop this therapy should be discussed during prenatal counseling (Hahn et al., 2019). Because information about the duration of testosterone exposure and the risk of teratogenicity is lacking, testosterone use should be discontinued prior to attempting pregnancy and before stopping contraception. Moreover, there is limited information regarding health outcomes of infants born to transgender men. Small case series attempting to evaluate this question have revealed no adverse physical or psychosocial differences between infants born to transgender men and infants in the general population (Chiland et al., 2013).

Chest/Breast feeding

In the limited studies evaluating lactation and chest/breast feeding, the majority of transgender men and TGD individuals AFAB who chose to chest/breast feed postpartum were successful, with research suggesting induction of lactation is in part dependent on preconception counseling and experienced lactation nursing support (MacDonald et al., 2016; Wolfe-Roubatis & Spatz, 2015). Specifically, transgender men and TGD people who use testosterone should be informed 1) although quantities are small, testosterone does pass through chest/breast milk; and 2) the impact on the developing neonate/child is unknown, and therefore gender-affirming testosterone use is not recommended during lactation but may be resumed after discontinuation of chest/breast feeding (Glaser et al., 2009). Transgender men and other TGD individuals AFAB should be made aware some patients who carry a pregnancy may experience undesired chest growth and/or lactation even after chest reconstruction and should therefore be supported if they desire to suppress lactation (MacDonald et al., 2016).

There is limited information concerning lactation in transgender women as well as other TGD AMAB but many also express the desire to chest/breast feed. While there is a case report of a transgender woman successfully lactating and chest/breast feeding her infant after hormonal support using a combination of estrogen, progesterone, domperidone, and breast pumping (Reisman & Goldstein, 2018), the nutritional and immunological profile of chest/breast milk under these conditions has not been studied. Therefore, patients need to be informed about the risks and benefits of this approach to child feeding (Reisman & Goldstein, 2018).

Statement 16.6

We recommend medical providers discuss contraception methods with transgender and gender diverse people who engage in sexual activity that can result in pregnancy.

Many TGD individuals may retain reproductive capacity, and they (if they retain a uterus, ovaries, and tubes) or their sexual partners (for sperm producing individuals) may experience unplanned pregnancies (James et al., 2016; Light et al., 2014; Moseson, Fix et al., 2020). Therefore, intentional family planning counseling, including contraception and abortion conducted in gender-expansive ways is needed (Klein, Berry-Bibee et al., 2018; Obedin-Maliver, 2015; Stroumsa & Wu, 2018). TGD people AFAB may not use contraception due to an erroneous assumption that testosterone is a reliable form of contraception (Abern & Maguire, 2018; Ingraham et al., 2018; Jones, Wood et al., 2017; Potter et al., 2015). However, based on current understanding, testosterone should not be considered a reliable form of contraception because of its incomplete suppression of the hypothalamic-pituitary-adrenal axis (Krempasky et al., 2020). Furthermore, pregnancies have occurred while individuals are amenorrheic due

to testosterone use, which may outlast active periods of administration (Light et al., 2014). Pregnancy can also occur in TGD people after long-term testosterone use (at least up to 10 years), although the effect on oocytes and baseline fertility is still unknown (Light et al., 2014).

TGD people AFAB may use a variety of contraceptive methods (Abern & Maguire, 2018; Bentsianov et al., 2018; Bonnington et al., 2020; Chrisler et al., 2016; Cipres et al., 2017; Jones, Wood et al., 2017; Krempasky et al., 2020; Light et al., 2018).These methods may be used explicitly for pregnancy prevention, menstrual suppression, abnormal bleeding, or other gynecological needs (Bonnington et al., 2020; Chrisler et al., 2016; Krempasky et al., 2020; Schwartz et al., 2019). Contraceptive research gaps within this population are profound. No studies have examined how the use of exogenous androgens (e.g., testosterone) may modify the efficacy or safety profile of hormonal contraceptive methods (e.g., combined estrogen and progestin hormonal contraceptives, progestin-only based contraceptives) or non-hormonal and barrier contraceptive methods (e.g., internal and external condoms, non-hormonal intrauterine devices, diaphragms, sponges, etc.).

Gender diverse individuals who currently have a penis and testicles may engage in sexual activity with individuals who have a uterus, ovaries, and tubes of any gender. Gender diverse people who have a penis and testicles can produce sperm even while on gender-affirming hormones (i.e., estrogen), and although semen parameters are diminished among those who are currently using or who have previously used gender-affirming hormones, azoospermia is not complete and sperm activity is not totally suppressed (Adeleye et al., 2019; Jindarak et al., 2018; Kent et al., 2018). Therefore, contraception needs to be considered if pregnancy is to be avoided in penis-in-vagina sexual activity between a person with a uterus, ovaries, and tubes and one with a penis and testicles, irrespective of the use of gender-affirming hormones by either partner. Currently, contraceptive methods available for use by the sperm-producing partner are primarily mechanical barriers (i.e., external condoms, internal condoms), permanent sterilization (i.e., vasectomy), and gender-affirming surgery (e.g., orchiectomy, which also results in sterilization). Contraceptive counseling that considers sperm producing, egg producing, and gestating partners (as relevant) is recommended.

Statement 16.7

We recommend providers who offer pregnancy termination services ensure procedural approaches are gender-affirming and serve transgender people and those of diverse genders.

Unplanned pregnancies and abortions have been reported among TGD individuals with a uterus (Abern & Maguire, 2018; Light et al., 2014; Light et al., 2018; Moseson, Fix et al., 2020) and documented through surveys of abortion-providing facilities (Jones et al., 2020). However, the population-based epidemiology of abortion provision and the experiences and preferences of TGD individuals AFAB undergoing abortion still represents a critical gap in research (Fix et al., 2020; Moseson, Fix et al., 2020; Moseson, Lunn et al., 2020). Nonetheless, given that pregnancy capacity exists among many TGD people and pregnancies may not always be planned or desired, access to safe, legal, and gender-affirming pregnancy medical and surgical termination services is necessary.

CHAPTER 17 Sexual Health

Sexual health has a profound impact on physical and psychological well-being, regardless of one's sex, gender, or sexual orientation. However, stigma about sex, gender and sexual orientation influences individual's opportunities to live out their sexuality and to receive appropriate sexual health care. Specifically, in most societies, cisnormativity and heteronormativity lead to the assumption that all people are cisgender and heterosexual (Bauer et al., 2009), and that this combination is superior to all other genders and sexual orientations (Nieder, Güldenring et al., 2020; Rider, Vencill et al., 2019). Hetero-cisnormativity negates the complexity of gender, sexual orientation, and sexuality and disregards diversity and fluidity. This is all the more important since sexual identities, orientations, and practices of transgender and gender diverse (TGD) people are characterized by an enormous diversity (Galupo et al., 2016; Jessen et al., 2021; Thurston & Allan, 2018; T'Sjoen et al., 2020). Likewise, a strong cross-cultural tendency toward allonormativity—the assumption that all people experience sexual attraction or interest in sexual activity—negates the diverse experiences of TGD people, especially those who locate themselves on the asexual spectrum (McInroy et al., 2021; Mollet, 2021; Rothblum et al., 2020).

The World Health Organization (WHO, 2010) emphasizes sexual health depends on respect for the sexual rights of all people, including the right to express diverse sexualities and to be treated respectfully, safely, and with freedom from discrimination and violence. Sexual health discourses have focused on agency and body autonomy, which include consent, sexual pleasure, sexual satisfaction, partnerships, and family life (Cornwall & Jolly, 2006; Lindley et al., 2021). In light of this, the WHO defines sexual health as "a state of physical, emotional, mental, and social well-being in relation to sexuality and not merely the absence of disease, dysfunction, or infirmity. Sexual health requires a positive and respectful approach to sexuality and sexual relationships as well as the possibility of having pleasurable and safe sexual experiences, free of coercion, discrimination, and violence. For sexual health to be attained and maintained, the sexual rights of all persons must be respected, protected, and fulfilled" (WHO, 2006, p. 5). This includes individuals on the asexual spectrum, who may not experience sexual attraction to others but may still choose to be sexual at times (e.g., via self-stimulation) and/or experience interest in forming and building romantic relationships (de Oliveira et al., 2021).

Scientific attention to the sexual experiences and behaviors of TGD people has grown in recent years (Gieles et al., 2022; Holmberg et al., 2019; Klein & Gorzalka, 2009; Kloer et al., 2021; Mattawanon et al., 2021; Stephenson et al., 2017; Tirapegui et al., 2020; Thurston & Allan, 2018). This expansion within the literature reflects a sex-positive framework (Harden, 2014), a framework that recognizes both the positive aspects such as sexual pleasure (Laan et al., 2021) and potential risks associated with sexuality (Goldhammer et al., 2022; Mujugira et al., 2021). Studies of TGD people's sexuality, however, often lack validated measures, an appropriate control group, or a prospective design (Holmberg et al., 2019). Additionally, most focus exclusively on sexual functioning (Kennis et al., 2022), and thus neglecting sexual satisfaction and broader operationalizations of sexual pleasure beyond functioning. The effects of current TGD-related medical treatments on sexuality are heterogeneous (Özer et al., 2022; T'Sjoen et al., 2020), and there has been little research on the sexuality of TGD adolescents (Bungener et al., 2017; Maheux et al., 2021; Ristori et al., 2021; Stübler & Becker-Hebly, 2019; Warwick et al., 2022). While sex-positive approaches to counseling and treatment for sexual difficulties experienced by TGD individuals have been proposed (Fielding, 2021; Jacobson et al., 2019; Richards, 2021), to date there is insufficient research on the effectiveness of such interventions. Focusing on the promotion of sexual health, the World Association for Sexual Health (WAS) asserts the importance of sexual pleasure and considers self-determination, consent, safety, privacy, confidence, and the ability to communicate and negotiate sexual relations as major facilitators (Kismödi et al., 2017). WAS asserts sexual pleasure is integral to sexual rights and human rights (Kismödi et al., 2017). To contribute to

Statements of Recommendations

17.1- We recommend health care professionals who provide care to transgender and gender diverse people acquire the knowledge and skills needed to address sexual health issues (relevant to their care provision).
17.2- We recommend health care professionals who provide care to transgender and gender diverse people discuss the impact of gender-affirming treatments on sexual function, pleasure, and satisfaction.
17.3- We recommend health care professionals who provide care to transgender and gender diverse people offer the possibility of including the partner(s) in sexuality-related care, if appropriate.
17.4- We recommend health care professionals counsel transgender and gender diverse people about the potential impact of stigma and trauma on sexual risk behavior, sexual avoidance, and sexual functioning.
17.5- We recommend any health care professional who offers care that may impact sexual health provide information, ask about the expectations of the transgender and gender diverse individual and assess their level of understanding of possible changes.
17.6.-We recommend health care professionals who provide care to transgender and gender diverse people counsel adolescents and adults regarding prevention of sexually transmitted infections.
17.7- We recommend health care professionals who provide care to transgender and gender diverse people follow local and World Health Organization guidelines for human immunodeficiency virus/sexual transmitted infections (HIV/STIs) screening, prevention, and treatment.
17.8- We recommend health care professionals who provide care to transgender and gender diverse people address concerns about potential interactions between antiretroviral medications and hormones.

the sexual health of TGD people, health care professionals (HCPs) need both transgender-related expertise and sensitivity (Nieder, Güldenring et al., 2020). With the goal of improving sexual health care for TGD people to an ethically-sound, evidence-based and high-quality level, HCPs must provide their health services with the same care (i.e., with transgender-related expertise), respect (i.e., with transgender-related sensitivity), and investment in sexual pleasure and sexual satisfaction as they provide for cisgender people (Holmberg et al., 2019).

In many societies, nonconforming gender expressions can elicit strong (emotional) reactions, including in HCPs. Thus, when initiating a health-related contact or establishing a therapeutic relationship, a nonjudgmental, open and welcoming manner is most likely ensured when HCPs reflect on their emotional, cognitive, and interactional reactions to the person (Nieder, Güldenring et al., 2020). In addition, transgender-related expertise refers to identifying the impact the TGD person's intersectional identities and experiences of marginalization and stigma may have had on their whole self (Rider, Vencill et al., 2019). To adequately address the specific physical, psychological, and social conditions of TGD people, HCPs must be aware these conditions are generally overlooked due to hetero-cis-normativity, lack of knowledge, and lack of skills (Rees et al., 2021). It is also important to consider cultural norms in relation to sexuality. For example, in some African cultures, the idea of sex as taboo restricts the number of acceptable terms to be used when taking a sexual history (Netshandama et al., 2017). Culturally respectful language can facilitate talking openly about one's sexual history and reduce ambiguity or shame (Duby et al., 2016). In addition, HCPs must be sensitive to the history of (mis)use of sexual identity and orientation as a gatekeeping function to exclude transgender people from gender-affirming health care (Nieder & Richter-Appelt, 2011; Richards et al., 2014). The following recommendations aim to improve sexual health care for TGD people.

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 17.1

We recommend health care professionals who provide care to transgender and gender diverse people acquire the knowledge and skills to address sexual health issues (relevant to their care provision).

It is important HCPs addressing the sexual health of TGD people be familiar with commonly used terminology (see Chapter 1—Terminology) and invite those seeking care to explain terms with which the provider may not be familiar. In this context, it is also important HCPs (are

prepared to) take a sexual history and offer treatment (according to their competencies) in a gender-affirming way with a sex-positive approach (Centers for Disease Control, 2020; Tomson et al., 2021). However, HCP's should apply greater importance to the terminology that the TGD person uses for their own body over more traditionally accepted or used medical terminology (Wesp, 2016). When talking about sexual practices, it is advisable to focus on body parts (e.g., "Do you have sex with people with a penis, people with a vagina, or both?"; ACON, 2022) and what role they play in their sexuality (e.g., "During Sex, do any parts of your body enter your partners body, such as their genitals, anus, or mouth?"; ACON, 2022).

Statement 17.2

We recommend health care professionals who provide care to transgender and gender diverse people discuss the impact of gender-affirming treatments on sexual function, pleasure, and satisfaction.

To achieve gender-affirming care, it is crucial HCPs providing transition-related medical interventions be sufficiently informed about the possible effects on sexual function, pleasure, and satisfaction (T'Sjoen et al., 2020). Since clinical data indicate that TGD people score significantly lower in sexual pleasure compared to cisgender individuals, this is even more important (Gieles et al., 2022). If the HCP cannot provide information about the effects of their treatment on sexual function, pleasure, and satisfaction, they are at least expected to refer the individual to someone qualified to do so. If the sexuality-related effects of their treatment are unknown, HCPs should inform their patients accordingly. As introduced above, the sexuality of TGD people often challenges heteronormative views. Nevertheless, there is a large amount of literature (e.g., Bauer, 2018; Laube et al., 2020; Hamm & Nieder, 2021; Stephenson et al., 2017) highlighting the spectrum character of sexuality that does not fit into expectations of what male and female sexuality entails (neither cis- nor transgender), let alone that of gender diverse people (e.g., nonbinary, agender, genderqueer). Thus, these aspects should be carefully considered by HCPs as cisnormativity, heteronormativity, and transition-related medical interventions, all have a strong impact on sexual health.

Sexual pleasure has been well documented as a factor in improving sexual, mental, and physical health outcomes (Anderson, 2013). Next to sexual function, HCPs providing sexual health care must address sexual pleasure and satisfaction as a key factor within sexual health. Historically sexual health care has been disease focused, and this is particularly true for research and clinical practice in working with TGD patients. Although competent sexual health care regarding HIV and STIs is necessary, integration of valuing sexual pleasure of TGD patients is also necessary. Calls for integrating sexual pleasure as a focal point in STI prevention education and interventions rest on the understanding that pleasure is a motivator of behavior (Philpott et al., 2006). TGD people are concerned about their sexual pleasure and need HCPs who are knowledgeable about the diversity of sexual practices and anatomical functioning particular to TGD health care.

Statement 17.3

We recommend health care professionals who provide care to transgender and gender diverse people offer the possibility of including the partner(s) in sexuality-related care, if appropriate.

When appropriate and relevant to clinical concerns, inclusion of a sexual and/or romantic partner(s) in sexual health care decision-making can increase TGD patients' sexual well-being and satisfaction outcomes (Kleinplatz, 2012). TGD people may choose a range of transition-related medical interventions, and these interventions may have mixed results in shifting experiences of anatomical dysphoria (Bauer & Hammond, 2015). When discussing the impact of medical interventions on sexual functioning, pleasure, and satisfaction, inclusion of partner(s) can increase knowledge of potential changes and encourage communication between partners (Dierckx et al., 2019). Because the process of transitioning is often not a completely solitary endeavor, the inclusion of sexual and/or romantic partners in transition-related health care can facilitate the process of "co-transitioning" (Lindley et al., 2020;

Siboni et al., 2022; Theron & Collier, 2013) and can also support sexual growth and adjustment both in the individual as well as in the relationship. Social and psychological barriers to sexual functioning and pleasure, including experiences of gender dysphoria, stigmatization, lack of sexual and relationship role models, and limited skills, can have negative impacts on overall sexual health (Kerckhof et al., 2019). Supportive, gender-affirming sexual communication between partners improves sexual satisfaction outcomes for TGD people (Stephenson et al., 2017; Wierckx, Elaut et al., 2011).

Inclusion of sexual and/or romantic partners offers an additional opportunity to set realistic expectations, disseminate helpful and accurate information, and facilitate gender-affirming positive communication related to sexual health. Ultimately, however, it is important to recognize individual choices related to gender health and transition are the patients to make, not a partner's decision. It is important the inclusion of partners in sexual health-related care occur only when appropriate and as desired by patients. Contraindications might include interpersonal dynamics that are abusive or violent, in which case patient safety overrides partner involvement. Finally, it is critical HCPs treat all people in an affirming and inclusive manner, including sexual and romantic partners. This means, for example, monitoring and addressing assumptions and potential biases about the gender or sexual orientation of a patient's partner(s) or a patient's relationship structure.

Statement 17.4

We recommend health care professionals counsel transgender and gender diverse people about the potential impact of stigma and trauma on sexual risk behavior, sexual avoidance, and sexual functioning.

The TGD community is disproportionately impacted by stigma, discrimination, and violence (de Vries et al., 2020; European Union Agency for Fundamental Rights, 2020; McLachlan, 2019). These experiences are often traumatic in nature (Burnes et al., 2016; Mizock & Lewis, 2008) and can create barriers to sexual health, functioning, and pleasure (Bauer & Hammond, 2015). For example, stigmatizing narratives about transgender sexualities can increase dysphoria and sexual shame, increasing potential avoidance of the sexual communication needed for safety and optimizing pleasure (Stephenson et al., 2017). Research demonstrates stigma, a history of sexual violence, and body image concerns can negatively impact sexual self-esteem and agency, for example the ability to assert what is pleasurable or to negotiate condom use (Clements-Nolle et al., 2008; Dharma et al., 2019). Additionally, gender dysphoria can be exacerbated by past trauma experiences and ongoing trauma-related symptoms (Giovanardi et al., 2018). It may be difficult for some TGD individuals to engage sexually using the genitals with which they were born, and they may choose to avoid such stimulation altogether, disrupting arousal and/or orgasmic processes (Anzani et al., 2021; Bauer & Hammond, 2015; Iantaffi & Bockting, 2011) or result in complex feelings about orgasm (Chadwick et al., 2019). HCPs providing gender-affirming counseling and interventions must be knowledgeable about the spectrum of sexual orientations and identities (including asexual identities and practices) to avoid assumptions based in heteronormative, cisnormative, allonormative modes of behavior or satisfaction while also affirming the potential impacts of stigma and trauma on sexual health and pleasure (Nieder, Güldenring et al., 2020). Some level of disconnect or dissociation may at times be present, particularly in the case of acute trauma symptoms (Colizzi et al., 2015). It is important HCPs be aware of these potential impacts on sexual health, functioning, pleasure, and satisfaction, so they may refer patients as needed to trauma-informed sexual counselors, mental health providers, or both, who may be of further assistance and may also normalize and validate TGD patients exploring multiple diverse pathways of healing and accessing sexual pleasure.

Statement 17.5

We recommend any health care professional who offers care that may impact sexual health provide information, ask about the expectation of the transgender and gender diverse individual, and assess their level of understanding of possible changes.

Transition-related care can affect sexual function, pleasure, and satisfaction, both in positive and negative ways (Holmberg et al., 2018; Kerckhof et al., 2019; Thurston & Allan, 2018; Tirapegui et al., 2020). On the positive side, gender-affirming care can help TGD people improve their sexual functioning and increase their sexual pleasure and satisfaction (Kloer et al., 2021; Özer et al., 2022; T'Sjoen et al., 2020). On the negative side, however, data indicate problematic sexual health outcomes due to hormonal and surgical treatments (Holmberg et al., 2018; Kerckhof et al., 2019, Stephenson et al., 2017; Weyers et al., 2009). Transition-related hormones may affect mood, sexual desire, the ability to have an erection and ejaculation, and genital tissue health, which in turn can impact sexual function, pleasure and sexual self-expression (Defreyne, Elaut et al., 2020; Garcia & Zaliznyak, 2020; Kerckhof et al., 2019; Klein & Gorzalka, 2009; Wierckx, Elaut et al., 2014). TGD people who wish to use their original genital anatomy for penetrative sex may benefit from medications that address sexual health side effects of hormone therapy, such as erectile dysfunction, medications for TGD persons taking estrogen or antiandrogens, and topical estrogen and/or moisturizers for TGD persons experiencing vaginal atrophy or dryness due to testosterone therapy.

Sexual desire, arousal, and function may also be affected by the use of psychotropic drugs (Montejo et al., 2015). As some TGD people are prescribed medication to treat depression (Heylens, Elaut et al., 2014), anxiety (Millet et al., 2017) or other mental health concerns (Dhejne et al., 2016), their potential side effects on sexual health should be considered.

Many gender-affirming surgeries can have significant effects on erogenous sensation, sexual desire and arousal as well as sexual function and pleasure. The impact of these changes for patients may be mixed (Holmberg et al., 2018). Chest surgeries (breast reduction, mastectomy, and breast augmentation) and body contouring surgeries, for example, may offer desired changes in form and appearance thereby reducing psychological distress that can disrupt sexual functioning but may adversely affect erogenous sensation (Bekeny et al., 2020; Claes et al., 2018; Rochlin et al., 2020). Genital surgeries in particular can potentially affect sexual function and pleasure in adverse ways, although they are likely to be experienced positively as the patient's body becomes more aligned with their gender, potentially opening new avenues for sexual pleasure and satisfaction (Hess et al., 2018; Holmberg et al., 2018; Kerckhof et al., 2019).

There are numerous examples of this in the extant literature:

- Surgery may result in a decrease, a total loss, or a possible increase in erogenous stimulation and/or experienced sensation compared with the patient's presurgery anatomy (Garcia, 2018; Sigurjónsson et al., 2017).
- A particular surgical option may be associated with specific limitations to sexual function that may manifest immediately, in the future, or at both timepoints, and which patients should consider before finalizing their choice when considering different surgical options (Frey et al., 2016; Garcia, 2018; Isaacson et al., 2017).
- Postsurgical complications can adversely affect sexual function by either decreasing the quality of sexual function (e.g., discomfort or pain with sexual activity) or by precluding satisfactory intercourse (Kerckhof et al., 2019; Schardein et al., 2019).

In general, satisfaction with any medical treatment is heavily influenced by the patient's expectations (Padilla et al., 2019). Furthermore, when patients have unrealistic expectations before treatment, they are much more likely to be dissatisfied with the outcome, their care, and with their HCP (Padilla et al., 2019). Therefore, it is important to both provide patients with adequate information about their treatment options and to understand and consider what is important to the patient with regard to outcomes (Garcia, 2021). Finally, it is important the HCP ensure patients understand the potential adverse effects of a treatment on their sexual function and pleasure so that a well-informed decision can be made. This is relevant for both meeting the standard of informed consent (i.e.,

discussion and understanding) and for providing an opportunity to offer further clarification to patients and, if desired, to their partners (Glaser et al., 2020).

Statement 17.6

We recommend health care professionals who provide care to transgender and gender diverse people counsel adolescents and adults regarding prevention of sexually transmitted infections.

The WHO (2015) recommends HCPs implement brief sexuality-related communication in primary care for all adolescents and adults. Therefore, TGD persons who are sexually active or considering sexual activity may benefit from sexuality-related communication or counseling for the purpose of HIV/STI prevention. These conversations are particularly important as TGD persons are disproportionately impacted by human immunodeficiency virus (HIV) and other sexually transmitted infections (STIs) relative to cisgender persons (Baral et al., 2013; Becasen et al., 2018; Poteat et al., 2016). However, few data are available for non-HIV STIs, such as chlamydia, gonorrhea, syphilis, viral hepatitis, and herpes simplex virus (Tomson et al., 2021). The United Nations Joint Programme on HIV/AIDS estimates transgender women are 12 times more likely than other adults to be living with HIV (UNAIDS, 2019). A meta-analysis estimated a pooled global HIV prevalence of 19% among transgender women who have sex with men (Baral et al., 2013). HIV/STI risk is concentrated among TGD subgroups at the confluence of multiple biological, psychological, interpersonal, and structural vulnerabilities. In particular, transfeminine persons who have sex with cisgender men, belong to minoritized racial/ethnic groups, live in poverty, and engage in survival sex work are at elevated HIV/STI risk (Becasen et al., 2018; Poteat et al., 2015; Poteat et al., 2016). Less is known about HIV/STI risk among transgender men or gender diverse persons AFAB. Small studies in high-income countries indicate a laboratory-confirmed HIV prevalence of 0-4% among transmasculine people (Becasen et al., 2018; Reisner & Murchison, 2016). Almost no research has been conducted with transmasculine people who have sex with cisgender men in high-HIV-prevalence countries. Despite limited epidemiologic data, transmasculine persons who have sex with cisgender men frequently report HIV/STI risk related to receptive vaginal and/or anal sex (Golub et al., 2019; Reisner et al., 2019; Scheim et al., 2017) and may be more susceptible to HIV acquisition from vaginal intercourse than (pre-menopausal) cisgender women due to hormone-related vaginal atrophy.

HCPs will need to supplement general guidelines by developing the knowledge and skills needed for discussing sexual health issues with TGD people, such as the use of gender-affirming language (see Statement 17.1 in this chapter). It is critical HCPs avoid assumptions about HIV/STI risk based solely on a patient's gender identity or anatomy. For example, many transgender people are not sexually active, and TGD persons may use prosthetics or toys for sex. To provide appropriate prevention counseling, HCPs should inquire about the specific sexual activities TGD people engage in, and the body parts (or prosthetics) involved in those activities (ACON, 2022). Well-prepared HCPs (including, but not limited to mental health providers) may also engage in in-depth counseling with their patients to address the underlying drivers of HIV/STI risk (see Statement 17.3 in this chapter).

In all cases, HCPs should be sensitive to the collective and individual histories of TGD people (e.g., stereotypes and stigma about trans sexualities and gender dysphoria) and should explain to patients the reasons for sexuality-related inquiries and the voluntary nature of such inquiries. In discussing HIV/STI prevention, HCPs should refer to the full range of prevention options including barrier methods, post-exposure prophylaxis, pre-exposure prophylaxis, and HIV treatment to prevent onwards transmission (WHO, 2021). Trans-specific considerations for pre-exposure prophylaxis are addressed in Statement 17.8.

Statement 17.7

We recommend health care professionals who provide care to transgender and gender diverse people follow local and World Health Organization guidelines for human immunodeficiency virus/sexual transmitted infections (HIV/STIs) screening, prevention, and treatment.

Like cisgender patients, TGD adolescents and adults should be offered screening for HIV/STIs in accordance with existing guidelines and based on their individual risk of HIV/STI acquisition, considering anatomy and behavior rather than gender identity alone. Where local or national guidelines are unavailable, WHO (2019a) offers global recommendations; more frequent screening is recommended for transgender people who have sex with cisgender men as a key population affected by HIV.

Gender-affirming genital surgeries and surgical techniques have implications for STI risks and screening needs, as outlined in recent guidelines from the US Centers for Disease Control (Workowski et al., 2021). For instance, transfeminine persons who have had penile inversion vaginoplasty using only penile and scrotal skin to line the vaginal canal are likely at lower risk of urogenital Chlamydia trachomatis *(C. trachomatis)* and Neisseria gonorrhoeae *(N. gonorrhoeae)*, but newer surgical techniques that employ buccal or urethral mucosa or peritoneum flaps could in theory increase susceptibility to bacterial STIs relative to the use of penile/scrotal skin alone (Van Gerwen et al., 2021). Routine STI screening of the neovagina (if exposed) is recommended for all transfeminine persons who have had vaginoplasty (Workowski et al., 2021). For transmasculine persons who have had metoidioplasty with urethral lengthening, but not vaginectomy, testing for bacterial urogenital STIs should include a cervical swab because infections may not be detected in urine (Workowski et al., 2021).

Further, it is important for HCPs to offer testing at multiple anatomical sites as STIs in transgender patients are often extragenital (Hiransuthikul et al., 2019; Pitasi et al., 2019). Consistent with WHO (2020) recommendations, self-collection of samples for STI testing should be offered as an option, particularly if patients are uncomfortable or unwilling to undergo provider-collected sampling due to gender dysphoria, trauma histories, or both. Where relevant, integration of HIV/STI testing with regular serology used to monitor hormone therapy may better facilitate access to care (Reisner, Radix et al., 2016; Scheim & Travers, 2017).

Statement 17.8

We recommend health care professionals who provide care to transgender and gender diverse people address concerns about potential interactions between antiretroviral medications and hormones.

For TGD adolescents and adults at substantial risk of HIV infection (generally defined as an ongoing serodiscordant relationship or condomless sex outside of a mutually monogamous relationship with a known HIV-negative partner; WHO, 2017), pre-exposure prophylaxis (PrEP) is an important HIV prevention option (Golub et al., 2019; Sevelius et al., 2016; WHO, 2021). To encourage uptake of PrEP, in 2021 the US Centers for Disease Control recommended all sexually active adolescents and adults be informed about PrEP and offered it if requested (CDC, 2021). For treatment among people living with HIV, transgender-specific guidelines are available in some settings (e.g., Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019).

For both HIV prevention and treatment, there are antiretroviral dosing and administration considerations specific to TGD persons. For oral PrEP, only daily dosing is currently recommended for TGD persons as studies demonstrating the effectiveness of event-driven PrEP with emtricitabine/tenofovir disoproxil fumarate (TDF) have been limited to cisgender men (WHO, 2019c). In addition, while emtricitabine/tenofovir alafenamide (TAF) is a new oral PrEP option, as of early 2022 it is not recommended for people at risk of HIV acquisition through receptive vaginal sex due to a lack of evidence (CDC, 2021). Finally, long-acting injectable formulations of both PrEP and HIV treatment are increasingly available (e.g., cabotegravir for PrEP), and while they are recommended for all patients who might benefit from injectable options, indicated injection sites (i.e., the gluteal muscle) may be unsuitable for individuals who have used soft tissue fillers (Rael et al., 2020).

There is little evidence supporting the occurrence of drug-drug interactions between gender-affirming hormones and PrEP medications. A few small studies, primarily relying on self-reported PrEP use, have shown reduced PrEP drug concentrations in transgender women undergoing hormone therapy, although

concentrations remained in the protective range (Yager & Anderson, 2020). A subsequent drug-drug interaction study using directly observed PrEP therapy failed to detect an impact of hormone therapy on PrEP drug concentrations in transgender women and found transgender women and men taking hormone therapy achieved high levels of protection against HIV infection (Grant et al., 2020). Most importantly, for many TGD people, no impact of PrEP on hormone concentrations has been detected. With regard to HIV treatment, specific antiretroviral medications may impact hormone concentrations; however, these can be managed by selecting alternative agents, monitoring and adjusting hormone dosing, or both (Cirrincione et al., 2020) as detailed in guidelines from the US Department of Health and Human Services (Panel on Antiretroviral Guidelines for Adults and Adolescents, 2019). Nevertheless, concerns about drug-drug interactions, particularly interactions that may limit hormone concentrations, represent a barrier to the implementation and adherence to antiretroviral therapy for HIV prevention or treatment (Radix et al., 2020; Sevelius et al., 2016). Therefore, it is advisable for HCPs to proactively address such concerns with those who are candidates for PrEP or HIV treatment. Integration of PrEP or HIV treatment with hormone therapy may further reduce barriers to implementation and adherence (Reisner, Radix et al., 2016). Integration may be achieved through colocation or through coordination with an HIV specialist if the primary care provider does not have the necessary expertise. Some TGD persons may benefit from standalone PrEP or sexual health services that provide greater privacy and flexibility, and thus differentiated service delivery models are needed (Wilson et al., 2021).

CHAPTER 18 Mental Health

This chapter is intended to provide guidance to health care professionals (HCPs) and mental health professionals (MHPs) who offer mental health care to transgender and gender diverse (TGD) adults. It is not meant to be a substitute for chapters on the assessment or evaluation of people for hormonal or surgical interventions. Many TGD people will not require therapy or other forms of mental health care as part of their transition, while others may benefit from the support of mental health providers and systems (Dhejne et al., 2016).

Some studies have shown a higher prevalence of depression (Witcomb et al., 2018), anxiety (Bouman et al., 2017), and suicidality (Arcelus et al., 2016; Bränström & Pachankis, 2022; Davey et al., 2016; Dhejne, 2011; Herman et al., 2019) among TGD people (Jones et al., 2019; Thorne, Witcomb et al., 2019) than in the general population, particularly in those requiring medically necessary gender-affirming medical treatment (see medically necessary statement in Chapter 2—Global Applicability, Statement 2.1). However, transgender identity is not a mental illness, and these elevated rates have been linked to complex trauma, societal stigma, violence, and discrimination (Nuttbrock et al., 2014; Peterson et al., 2021). In addition, psychiatric symptoms lessen with appropriate gender-affirming medical and surgical care (Aldridge et al., 2020; Almazan and Keuroghlian; 2021; Bauer et al., 2015; Grannis et al., 2021) and with interventions that lessen discrimination and minority stress (Bauer et al., 2015; Heylens, Verroken et al., 2014; McDowell et al., 2020).

Mental health treatment needs to be provided by staff and implemented through the use of systems that respect patient autonomy and recognize gender diversity. MHPs working with transgender people should use active listening as a method to encourage exploration in individuals who are uncertain about their gender identity. Rather than impose their own narratives or preconceptions, MHPs should assist their clients in determining their own paths. While many transgender people require medical or surgical interventions or seek mental health care, others do not (Margulies et al., 2021). Therefore, findings from research involving clinical populations should not be extrapolated to the entire transgender population.

Addressing mental illness and substance use disorders is important but should not be a barrier to transition-related care. Rather, these interventions to address mental health and substance use disorders can facilitate successful outcomes from

Statements of Recommendations

18.1- We recommend mental health professionals address mental health symptoms that interfere with a person's capacity to consent to gender-affirming treatment before gender-affirming treatment is initiated.
18.2- We recommend mental health professionals offer care and support to transgender and gender diverse people to address mental health symptoms that interfere with a person's capacity to participate in essential perioperative care before gender-affirmation surgery.
18.3- We recommend when significant mental health symptoms or substance abuse exists, mental health professionals assess the potential negative impact that mental health symptoms may have on outcomes based on the nature of the specific gender-affirming surgical procedure.
18.4- We recommend health care professionals assess the need for psychosocial and practical support of transgender and gender diverse people in the perioperative period surrounding gender- affirmation surgery.
18.5- We recommend health care professionals counsel and assist transgender and gender diverse people in becoming abstinent from tobacco/nicotine prior to gender-affirmation surgery.
18.6- We recommend health care professionals maintain existing hormone treatment if a transgender and gender diverse individual requires admission to a psychiatric or medical inpatient unit, unless contraindicated.
18.7- We recommend health care professionals ensure if transgender and gender diverse people need in-patient or residential mental health, substance abuse or medical care, all staff use the correct name and pronouns (as provided by the patient), as well as provide access to bathroom and sleeping arrangements that are aligned with the person's gender identity.
18.8- We recommend mental health professionals encourage, support, and empower transgender and gender diverse people to develop and maintain social support systems, including peers, friends, and families.
18.9- We recommend health care professionals should not make it mandatory for transgender and gender diverse people to undergo psychotherapy prior to the initiation of gender-affirming treatment, while acknowledging psychotherapy may be helpful for some transgender and gender diverse people.
18.10- We recommend "reparative" and "conversion" therapy aimed at trying to change a person's gender identity and lived gender expression to become more congruent with the sex assigned at birth should not be offered.

transition-related care, which can improve quality of life (Nobili et al., 2018).

All the statements in this chapter have been recommended based on a thorough review of evidence, an assessment of the benefits and harms, values and preferences of providers and patients, and resource use and feasibility. In some cases, we recognize evidence is limited and/or services may not be accessible or desirable.

Statement 18.1

We recommend mental health professionals address mental health symptoms that interfere with a person's capacity to consent to gender-affirming treatment before gender-affirming treatment is initiated.

Because patients generally are assumed to be capable of providing consent for care, whether the presence of cognitive impairment, psychosis, or other mental illness impairs the ability to give informed consent is subject to individual examination (Applebaum, 2007). Informed consent is central to the provision of health care. The health care provider must educate the patient about the risks, benefits, and alternatives to any care that is offered so the patient can make an informed, voluntary choice (Berg et al., 2001). Both the primary care provider or endocrinologist prescribing hormones and the surgeon performing surgery must obtain informed consent. Similarly, MHPs obtain informed consent for mental health treatment and may consult on a patient's capacity to give informed consent when this is in question. Psychiatric illness and substance use disorders, in particular cognitive impairment and psychosis, may impair an individual's ability to understand the risks and benefits of the treatment (Hostiuc et al., 2018). Conversely, a patient may also have significant mental illness, yet still be able to understand the risks and benefits of a particular treatment (Carpenter et al., 2000). Multidisciplinary communication is important in challenging cases, and expert consultation should be utilized as needed (Karasic & Fraser, 2018). For many patients, difficulty understanding the risks and benefits of a particular treatment can be overcome with time and careful explanation. For some patients, treatment of the underlying condition that is interfering with the capacity to give informed consent—for example treating an underlying psychosis—will allow the patient to gain the capacity to consent to the required treatment. However, mental health symptoms such as anxiety or depressive symptoms that do not affect the capacity to give consent should not be a barrier for gender-affirming medical treatment, particularly as this treatment has been found to reduce mental health symptomatology (Aldridge et al., 2020).

Statement 18.2

We recommend mental health professionals offer care and support to transgender and gender diverse people to address mental health symptoms that interfere with a person's capacity to participate in essential perioperative care before gender-affirmation surgery.

The inability to adequately participate in perioperative care due to mental illness or substance use should not be viewed as an obstacle to needed transition care, but should be seen as an indication mental health care and social support be provided (Karasic, 2020). Mental illness and substance use disorders may impair the ability of the patient to participate in perioperative care (Barnhill, 2014). Visits to health care providers, wound care, and other aftercare procedures (e.g., dilation after vaginoplasty) may be necessary for a good outcome. A patient with a substance use disorder might have difficulty keeping necessary appointments to the primary care provider and the surgeon. A patient with psychosis or severe depression might neglect their wound or not be attentive to infection or signs of dehiscence (Lee, Marsh et al., 2016). Active mental illness is associated with a greater need for further acute medical and surgical care after the initial surgery (Wimalawansa et al., 2014).

In these cases, treatment of the mental illness or substance use disorder may assist in achieving successful outcomes. Arranging more support for the patient from family and friends or a home health care worker may help the patient participate sufficiently in perioperative care for surgery to proceed. The benefits of mental health treatments that may delay surgery should be weighed against the risks of delaying surgery and should

include an assessment of the impact on the patients' mental health delays may cause in addressing gender dysphoria (Byne et al., 2018).

Statement 18.3

We recommend when significant mental health symptoms or substance abuse exists, mental health professionals assess the potential negative impact mental health symptoms may have on outcomes based on the nature of the specific gender-affirming surgical procedure.

Gender-affirming surgical procedures vary in terms of their impact on the patient. Some procedures require a greater ability to follow preoperative planning as well as engage in peri- and postoperative care to achieve the best outcomes (Tollinche et al., 2018). Mental health symptoms can influence a patient's ability to participate in the planning and perioperative care necessary for any surgical procedure (Paredes et al., 2020). The mental health assessment can provide an opportunity to develop strategies to address the potential negative impact mental health symptoms may have on outcomes and to plan support for the patient's ability to participate in the planning and care. Gender-affirming surgical procedures have been shown to relieve symptoms of gender dysphoria and improve mental health (Owen-Smith et al., 2018; van de Grift, Elaut et al., 2017). These benefits are weighed against the risks of each procedure when the patient and provider are deciding whether to proceed with the treatment. HCPs can assist TGD people in reviewing preplanning and perioperative care instructions for each surgical procedure (Karasic, 2020). Provider and patient can collaboratively determine the necessary support or resources needed to assist with keeping appointments for perioperative care, obtaining necessary supplies, addressing financial issues, and handling other preoperative coordination and planning. In addition, issues surrounding appearance-related and functional expectations, including the impact of these various factors on gender dysphoria, can be explored.

Statement 18.4

We recommend health care professionals assess the need for psychosocial and practical support of transgender and gender diverse people in the perioperative period surrounding gender-affirmation surgery.

Regardless of specialty, all HCPs have a responsibility to support patients in accessing medically necessary care. When HCPs are working with TGD people as they prepare for gender-affirming surgical procedures, they should assess the levels of psychosocial and practical support required (Deutsch, 2016b). Assessment is the first step in recognizing where additional support may be needed and enhancing the ability to work collaboratively with the individual to successfully navigate the pre-, peri-, and postsurgical periods (Tollinche et al., 2018). In the perioperative period, it is important to help patients optimize functioning, secure stable housing, when possible, build social and family supports by assessing their unique situation, plan ways of responding to medical complications, navigate the potential impact on work/income, and overcome additional hurdles some patients may encounter, such as coping with electrolysis and tobacco cessation (Berli et al., 2017). In a complex medical system, not all patients will be able to independently navigate the procedures required to obtain care, and HCPs and peer navigators can support patients through this process (Deutsch, 2016a).

Statement 18.5

We recommend health care professionals counsel and assist transgender and gender diverse people in becoming abstinent from tobacco/nicotine prior to gender-affirmation surgery.

Transgender populations have higher rates of tobacco and nicotine use (Kidd et al., 2018). However, many are unaware of the well-documented smoking-associated health risks (Bryant et al., 2014). Tobacco consumption increases the risk of developing health problems (e.g., thrombosis) in individuals receiving gender-affirming hormone treatment, particularly estrogens (Chipkin & Kim, 2017).

Tobacco use has been associated with worse outcomes in plastic surgery, including overall complications, tissue necrosis, and the need for surgical revision (Coon et al., 2013). Smoking also increases the risk for postoperative infection (Kaoutzanis et al., 2019). Tobacco use has been shown to affect

the healing process following any surgery, including gender-related surgeries (e.g., chest reconstructive surgery, genital surgery) (Pluvy, Garrido et al., 2015). Tobacco users have a higher risk of cutaneous necrosis, delayed wound healing, and scarring disorders due to hypoxia and tissue ischemia (Pluvy, Panouilleres et al., 2015). In view of this, surgeons recommend stopping the use of tobacco/nicotine prior to gender-affirmation surgery and abstaining from smoking up to several weeks postoperatively until the wound has completely healed (Matei & Danino, 2015). Despite the risks, cessation may be difficult. Tobacco smoking and nicotine use is addictive and is also used as a coping mechanism (Matei et al., 2015). HCPs who see patients longitudinally before surgery, including mental health and primary care providers, should address the use of tobacco/nicotine with individuals in their care, and either assist TGD people in accessing smoking cessation programs or provide treatment directly (e.g., varenicline or bupropion).

Statement 18.6

We recommend health care professionals maintain existing hormone treatment if a transgender and gender diverse individual requires admission to a psychiatric or medical inpatient unit, unless contraindicated.

TGD people entering inpatient psychiatric, substance use treatment, or medical units should be maintained on their current hormone regimens. There is an absence of evidence supporting routine cessation of hormones prior to medical or psychiatric admissions. Rarely, a newly admitted patient may be diagnosed with a medical complication necessitating suspension of hormone treatment, for example an acute venous thromboembolism (Deutsch, 2016a). There is no strong evidence for routinely stopping hormone treatment prior to surgery, and the risks and benefits for each individual patient should be assessed before doing so (Boskey et al., 2018).

Hormone treatment has been shown to improve quality of life and to decrease depression and anxiety (Aldridge et al., 2020; Nguyen et al., 2018; Nobili et al., 2018; Owen-Smith et al., 2018, Rowniak et al., 2019). Access to gender-affirming medical treatment is associated with a substantial reduction in the risk of suicide attempt (Bauer et al., 2015). Halting a patient's regularly prescribed hormones denies the patient of these salutary effects, and therefore may be counter to the goals of hospitalization.

Some providers may be unaware of the low risk of harm and the high potential benefit of continuing transition-related treatment in the inpatient setting. A study of US and Canadian medical schools revealed that students received an average of 5 hours of LGBT-related course content over their entire four years of education (Obedin-Maliver et al., 2011). According to a survey of Emergency Medicine physicians, who are often responsible for making quick decisions about medications as patients are being admitted, while 88% reported caring for transgender patients, only 17.5% had received any formal training about this population (Chisolm-Straker et al., 2018). As education about transgender topics increases, more providers will become aware of the importance of maintaining transgender patients on their hormone regimens during hospitalization.

Statement 18.7

We recommend health care professionals ensure if transgender and gender diverse people need inpatient or residential mental health, substance abuse, or medical care, all staff use the correct name and pronouns (as provided by the patient), as well as provide access to bathroom and sleeping arrangements that are aligned with the person's gender identity.

Many TGD patients encounter discrimination in a wide range of health settings, including hospitals, mental health treatment settings, and drug treatment programs (Grant et al., 2011). When health systems fail to accommodate TGD individuals, they reinforce the longstanding societal exclusion many have experienced (Karasic, 2016). Experiences of discrimination in health settings lead to avoidance of needed health care due to anticipated discrimination (Kcomt et al., 2020).

The experience of discrimination experienced by TGD individuals is predictive of suicidal ideation (Rood et al., 2015; Williams et al., 2021). Gender minority stress associated with rejection and nonaffirmation has also been associated with suicidality (Testa et al., 2017). Denial of access to gender appropriate bathrooms has been

associated with increased suicidality (Seelman, 2016). However, the use of chosen names for TGD people has been associated with lower depression and suicidality (Russell et al., 2018). Structural as well as internalized transphobia must be addressed to reduce the incidence of suicide attempts in TGD people (Brumer et al., 2015). To successfully provide care, health settings must minimize the harm done to patients because of transphobia by respecting and accommodating TGD identities.

Statement 18.8

We recommend mental health professionals encourage, support, and empower transgender and gender diverse people to develop and maintain social support systems, including peers, friends, and families.

While minority stress and the direct effects of discriminatory societal discrimination can be harmful to the mental health of TGD people, strong social support can help lessen this harm (Trujillo et al., 2017). TGD children often internalize rejection from family and peers as well as the transphobia that surrounds them (Amodeo et al., 2015). Furthermore, exposure to transphobic abuse may be impactful across a person's lifespan and may be particularly acute during the adolescent years (Nuttbrock et al., 2010).

The development of affirming social support is protective of mental health. Social support can act as a buffer against the adverse mental health consequences of violence, stigma, and discrimination (Bockting et al., 2013), can assist in navigating health systems (Jackson Levin et al., 2020), and can contribute to psychological resilience in TGD people (Bariola et al., 2015; Başar and Öz, 2016). Diverse sources of social support, especially LGBTQ+peers and family, have been found to be associated with better mental health outcomes, well-being, and quality of life (Bariola et al., 2015; Başar et al., 2016; Kuper, Adams et al., 2018; Puckett et al., 2019). Social support has been proposed to facilitate the development of coping mechanisms and lead to positive emotional experiences throughout the transition process (Budge et al., 2013).

HCPs can support patients in developing social support systems that allow them to be recognized and accepted as their authentic identity and help them cope with symptoms of gender dysphoria. Interpersonal problems and lack of social support have been associated with a greater incidence of mental health difficulties in TGD people (Bouman, Davey et al., 2016; Davey et al., 2015) and have been shown to be an outcome predictor of gender-affirming medical treatment (Aldridge et al., 2020). Therefore, HCPs should encourage, support, and empower TGD people to develop and maintain social support systems. These experiences can foster the development of interpersonal skills and help with coping with societal discrimination, potentially reducing suicidality and improving mental health (Pflum et al., 2015).

Statement 18.9

We recommend health care professionals should not make it mandatory for transgender and gender diverse people to undergo psychotherapy prior to the initiation of gender-affirming treatment, while acknowledging psychotherapy may be helpful for some transgender and gender diverse people.

Psychotherapy has a long history of being used in clinical work with TGD people (Fraser, 2009b). The aims, requirements, methods and principles of psychotherapy have been an evolving component of the Standards of Care from the initial versions (Fraser, 2009a). At present, psychotherapeutic assistance and counseling with adult TGD people may be sought to address common psychological concerns related to coping with gender dysphoria and may also help some individuals with the coming-out process (Hunt, 2014). Psychological interventions, including psychotherapy, offer effective tools and provide context for the individual, such as exploring gender identity and its expression, enhancing self-acceptance and hope, and improving resilience in hostile and disabling environments (Matsuno and Israel, 2018). Psychotherapy is an established alternative therapeutic approach for addressing mental health symptoms that may be revealed during the initial assessment or later during the follow-up for gender-affirming medical interventions. Recent research shows, although mental health symptoms are reduced following gender-affirming medical treatment, levels of anxiety remain high (Aldridge et al., 2020) suggesting psychological therapy can play a role in helping

individuals suffering from anxiety symptoms following gender-affirming treatment.

In recent years, the uses and potential benefits of specific psychotherapeutic modalities have been reported (Austin et al., 2017; Budge, 2013; Budge et al., 2021; Embaye, 2006; Fraser, 2009b; Heck et al., 2015). Specific models of psychotherapy have been proposed for adult transgender and nonbinary individuals (Matsuno & Israel, 2018). However, more empiric data is needed on the comparative benefits of different psychotherapeutic models (Catelan et al., 2017). Psychotherapy can be experienced by transgender persons as a fearful as well as a beneficial experience (Applegarth & Nuttall, 2016) and presents challenges to the therapist and to alliance formation when it is associated with gatekeeping for medical interventions (Budge, 2015).

Experience suggests many transgender and nonbinary individuals decide to undergo gender-affirming medical treatment with little or no use of psychotherapy (Spanos et al., 2021). Although various modalities of psychotherapy may be beneficial for different reasons before, during, and after gender-affirming medical treatments and varying rates of desire for psychotherapy have been reported during different stages of transition (Mayer et al., 2019), a requirement for psychotherapy for initiating gender-affirming medical procedures has not been shown to be beneficial and may be a harmful barrier to care for those who do not need this type of treatment or who lack access to it.

Statement 18.10

We recommend "reparative" and "conversion" therapy aimed at trying to change a person's gender identity and lived gender expression to become more congruent with the sex assigned at birth should not be offered.

The use of "reparative" or "conversion" therapy or gender identity "change" efforts is opposed by many major medical and mental health organizations across the world, including the World Psychiatric Association, Pan American Health Organization, American Psychiatric and American Psychological Associations, Royal College of Psychiatrists, and British Psychological Society. Many states in the US have instituted bans on practicing conversion therapy with minors. Gender identity change efforts refers to interventions by MHPs or others that attempt to change gender identity or expression to be more in line with those typically associated with the person's sex assigned at birth (American Psychological Association, 2021).

Advocates of "conversion therapy" have suggested it could potentially allow a person to fit better into their social world. They also point out some clients specifically ask for help changing their gender identities or expressions and therapists should be allowed to help clients achieve their goals. However, "conversion therapy" has not been shown to be effective (APA, 2009; Przeworski et al., 2020). In addition, there are numerous potential harms. In retrospective studies, a history of having undergone conversion therapy is linked to increased levels of depression, substance abuse, suicidal thoughts, and suicide attempts, as well as lower educational attainment and less weekly income (Ryan et al., 2020; Salway et al., 2020; Turban, Beckwith et al., 2020). In 2021, the American Psychological Association resolutions states that "scientific evidence and clinical experience indicate that GICEs [gender identity change efforts] put individuals at significant risk of harm" (APA, 2021).

While there are barriers to ending gender identity "change" efforts, education about the lack of benefit and the potential harm of these practices may lead to fewer providers offering "conversion therapy" and fewer individuals and families choosing this option.

Statement 13.7

We recommend surgeons consider gender-affirming surgical interventions for eligible* transgender and gender diverse adolescents when there is evidence a multidisciplinary approach that includes mental health and medical professionals has been involved in the decision-making process.

Substantial evidence (i.e., observational studies (Monstrey et al., 2001; Stojanovic et al., 2017), literature reviews and expert opinions (Esteva de Antonio et al., 2013; Frey et al., 2017; Hadj-Moussa et al., 2019; Pan & Honig, 2018), established guidelines (Byne et al., 2018; Chen, Fuqua et al., 2016; Hembree et al., 2017; Karasic & Fraser, 2018; Klein, Paradise et al., 2018; Weissler et al., 2018), and a thematic content analysis (Gerritse et al., 2018), support the importance of a multidisciplinary (i.e., medical, mental health, and surgery) approach to transgender health care.

A multidisciplinary approach is especially important in managing mental health issues if these are experienced by a TGD person undergoing GAS (de Freitas et al., 2020; Dhejne et al., 2016; van der Miesen et al., 2016). In addition, primary care providers and medical specialists can help support decisions regarding the timing of surgery, surgical outcomes and expectations, perioperative hormone management, and optimization of medical conditions (Elamin et al., 2010; Hembree et al., 2017).

For specific recommendations regarding presurgical assessment in adolescents, see Chapter 6—Adolescents.

Statement 13.8

We recommend surgeons consult a comprehensive, multidisciplinary team of professionals in the field of transgender health when eligible* transgender and gender diverse people request individually customized (previously termed "non-standard") surgeries as part of a gender-affirming surgical intervention.

Gender identities may present along a spectrum, and the expression of a person's identity may vary quite widely amongst individuals (Beek et al., 2015; Koehler et al., 2018). While the overall goal of a particular procedure usually includes reduction of gender dysphoria (van de Grift, Elaut et al., 2017) or achieving gender congruence, gender diverse presentations may lead to individually customized surgical requests some may consider "non-standard" (Beek et al., 2015; Bizic et al., 2018). Individually customized surgical requests can be defined as 1) a procedure that alters an individual's gender expression without necessarily aiming to express an alternative, binary gender; 2) the "non-standard" combination of well-established procedures; or 3) both.

This is designed to help counsel and inform the patient as well as to ensure their goals can be achieved. The patient and their surgeon need to work together to ensure the patient's expectations are realistic and achievable, and the proposed interventions are safe and technically feasible. The patient and their surgical team need to engage in a shared decision-making process (Cavanaugh et al., 2016). This informed consent process needs to address the irreversibility of some procedures, the newer nature of some procedures, and the limited information available about the long-term outcomes of some procedures.

Statement 13.9

We suggest surgeons caring for transgender men and gender diverse people who have undergone metoidioplasty/phalloplasty encourage lifelong urological follow-up.

Postoperative complications following metoidioplasty/phalloplasty comprise the urinary tract and sexual function (Kang et al., 2019; Monstrey et al., 2009; Santucci, 2018; Schardein et al., 2019). Reported urethral complications (related to urethral lengthening) include urethral strictures 35–58%, urethral fistulae 15–70% (Monstrey et al., 2009; Santucci, 2018; Schardein et al., 2019), diverticulae, mucocele due to vaginal remnant, and hair growth within the neourethra (Berli et al., 2021; Veerman et al., 2020). Complications related to sexual function include limited to absent tactile and/or erogenous sensation, difficulties with orgasm function, and complications with penile prosthetics (Kang et al., 2019; Santucci, 2018). Penile prosthesis-related complications are estimated to involve infection (incidence 8–12%),

often have specific aftercare requirements, such as postsurgery resources (stable, safe housing; resources for travel and follow-up care), instructions in health-positive habits (e.g., personal hygiene, healthy living, prevention of urinary tract infections (UTIs) and sexually-transmitted infections (STIs) (Wierckx, Van Caenegem et al., 2011)), postsurgery precautions or limitations on activities of daily life (e.g., bathing, physical activity, exercise, nutritional guidance, resumption of sexual activity) (Capitán et al., 2020), postsurgery resumption of medications (i.e., anticoagulants, hormones, etc.), and detailed postsurgery self-care activities (e.g., postvaginoplasty dilation and douching regimens, activation of a penile prosthesis, strategies to optimize postphalloplasty urination, recommendations for hair transplant care) (Capitán et al., 2017; Falcone et al., 2018; Garcia, 2018; Hoebeke et al., 2005). Some aspects of postsurgery self-care activities may be introduced prior to surgery and are reinforced after surgery (Falcone et al., 2018). As issues such as wound disruptions, difficulty with dilation, and UTIs may occur (Dy et al., 2019), the follow-up period provides an opportunity to intervene, mitigate, and prevent complications (Buncamper et al., 2016; Garcia, 2021).

Statement 13.4

We recommend surgeons confirm reproductive options have been discussed prior to gonadectomy in transgender and gender diverse people.

Infertility is often a consequence of both gender-affirming hormone therapy (temporary) and GAS (permanent), and fertility preservation is discussed prior to medical interventions, surgical interventions, or both (Defreyne, van Schuylenbergh et al., 2020; Jahromi et al., 2021; Jones et al., 2021). Surgical interventions that alter reproductive anatomy or function may limit future reproductive options to varying degrees (Nahata et al., 2019). It is thus critical to discuss infertility risk and fertility preservation (FP) options with transgender individuals and their families prior to initiating any of these interventions and on an ongoing basis thereafter (Hembree et al., 2017).

For specific recommendations regarding reproductive options, see Chapter 16—Reproductive Health.

Statement 13.5

We suggest surgeons consider offering gonadectomy to eligible* transgender and gender diverse adults when there is evidence they have tolerated a minimum of 6 months of hormone therapy (unless hormone replacement therapy or gonadal suppression is not clinically indicated or the procedure is inconsistent with the patient's desires, goals, or expressions of individual gender identity). For supporting text, see Statement 13.6.

Statement 13.6

We suggest health care professionals consider gender-affirming genital procedures in eligible* transgender and gender diverse adults seeking these interventions when there is evidence the individual has been stable on their current treatment regime (which may include at least 6 months of hormone treatment or a longer period if required to achieve the desired surgical result unless hormone therapy is either not desired or is medically contraindicated).

GAHT leads to anatomical, physiological, and psychological changes. The onset of the anatomic effects (e.g., clitoral growth, vaginal mucosal atrophy) may begin early after the initiation of therapy, and the peak effect is expected at 1–2 years (T'Sjoen et al., 2019). Depending upon the surgical result required, a period of hormone treatment may be required (e.g., sufficient clitoral virilization prior to metoidioplasty/phalloplasty) or preferred for psychological reasons, anatomical reasons, or both (breast growth and skin expansion prior to breast augmentation, softening of skin and changes in facial fat distribution prior to facial GAS) (de Blok et al., 2021).

For individuals who are not taking hormones prior to surgical interventions, it is important surgeons review the impact of this on the proposed surgery.

For individuals undergoing gonadectomy who are not taking hormones, a plan for hormone replacement can be developed with their prescribing professional prior to surgery.

Endocrine Treatment of Gender-Dysphoric/ Gender-Incongruent Persons: An Endocrine Society* Clinical Practice Guideline

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*Cosponsoring Associations: American Association of Clinical Endocrinologists, American Society of Andrology, European Society for Pediatric Endocrinology, European Society of Endocrinology, Pediatric Endocrine Society, and World Professional Association for Transgender Health.

Objective: To update the "Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline," published by the Endocrine Society in 2009.

Participants: The participants include an Endocrine Society–appointed task force of nine experts, a methodologist, and a medical writer.

Evidence: This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation approach to describe the strength of recommendations and the quality of evidence. The task force commissioned two systematic reviews and used the best available evidence from other published systematic reviews and individual studies.

Consensus Process: Group meetings, conference calls, and e-mail communications enabled consensus. Endocrine Society committees, members and cosponsoring organizations reviewed and commented on preliminary drafts of the guidelines.

Conclusion: Gender affirmation is multidisciplinary treatment in which endocrinologists play an important role. Gender-dysphoric/gender-incongruent persons seek and/or are referred to endocrinologists to develop the physical characteristics of the affirmed gender. They require a safe and effective hormone regimen that will (1) suppress endogenous sex hormone secretion determined by the person's genetic/gonadal sex and (2) maintain sex hormone levels within the normal range for the person's affirmed gender. Hormone treatment is not recommended for prepubertal gender-dysphoric/gender-incongruent persons. Those clinicians who recommend gender-affirming endocrine treatments—appropriately trained diagnosing clinicians (required), a mental health provider for adolescents (required) and mental health

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Abbreviations: BMD, bone mineral density; DSD, disorder/difference of sex development; DSM, Diagnostic and Statistical Manual of Mental Disorders; GD, gender dysphoria; GnRH, gonadotropin-releasing hormone; ICD, International Statistical Classification of Diseases and Related Health Problems; MHP, mental health professional; VTE, venous thromboembolism.

professional for adults (recommended)—should be knowledgeable about the diagnostic criteria and criteria for gender-affirming treatment, have sufficient training and experience in assessing psychopathology, and be willing to participate in the ongoing care throughout the endocrine transition. We recommend treating gender-dysphoric/gender-incongruent adolescents who have entered puberty at Tanner Stage G2/B2 by suppression with gonadotropin-releasing hormone agonists. Clinicians may add gender-affirming hormones after a multidisciplinary team has confirmed the persistence of gender dysphoria/gender incongruence and sufficient mental capacity to give informed consent to this partially irreversible treatment. Most adolescents have this capacity by age 16 years old. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to age 16 years, although there is minimal published experience treating prior to 13.5 to 14 years of age. For the care of peripubertal youths and older adolescents, we recommend that an expert multidisciplinary team comprised of medical professionals and mental health professionals manage this treatment. The treating physician must confirm the criteria for treatment used by the referring mental health practitioner and collaborate with them in decisions about gender-affirming surgery in older adolescents. For adult gender-dysphoric/gender-incongruent persons, the treating clinicians (collectively) should have expertise in transgender-specific diagnostic criteria, mental health, primary care, hormone treatment, and surgery, as needed by the patient. We suggest maintaining physiologic levels of gender-appropriate hormones and monitoring for known risks and complications. When high doses of sex steroids are required to suppress endogenous sex steroids and/or in advanced age, clinicians may consider surgically removing natal gonads along with reducing sex steroid treatment. Clinicians should monitor both transgender males (female to male) and transgender females (male to female) for reproductive organ cancer risk when surgical removal is incomplete. Additionally, clinicians should persistently monitor adverse effects of sex steroids. For gender-affirming surgeries in adults, the treating physician must collaborate with and confirm the criteria for treatment used by the referring physician. Clinicians should avoid harming individuals (via hormone treatment) who have conditions other than gender dysphoria/gender incongruence and who may not benefit from the physical changes associated with this treatment. (***J Clin Endocrinol Metab*** **102: 3869–3903, 2017)**

Summary of Recommendations

1.0 Evaluation of youth and adults

1.1. We advise that only trained mental health professionals (MHPs) who meet the following criteria should diagnose gender dysphoria (GD)/gender incongruence in adults: (1) competence in using the Diagnostic and Statistical Manual of Mental Disorders (DSM) and/or the International Statistical Classification of Diseases and Related Health Problems (ICD) for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or the ICD for diagnostic purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

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1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 ⊕◯◯◯)

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 ⊕⊕⊕◯)

2.0 Treatment of adolescents

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment, and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty. (2 ⊕⊕◯◯)

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕⊕◯◯)

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years. (1 ⊕⊕◯◯).

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 ⊕◯◯◯)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment. (2 ⊕⊕◯◯)

3.0 Hormonal therapy for transgender adults

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 ⊕⊕⊕◯)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment. (1 ⊕⊕⊕◯)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 ⊕⊕◯◯)

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕◯◯◯)

4.0 Adverse outcome prevention and long-term care

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕◯◯)

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕◯◯)

4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕◯◯)

4.4. We recommend that clinicians obtain bone mineral density (BMD) measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕◯◯)

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for non-transgender females. (2 ⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕◯◯◯)

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

5.0 Surgery for sex reassignment and gender confirmation

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕◯◯◯)

Changes Since the Previous Guideline

Both the current guideline and the one published in 2009 contain similar sections. Listed here are the sections contained in the current guideline and the corresponding number of recommendations: Introduction, Evaluation of Youth and Adults (5), Treatment of Adolescents (6), Hormonal Therapy for Transgender Adults (4), Adverse Outcomes Prevention and Long-term Care (7), and Surgery for Sex Reassignment and Gender Confirmation (6). The current introduction updates the diagnostic classification of "gender dysphoria/gender incongruence." It also reviews the development of "gender identity" and summarizes its natural development. The section on clinical evaluation of both youth and adults, defines in detail the professional qualifications required of those who diagnose and treat both adolescents and adults. We advise that decisions regarding the social transition of prepubertal youth are made with the assistance of a mental health professional or similarly experienced professional. We recommend against puberty blocking followed by gender-affirming hormone treatment of prepubertal children. Clinicians should inform pubertal children, adolescents, and adults seeking gender-confirming treatment of their options for fertility preservation. Prior to treatment, clinicians should evaluate the presence of medical conditions that may be worsened by hormone depletion and/or treatment. A multidisciplinary team, preferably composed of medical and mental health professionals, should monitor treatments. Clinicians evaluating transgender adults for endocrine treatment should confirm the diagnosis of persistent gender dysphoria/gender incongruence. Physicians should educate transgender persons regarding the time course of steroid-induced physical changes. Treatment should include periodic monitoring of hormone levels and metabolic parameters, as well as assessments of bone density and the impact upon prostate, gonads, and uterus. We also make recommendations for transgender persons who plan genital gender-affirming surgery.

Method of Development of Evidence-Based Clinical Practice Guidelines

The Clinical Guidelines Subcommittee (CGS) of the Endocrine Society deemed the diagnosis and treatment of individuals with GD/gender incongruence a priority area for revision and appointed a task force to formulate evidence-based recommendations. The task force followed the approach recommended by the Grading of Recommendations, Assessment, Development, and Evaluation group, an international group with expertise in the development and implementation of evidence-based guidelines (1). A detailed description of the grading scheme has been published elsewhere (2). The task force used the best available research evidence to develop the recommendations. The task force also used consistent language and graphical descriptions of both the strength of a recommendation and the quality of evidence. In terms of the strength of the recommendation, strong recommendations use the phrase "we recommend" and the number 1, and weak recommendations use the phrase "we suggest" and the number 2. Cross-filled circles indicate the quality of the evidence, such that ⊕◯◯◯ denotes very low–quality evidence; ⊕⊕◯◯, low quality; ⊕⊕⊕◯, moderate quality; and ⊕⊕⊕⊕, high quality. The task force has confidence that persons who receive care according to the strong recommendations will derive, on average, more benefit than harm. Weak recommendations require more careful consideration of the person's circumstances, values, and preferences to determine the best course of action. Linked to each recommendation is a description of the evidence and the

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values that the task force considered in making the recommendation. In some instances, there are remarks in which the task force offers technical suggestions for testing conditions, dosing, and monitoring. These technical comments reflect the best available evidence applied to a typical person being treated. Often this evidence comes from the unsystematic observations of the task force and their preferences; therefore, one should consider these remarks as suggestions.

In this guideline, the task force made several statements to emphasize the importance of shared decision-making, general preventive care measures, and basic principles of the treatment of transgender persons. They labeled these "Ungraded Good Practice Statement." Direct evidence for these statements was either unavailable or not systematically appraised and considered out of the scope of this guideline. The intention of these statements is to draw attention to these principles.

The Endocrine Society maintains a rigorous conflict-of-interest review process for developing clinical practice guidelines. All task force members must declare any potential conflicts of interest by completing a conflict-of-interest form. The CGS reviews all conflicts of interest before the Society's Council approves the members to participate on the task force and periodically during the development of the guideline. All others participating in the guideline's development must also disclose any conflicts of interest in the matter under study, and most of these participants must be without any conflicts of interest. The CGS and the task force have reviewed all disclosures for this guideline and resolved or managed all identified conflicts of interest.

Conflicts of interest are defined as remuneration in any amount from commercial interests; grants; research support; consulting fees; salary; ownership interests [*e.g.*, stocks and stock options (excluding diversified mutual funds)]; honoraria and other payments for participation in speakers' bureaus, advisory boards, or boards of directors; and all other financial benefits. Completed forms are available through the Endocrine Society office.

The Endocrine Society provided the funding for this guideline; the task force received no funding or remuneration from commercial or other entities.

Commissioned Systematic Review

The task force commissioned two systematic reviews to support this guideline. The first one aimed to summarize the available evidence on the effect of sex steroid use in transgender individuals on lipids and cardiovascular outcomes. The review identified 29 eligible studies at moderate risk of bias. In transgender males (female to male), sex steroid therapy was associated with a statistically significant increase in serum triglycerides and low-density lipoprotein cholesterol levels. High-density lipoprotein cholesterol levels decreased significantly across all follow-up time periods. In transgender females (male to female), serum triglycerides were significantly higher without any changes in other parameters. Few myocardial infarction, stroke, venous thromboembolism (VTE), and death events were reported. These events were more frequent in transgender females. However, the quality of the evidence was low. The second review summarized the available evidence regarding the effect of sex steroids on bone health in transgender individuals and identified 13 studies. In transgender males, there was no statistically significant difference in the lumbar spine, femoral neck, or total hip BMD at 12 and 24 months compared with baseline values before initiating masculinizing hormone therapy. In transgender females, there was a statistically significant increase in lumbar spine BMD at 12 months and 24 months compared with baseline values before initiation of feminizing hormone therapy. There was minimal information on fracture rates. The quality of evidence was also low.

Introduction

Throughout recorded history (in the absence of an endocrine disorder) some men and women have experienced confusion and anguish resulting from rigid, forced conformity to sexual dimorphism. In modern history, there have been numerous ongoing biological, psychological, cultural, political, and sociological debates over various aspects of gender variance. The 20th century marked the emergence of a social awakening for men and women with the belief that they are "trapped" in the wrong body (3). Magnus Hirschfeld and Harry Benjamin, among others, pioneered the medical responses to those who sought relief from and a resolution to their profound discomfort. Although the term transsexual became widely known after Benjamin wrote "The Transsexual Phenomenon" (4), it was Hirschfeld who coined the term "transsexual" in 1923 to describe people who want to live a life that corresponds with their experienced gender vs their designated gender (5). Magnus Hirschfeld (6) and others (4, 7) have described other types of trans phenomena besides transsexualism. These early researchers proposed that the gender identity of these people was located somewhere along a unidimensional continuum. This continuum ranged from all male through "something in between" to all female. Yet such a classification does not take into account that people may have gender identities outside this continuum. For instance, some experience themselves as having both a male and female gender identity, whereas others completely renounce any gender classification (8, 9). There are also reports of individuals experiencing a continuous and rapid involuntary alternation between a male and female identity (10) or men who do not experience themselves as men but do not want to live as women (11, 12). In some countries, (*e.g.*, Nepal, Bangladesh, and Australia), these nonmale or nonfemale genders are officially recognized (13). Specific treatment protocols, however, have not yet been developed for these groups.

Instead of the term transsexualism, the current classification system of the American Psychiatric Association uses the term gender dysphoria in its diagnosis of persons who are not satisfied with their designated gender (14). The current version of the World Health Organization's ICD-10 still uses the term transsexualism when diagnosing adolescents and adults. However, for the ICD-11, the World Health Organization has proposed using the term "gender incongruence" (15).

Treating persons with GD/gender incongruence (15) was previously limited to relatively ineffective elixirs or creams. However, more effective endocrinology-based treatments became possible with the availability of testosterone in 1935 and diethylstilbestrol in 1938. Reports of individuals with GD/gender incongruence who were treated with hormones and gender-affirming surgery appeared in the press during the second half of the 20th century. The Harry Benjamin International Gender Dysphoria Association was founded in September 1979 and is now called the World Professional Association for Transgender Health (WPATH). WPATH published its first Standards of Care in 1979. These standards have since been regularly updated, providing guidance for treating persons with GD/gender incongruence (16).

Prior to 1975, few peer-reviewed articles were published concerning endocrine treatment of transgender persons. Since then, more than two thousand articles about various aspects of transgender care have appeared.

It is the purpose of this guideline to make detailed recommendations and suggestions, based on existing medical literature and clinical experience, that will enable treating physicians to maximize benefit and minimize risk when caring for individuals diagnosed with GD/gender incongruence.

In the future, we need more rigorous evaluations of the effectiveness and safety of endocrine and surgical protocols. Specifically, endocrine treatment protocols for GD/gender incongruence should include the careful assessment of the following: (1) the effects of prolonged delay of puberty in adolescents on bone health, gonadal function, and the brain (including effects on cognitive, emotional, social, and sexual development); (2) the effects of treatment in adults on sex hormone levels; (3) the requirement for and the effects of progestins and other agents used to suppress endogenous sex steroids during treatment; and (4) the risks and benefits of gender-affirming hormone treatment in older transgender people.

To successfully establish and enact these protocols, a commitment of mental health and endocrine investigators is required to collaborate in long-term, large-scale studies across countries that use the same diagnostic and inclusion criteria, medications, assay methods, and response assessment tools (*e.g.*, the European Network for the Investigation of Gender Incongruence) (17, 18).

Terminology and its use vary and continue to evolve. Table 1 contains the definitions of terms as they are used throughout this guideline.

Biological Determinants of Gender Identity Development

One's self-awareness as male or female changes gradually during infant life and childhood. This process of cognitive and affective learning evolves with interactions with parents, peers, and environment. A fairly accurate timetable exists outlining the steps in this process (19). Normative psychological literature, however, does not address if and when gender identity becomes crystallized and what factors contribute to the development of a gender identity that is not congruent with the gender of rearing. Results of studies from a variety of biomedical disciplines—genetic, endocrine, and neuroanatomic—support the concept that gender identity and/or gender expression (20) likely reflect a complex interplay of biological, environmental, and cultural factors (21, 22).

With respect to endocrine considerations, studies have failed to find differences in circulating levels of sex steroids between transgender and nontransgender individuals (23). However, studies in individuals with a disorder/difference of sex development (DSD) have informed our understanding of the role that hormones may play in gender identity outcome, even though most persons with GD/gender incongruence do not have a DSD. For example, although most 46,XX adult individuals with virilizing congenital adrenal hyperplasia caused by mutations in *CYP21A2* reported a female gender identity, the prevalence of GD/gender incongruence was much greater in this group than in the general population without a DSD. This supports the concept that there is a role for prenatal/postnatal androgens in gender development (24–26), although some studies indicate that prenatal androgens are more likely to affect gender behavior and sexual orientation rather than gender identity *per se* (27, 28).

Researchers have made similar observations regarding the potential role of androgens in the development of gender identity in other individuals with DSD. For example, a review of two groups of 46,XY persons, each with androgen synthesis deficiencies and female raised, reported transgender male (female-to-male) gender role changes in 56% to 63% and 39% to 64% of patients, respectively (29). Also, in 46,XY female-raised individuals with cloacal

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Table 1. Definitions of Terms Used in This Guideline

Biological sex, biological male or female: These terms refer to physical aspects of maleness and femaleness. As these may not be in line with each other (*e.g.*, a person with XY chromosomes may have female-appearing genitalia), the terms biological sex and biological male or female are imprecise and should be avoided.
Cisgender: This means not transgender. An alternative way to describe individuals who are not transgender is "non-transgender people."
Gender-affirming (hormone) treatment: See "gender reassignment"
Gender dysphoria: This is the distress and unease experienced if gender identity and designated gender are not completely congruent (see Table 2). In 2013, the American Psychiatric Association released the fifth edition of the DSM-5, which replaced "gender identity disorder" with "gender dysphoria" and changed the criteria for diagnosis.
Gender expression: This refers to external manifestations of gender, expressed through one's name, pronouns, clothing, haircut, behavior, voice, or body characteristics. Typically, transgender people seek to make their gender expression align with their gender identity, rather than their designated gender.
Gender identity/experienced gender: This refers to one's internal, deeply held sense of gender. For transgender people, their gender identity does not match their sex designated at birth. Most people have a gender identity of man or woman (or boy or girl). For some people, their gender identity does not fit neatly into one of those two choices. Unlike gender expression (see below), gender identity is not visible to others.
Gender identity disorder: This is the term used for GD/gender incongruence in previous versions of DSM (see "gender dysphoria"). The ICD-10 still uses the term for diagnosing child diagnoses, but the upcoming ICD-11 has proposed using "gender incongruence of childhood."
Gender incongruence: This is an umbrella term used when the gender identity and/or gender expression differs from what is typically associated with the designated gender. Gender incongruence is also the proposed name of the gender identity–related diagnoses in ICD-11. Not all individuals with gender incongruence have gender dysphoria or seek treatment.
Gender variance: See "gender incongruence"
Gender reassignment: This refers to the treatment procedure for those who want to adapt their bodies to the experienced gender by means of hormones and/or surgery. This is also called gender-confirming or gender-affirming treatment.
Gender-reassignment surgery (gender-confirming/gender-affirming surgery): These terms refer only to the surgical part of gender-confirming/gender-affirming treatment.
Gender role: This refers to behaviors, attitudes, and personality traits that a society (in a given culture and historical period) designates as masculine or feminine and/or that society associates with or considers typical of the social role of men or women.
Sex designated at birth: This refers to sex assigned at birth, usually based on genital anatomy.
Sex: This refers to attributes that characterize biological maleness or femaleness. The best known attributes include the sex-determining genes, the sex chromosomes, the H-Y antigen, the gonads, sex hormones, internal and external genitalia, and secondary sex characteristics.
Sexual orientation: This term describes an individual's enduring physical and emotional attraction to another person. Gender identity and sexual orientation are not the same. Irrespective of their gender identity, transgender people may be attracted to women (gynephilic), attracted to men (androphilic), bisexual, asexual, or queer.
Transgender: This is an umbrella term for people whose gender identity and/or gender expression differs from what is typically associated with their sex designated at birth. Not all transgender individuals seek treatment.
Transgender male (also: trans man, female-to-male, transgender male): This refers to individuals assigned female at birth but who identify and live as men.
Transgender woman (also: trans woman, male-to female, transgender female): This refers to individuals assigned male at birth but who identify and live as women.
Transition: This refers to the process during which transgender persons change their physical, social, and/or legal characteristics consistent with the affirmed gender identity. Prepubertal children may choose to transition socially.
Transsexual: This is an older term that originated in the medical and psychological communities to refer to individuals who have permanently transitioned through medical interventions or desired to do so.

exstrophy and penile agenesis, the occurrence of transgender male changes was significantly more prevalent than in the general population (30, 31). However, the fact that a high percentage of individuals with the same conditions did not change gender suggests that cultural factors may play a role as well.

With respect to genetics and gender identity, several studies have suggested heritability of GD/gender incongruence (32, 33). In particular, a study by Heylens *et al.* (33) demonstrated a 39.1% concordance rate for gender identity disorder (based on the DSM-IV criteria) in 23 monozygotic twin pairs but no concordance in 21 same-sex dizygotic or seven opposite-sex twin pairs. Although numerous investigators have sought to identify specific genes associated with GD/gender incongruence, such studies have been inconsistent and without strong statistical significance (34–38).

Studies focusing on brain structure suggest that the brain phenotypes of people with GD/gender incongruence differ in various ways from control males and females, but that there is not a complete sex reversal in brain structures (39).

In summary, although there is much that is still unknown with respect to gender identity and its expression, compelling studies support the concept that biologic factors, in addition to environmental factors, contribute to this fundamental aspect of human development.

Natural History of Children With GD/Gender Incongruence

With current knowledge, we cannot predict the psychosexual outcome for any specific child. Prospective follow-up studies show that childhood GD/gender incongruence does not invariably persist into adolescence and adulthood (so-called "desisters"). Combining all outcome studies to date, the GD/gender incongruence of a minority of prepubertal children appears to persist in adolescence (20, 40). In adolescence, a significant number of these desisters identify as homosexual or bisexual. It may be that children who only showed some gender nonconforming characteristics have been included in the follow-up studies, because the DSM-IV text revision criteria for a diagnosis were rather broad. However, the persistence of GD/gender incongruence into adolescence is more likely if it had been extreme in childhood (41, 42). With the newer, stricter criteria of the DSM-5 (Table 2), persistence rates may well be different in future studies.

1.0 Evaluation of Youth and Adults

Gender-affirming treatment is a multidisciplinary effort. After evaluation, education, and diagnosis, treatment may include mental health care, hormone therapy, and/or surgical therapy. Together with an MHP, hormone-prescribing clinicians should examine the psychosocial impact of the potential changes on people's lives, including mental health, friends, family, jobs, and their role in society. Transgender individuals should be encouraged to experience living in the new gender role and assess whether this improves their quality of life. Although the focus of this guideline is gender-affirming hormone therapy, collaboration with appropriate professionals responsible for each aspect of treatment maximizes a successful outcome.

Diagnostic assessment and mental health care

GD/gender incongruence may be accompanied with psychological or psychiatric problems (43–51). It is therefore necessary that clinicians who prescribe hormones and are involved in diagnosis and psychosocial assessment meet the following criteria: (1) are competent in using the DSM and/or the ICD for diagnostic purposes, (2) are able to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) are trained in diagnosing psychiatric conditions, (4) undertake or refer for appropriate treatment, (5) are able to do a psychosocial assessment of the patient's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) regularly attend relevant professional meetings.

Because of the psychological vulnerability of many individuals with GD/gender incongruence, it is important that mental health care is available before, during, and sometimes also after transitioning. For children and adolescents, an MHP who has training/experience in child and adolescent gender development (as well as child and adolescent psychopathology) should make the diagnosis, because assessing GD/gender incongruence in children and adolescents is often extremely complex.

During assessment, the clinician obtains information from the individual seeking gender-affirming treatment. In the case

Table 2. DSM-5 Criteria for Gender Dysphoria in Adolescents and Adults

A. A marked incongruence between one's experienced/expressed gender and natal gender of at least 6 mo in duration, as manifested by at least two of the following:
1. A marked incongruence between one's experienced/expressed gender and primary and/or secondary sex characteristics (or in young adolescents, the anticipated secondary sex characteristics)
2. A strong desire to be rid of one's primary and/or secondary sex characteristics because of a marked incongruence with one's experienced/expressed gender (or in young adolescents, a desire to prevent the development of the anticipated secondary sex characteristics)
3. A strong desire for the primary and/or secondary sex characteristics of the other gender
4. A strong desire to be of the other gender (or some alternative gender different from one's designated gender)
5. A strong desire to be treated as the other gender (or some alternative gender different from one's designated gender)
6. A strong conviction that one has the typical feelings and reactions of the other gender (or some alternative gender different from one's designated gender)

B. The condition is associated with clinically significant distress or impairment in social, occupational, or other important areas of functioning.

Specify if:
1. The condition exists with a disorder of sex development.
2. The condition is posttransitional, in that the individual has transitioned to full-time living in the desired gender (with or without legalization of gender change) and has undergone (or is preparing to have) at least one sex-related medical procedure or treatment regimen—namely, regular sex hormone treatment or gender reassignment surgery confirming the desired gender (*e.g.*, penectomy, vaginoplasty in natal males; mastectomy or phalloplasty in natal females).

Reference: American Psychiatric Association (14).

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of adolescents, the clinician also obtains information from the parents or guardians regarding various aspects of the child's general and psychosexual development and current functioning. On the basis of this information, the clinician:

- decides whether the individual fulfills criteria for treatment (see Tables 2 and 3) for GD/gender incongruence (DSM-5) or transsexualism (DSM-5 and/or ICD-10);
- informs the individual about the possibilities and limitations of various kinds of treatment (hormonal/surgical and nonhormonal), and if medical treatment is desired, provides correct information to prevent unrealistically high expectations;
- assesses whether medical interventions may result in unfavorable psychological and social outcomes.

In cases in which severe psychopathology, circumstances, or both seriously interfere with the diagnostic work or make satisfactory treatment unlikely, clinicians should assist the adolescent in managing these other issues. Literature on postoperative regret suggests that besides poor quality of surgery, severe psychiatric comorbidity and lack of support may interfere with positive outcomes (52–56).

For adolescents, the diagnostic procedure usually includes a complete psychodiagnostic assessment (57) and an assessment of the decision-making capability of the youth. An evaluation to assess the family's ability to endure stress, give support, and deal with the complexities of the adolescent's situation should be part of the diagnostic phase (58).

Social transitioning

A change in gender expression and role (which may involve living part time or full time in another gender role that is consistent with one's gender identity) may test the person's resolve, the capacity to function in the affirmed gender, and the adequacy of social, economic, and psychological supports. It assists both the individual and the clinician in their judgments about how to proceed (16). During social transitioning, the person's feelings about the social transformation (including coping with the responses of others) is a major focus of the counseling. The optimal timing for social transitioning may differ between individuals. Sometimes people wait until they start gender-affirming hormone treatment to make social transitioning easier, but individuals increasingly start social transitioning long before they receive medically supervised, gender-affirming hormone treatment.

Criteria

Adolescents and adults seeking gender-affirming hormone treatment and surgery should satisfy certain criteria before proceeding (16). Criteria for gender-affirming hormone therapy for adults are in Table 4, and criteria for gender-affirming hormone therapy for adolescents are in Table 5. Follow-up studies in adults meeting these criteria indicate a high satisfaction rate with treatment (59). However, the quality of evidence is usually low. A few follow-up studies on adolescents who fulfilled these criteria also indicated good treatment results (60–63).

Recommendations for Those Involved in the Gender-Affirming Hormone Treatment of Individuals With GD/Gender Incongruence

1.1. We advise that only trained MHPs who meet the following criteria should diagnose GD/gender incongruence in adults: (1) competence in using the DSM and/or the ICD for diagnostic purposes, (2) the ability to diagnose GD/gender incongruence and make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (3) training in diagnosing psychiatric conditions, (4) the ability to undertake or refer for appropriate treatment, (5) the ability to psychosocially assess the person's understanding, mental health, and social conditions that can impact gender-affirming hormone therapy, and (6) a practice of regularly attending relevant professional meetings. (Ungraded Good Practice Statement)

1.2. We advise that only MHPs who meet the following criteria should diagnose GD/gender incongruence in children and adolescents: (1) training in child and adolescent developmental psychology and psychopathology, (2) competence in using the DSM and/or ICD for diagnostic

Table 3. ICD-10 Criteria for Transsexualism

Transsexualism (F64.0) has three criteria:
1. The desire to live and be accepted as a member of the opposite sex, usually accompanied by the wish to make his or her body as congruent as possible with the preferred sex through surgery and hormone treatments.
2. The transsexual identity has been present persistently for at least 2 y.
3. The disorder is not a symptom of another mental disorder or a genetic, DSD, or chromosomal abnormality.

Table 4. Criteria for Gender-Affirming Hormone Therapy for Adults

1. Persistent, well-documented gender dysphoria/gender incongruence
2. The capacity to make a fully informed decision and to consent for treatment
3. The age of majority in a given country (if younger, follow the criteria for adolescents)
4. Mental health concerns, if present, must be reasonably well controlled

Reproduced from World Professional Association for Transgender Health (16).

purposes, (3) the ability to make a distinction between GD/gender incongruence and conditions that have similar features (*e.g.*, body dysmorphic disorder), (4) training in diagnosing psychiatric conditions, (5) the ability to undertake or refer for appropriate treatment, (6) the ability to psychosocially assess the person's understanding and social conditions that can impact gender-affirming hormone therapy, (7) a practice of regularly attending relevant professional meetings, and (8) knowledge of the criteria for puberty blocking and gender-affirming hormone treatment in adolescents. (Ungraded Good Practice Statement)

Evidence

Individuals with gender identity issues may have psychological or psychiatric problems (43–48, 50, 51, 64, 65). It is therefore necessary that clinicians making the diagnosis are able to make a distinction between GD/gender incongruence and conditions that have similar features. Examples of conditions with similar features are body dysmorphic disorder, body identity integrity disorder (a condition in which individuals have a sense that their anatomical configuration as an able-bodied person is somehow wrong or inappropriate) (66), or certain forms of eunuchism (in which a person is preoccupied with or engages in castration and/or penectomy for

Table 5. Criteria for Gender-Affirming Hormone Therapy for Adolescents

Adolescents are eligible for GnRH agonist treatment if:

1. A qualified MHP has confirmed that:
   - the adolescent has demonstrated a long-lasting and intense pattern of gender nonconformity or gender dysphoria (whether suppressed or expressed),
   - gender dysphoria worsened with the onset of puberty,
   - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start treatment,
   - the adolescent has sufficient mental capacity to give informed consent to this (reversible) treatment,
2. And the adolescent:
   - has been informed of the effects and side effects of treatment (including potential loss of fertility if the individual subsequently continues with sex hormone treatment) and options to preserve fertility,
   - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal assessment
   - agrees with the indication for GnRH agonist treatment,
   - has confirmed that puberty has started in the adolescent (Tanner stage ≥G2/B2),
   - has confirmed that there are no medical contraindications to GnRH agonist treatment.

Adolescents are eligible for subsequent sex hormone treatment if:

1. A qualified MHP has confirmed:
   - the persistence of gender dysphoria,
   - any coexisting psychological, medical, or social problems that could interfere with treatment (*e.g.*, that may compromise treatment adherence) have been addressed, such that the adolescent's situation and functioning are stable enough to start sex hormone treatment,
   - the adolescent has sufficient mental capacity (which most adolescents have by age 16 years) to estimate the consequences of this (partly) irreversible treatment, weigh the benefits and risks, and give informed consent to this (partly) irreversible treatment,
2. And the adolescent:
   - has been informed of the (irreversible) effects and side effects of treatment (including potential loss of fertility and options to preserve fertility),
   - has given informed consent and (particularly when the adolescent has not reached the age of legal medical consent, depending on applicable legislation) the parents or other caretakers or guardians have consented to the treatment and are involved in supporting the adolescent throughout the treatment process,
3. And a pediatric endocrinologist or other clinician experienced in pubertal induction:
   - agrees with the indication for sex hormone treatment,
   - has confirmed that there are no medical contraindications to sex hormone treatment.

Reproduced from World Professional Association for Transgender Health (16).

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reasons that are not gender identity related) (11). Clinicians should also be able to diagnose psychiatric conditions accurately and ensure that these conditions are treated appropriately, particularly when the conditions may complicate treatment, affect the outcome of gender-affirming treatment, or be affected by hormone use.

Values and preferences

The task force placed a very high value on avoiding harm from hormone treatment in individuals who have conditions other than GD/gender incongruence and who may not benefit from the physical changes associated with this treatment and placed a low value on any potential benefit these persons believe they may derive from hormone treatment. This justifies the good practice statement.

1.3. We advise that decisions regarding the social transition of prepubertal youths with GD/gender incongruence are made with the assistance of an MHP or another experienced professional. (Ungraded Good Practice Statement).

1.4. We recommend against puberty blocking and gender-affirming hormone treatment in prepubertal children with GD/gender incongruence. (1 l⊕⊕OO)

Evidence

In most children diagnosed with GD/gender incongruence, it did not persist into adolescence. The percentages differed among studies, probably dependent on which version of the DSM clinicians used, the patient's age, the recruitment criteria, and perhaps cultural factors. However, the large majority (about 85%) of prepubertal children with a childhood diagnosis did not remain GD/gender incongruent in adolescence (20). If children have completely socially transitioned, they may have great difficulty in returning to the original gender role upon entering puberty (40). Social transition is associated with the persistence of GD/gender incongruence as a child progresses into adolescence. It may be that the presence of GD/gender incongruence in prepubertal children is the earliest sign that a child is destined to be transgender as an adolescent/adult (20). However, social transition (in addition to GD/gender incongruence) has been found to contribute to the likelihood of persistence.

This recommendation, however, does not imply that children should be discouraged from showing gender-variant behaviors or should be punished for exhibiting such behaviors. In individual cases, an early complete social transition may result in a more favorable outcome, but there are currently no criteria to identify the GD/gender-incongruent children to whom this applies. At the present time, clinical experience suggests that persistence of GD/gender incongruence can only be reliably assessed after the first signs of puberty.

Values and preferences

The task force placed a high value on avoiding harm with gender-affirming hormone therapy in prepubertal children with GD/gender incongruence. This justifies the strong recommendation in the face of low-quality evidence.

1.5. We recommend that clinicians inform and counsel all individuals seeking gender-affirming medical treatment regarding options for fertility preservation prior to initiating puberty suppression in adolescents and prior to treating with hormonal therapy of the affirmed gender in both adolescents and adults. (1 l⊕⊕⊕O)

Remarks

Persons considering hormone use for gender affirmation need adequate information about this treatment in general and about fertility effects of hormone treatment in particular to make an informed and balanced decision (67, 68). Because young adolescents may not feel qualified to make decisions about fertility and may not fully understand the potential effects of hormonal interventions, consent and protocol education should include parents, the referring MHP(s), and other members of the adolescent's support group. To our knowledge, there are no formally evaluated decision aids available to assist in the discussion and decision regarding the future fertility of adolescents or adults beginning gender-affirming treatment.

Treating early pubertal youth with GnRH analogs will temporarily impair spermatogenesis and oocyte maturation. Given that an increasing number of transgender youth want to preserve fertility potential, delaying or temporarily discontinuing GnRH analogs to promote gamete maturation is an option. This option is often not preferred, because mature sperm production is associated with later stages of puberty and with the significant development of secondary sex characteristics.

For those designated male at birth with GD/gender incongruence and who are in early puberty, sperm production and the development of the reproductive tract are insufficient for the cryopreservation of sperm. However, prolonged pubertal suppression using GnRH analogs is reversible and clinicians should inform these individuals that sperm production can be initiated following prolonged gonadotropin suppression. This can be accomplished by spontaneous gonadotropin recovery after

cessation of GnRH analogs or by gonadotropin treatment and will probably be associated with physical manifestations of testosterone production, as stated above. Note that there are no data in this population concerning the time required for sufficient spermatogenesis to collect enough sperm for later fertility. In males treated for precocious puberty, spermarche was reported 0.7 to 3 years after cessation of GnRH analogs (69). In adult men with gonadotropin deficiency, sperm are noted in seminal fluid by 6 to 12 months of gonadotropin treatment. However, sperm numbers when partners of these patients conceive are far below the "normal range" (70, 71).

In girls, no studies have reported long-term, adverse effects of pubertal suppression on ovarian function after treatment cessation (72, 73). Clinicians should inform adolescents that no data are available regarding either time to spontaneous ovulation after cessation of GnRH analogs or the response to ovulation induction following prolonged gonadotropin suppression.

In males with GD/gender incongruence, when medical treatment is started in a later phase of puberty or in adulthood, spermatogenesis is sufficient for cryopreservation and storage of sperm. *In vitro* spermatogenesis is currently under investigation. Restoration of spermatogenesis after prolonged estrogen treatment has not been studied.

In females with GD/gender incongruence, the effect of prolonged treatment with exogenous testosterone on ovarian function is uncertain. There have been reports of an increased incidence of polycystic ovaries in transgender males, both prior to and as a result of androgen treatment (74–77), although these reports were not confirmed by others (78). Pregnancy has been reported in transgender males who have had prolonged androgen treatment and have discontinued testosterone but have not had genital surgery (79, 80). A reproductive endocrine gynecologist can counsel patients before gender-affirming hormone treatment or surgery regarding potential fertility options (81). Techniques for cryopreservation of oocytes, embryos, and ovarian tissue continue to improve, and oocyte maturation of immature tissue is being studied (82).

2.0 Treatment of Adolescents

During the past decade, clinicians have progressively acknowledged the suffering of young adolescents with GD/gender incongruence. In some forms of GD/gender incongruence, psychological interventions may be useful and sufficient. However, for many adolescents with GD/gender incongruence, the pubertal physical changes are unbearable. As early medical intervention may prevent psychological harm, various clinics have decided to start treating young adolescents with GD/gender incongruence with puberty-suppressing medication (a GnRH analog). As compared with starting gender-affirming treatment long after the first phases of puberty, a benefit of pubertal suppression at early puberty may be a better psychological and physical outcome.

In girls, the first physical sign of puberty is the budding of the breasts followed by an increase in breast and fat tissue. Breast development is also associated with the pubertal growth spurt, and menarche occurs ~2 years later. In boys, the first physical change is testicular growth. A testicular volume ≥4 mL is seen as consistent with the initiation of physical puberty. At the beginning of puberty, estradiol and testosterone levels are still low and are best measured in the early morning with an ultrasensitive assay. From a testicular volume of 10 mL, daytime testosterone levels increase, leading to virilization (83). Note that pubic hair and/or axillary hair/odor may not reflect the onset of gonadarche; instead, it may reflect adrenarche alone.

2.1. We suggest that adolescents who meet diagnostic criteria for GD/gender incongruence, fulfill criteria for treatment (Table 5), and are requesting treatment should initially undergo treatment to suppress pubertal development. (2 ⊕⊕◯◯)

2.2. We suggest that clinicians begin pubertal hormone suppression after girls and boys first exhibit physical changes of puberty (Tanner stages G2/B2). (2 ⊕⊕◯◯)

Evidence

Pubertal suppression can expand the diagnostic phase by a long period, giving the subject more time to explore options and to live in the experienced gender before making a decision to proceed with gender-affirming sex hormone treatments and/or surgery, some of which is irreversible (84, 85). Pubertal suppression is fully reversible, enabling full pubertal development in the natal gender, after cessation of treatment, if appropriate. The experience of full endogenous puberty is an undesirable condition for the GD/gender-incongruent individual and may seriously interfere with healthy psychological functioning and well-being. Treating GD/gender-incongruent adolescents entering puberty with GnRH analogs has been shown to improve psychological functioning in several domains (86).

Another reason to start blocking pubertal hormones early in puberty is that the physical outcome is improved compared with initiating physical transition after puberty has been completed (60, 62). Looking like a man or woman when living as the opposite sex creates difficult

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barriers with enormous life-long disadvantages. We therefore advise starting suppression in early puberty to prevent the irreversible development of undesirable secondary sex characteristics. However, adolescents with GD/gender incongruence should experience the first changes of their endogenous spontaneous puberty, because their emotional reaction to these first physical changes has diagnostic value in establishing the persistence of GD/gender incongruence (85). Thus, Tanner stage 2 is the optimal time to start pubertal suppression. However, pubertal suppression treatment in early puberty will limit the growth of the penis and scrotum, which will have a potential effect on future surgical treatments (87).

Clinicians can also use pubertal suppression in adolescents in later pubertal stages to stop menses in transgender males and prevent facial hair growth in transgender females. However, in contrast to the effects in early pubertal adolescents, physical sex characteristics (such as more advanced breast development in transgender boys and lowering of the voice and outgrowth of the jaw and brow in transgender girls) are not reversible.

Values and preferences

These recommendations place a high value on avoiding an unsatisfactory physical outcome when secondary sex characteristics have become manifest and irreversible, a higher value on psychological well-being, and a lower value on avoiding potential harm from early pubertal suppression.

Remarks

Table 6 lists the Tanner stages of breast and male genital development. Careful documentation of hallmarks of pubertal development will ensure precise timing when initiating pubertal suppression once puberty has started. Clinicians can use pubertal LH and sex steroid levels to confirm that puberty has progressed sufficiently before starting pubertal suppression (88). Reference ranges for sex steroids by Tanner stage may vary depending on the assay used. Ultrasensitive sex steroid and gonadotropin assays will help clinicians document early pubertal changes.

Irreversible and, for GD/gender-incongruent adolescents, undesirable sex characteristics in female puberty are breasts, female body habitus, and, in some cases, relative short stature. In male puberty, they are a prominent Adam's apple; low voice; male bone configuration, such as a large jaw, big feet and hands, and tall stature; and male hair pattern on the face and extremities.

2.3. We recommend that, where indicated, GnRH analogues are used to suppress pubertal hormones. (1 ⊕⊕OO)

Evidence

Clinicians can suppress pubertal development and gonadal function most effectively via gonadotropin suppression using GnRH analogs. GnRH analogs are long-acting agonists that suppress gonadotropins by GnRH receptor desensitization after an initial increase of gonadotropins during ~10 days after the first and (to a lesser degree) the second injection (89). Antagonists immediately suppress pituitary gonadotropin secretion (90, 91). Long-acting GnRH analogs are the currently preferred treatment option. Clinicians may consider long-acting GnRH antagonists when evidence on their safety and efficacy in adolescents becomes available.

During GnRH analog treatment, slight development of secondary sex characteristics may regress, and in a later phase of pubertal development, it will stop. In girls, breast tissue will become atrophic, and menses will stop. In boys, virilization will stop, and testicular volume may decrease (92).

An advantage of using GnRH analogs is the reversibility of the intervention. If, after extensive exploration of his/her transition wish, the individual no longer desires transition, they can discontinue pubertal suppression. In subjects with

Table 6. Tanner Stages of Breast Development and Male External Genitalia

The description of Tanner stages for breast development:
1. Prepubertal
2. Breast and papilla elevated as small mound; areolar diameter increased
3. Breast and areola enlarged, no contour separation
4. Areola and papilla form secondary mound
5. Mature; nipple projects, areola part of general breast contour

For penis and testes:
1. Prepubertal, testicular volume <4 mL
2. Slight enlargement of penis; enlarged scrotum, pink, texture altered, testes 4–6 mL
3. Penis longer, testes larger (8–12 mL)
4. Penis and glans larger, including increase in breadth; testes larger (12–15 mL), scrotum dark
5. Penis adult size; testicular volume > 15 ml

Adapted from Lawrence (56).

precocious puberty, spontaneous pubertal development has been shown to resume after patients discontinue taking GnRH analogs (93).

Recommendations 2.1 to 2.3 are supported by a prospective follow-up study from The Netherlands. This report assessed mental health outcomes in 55 transgender adolescents/young adults (22 transgender females and 33 transgender males) at three time points: (1) before the start of GnRH agonist (average age of 14.8 years at start of treatment), (2) at initiation of gender-affirming hormones (average age of 16.7 years at start of treatment), and (3) 1 year after "gender-reassignment surgery" (average age of 20.7 years) (63). Despite a decrease in depression and an improvement in general mental health functioning, GD/gender incongruence persisted through pubertal suppression, as previously reported (86). However, following sex hormone treatment and gender-reassignment surgery, GD/gender incongruence was resolved and psychological functioning steadily improved (63). Furthermore, well-being was similar to or better than that reported by age-matched young adults from the general population, and none of the study participants regretted treatment. This study represents the first long-term follow-up of individuals managed according to currently existing clinical practice guidelines for transgender youth, and it underscores the benefit of the multidisciplinary approach pioneered in The Netherlands; however, further studies are needed.

Side effects

The primary risks of pubertal suppression in GD/gender-incongruent adolescents may include adverse effects on bone mineralization (which can theoretically be reversed with sex hormone treatment), compromised fertility if the person subsequently is treated with sex hormones, and unknown effects on brain development. Few data are available on the effect of GnRH analogs on BMD in adolescents with GD/gender incongruence. Initial data in GD/gender-incongruent subjects demonstrated no change of absolute areal BMD during 2 years of GnRH analog therapy but a decrease in BMD z scores (85). A recent study also suggested suboptimal bone mineral accrual during GnRH analog treatment. The study reported a decrease in areal BMD z scores and of bone mineral apparent density z scores (which takes the size of the bone into account) in 19 transgender males treated with GnRH analogs from a mean age of 15.0 years (standard deviation = 2.0 years) for a median duration of 1.5 years (0.3 to 5.2 years) and in 15 transgender females treated from 14.9 (±1.9) years for 1.3 years (0.5 to 3.8 years), although not all changes were statistically significant (94). There was incomplete catch-up at age 22 years after sex hormone treatment from age 16.6 (±1.4) years for a median duration of 5.8 years (3.0 to 8.0 years) in transgender females and from age 16.4 (±2.3) years for 5.4 years (2.8 to 7.8 years) in transgender males. Little is known about more prolonged use of GnRH analogs. Researchers reported normal BMD z scores at age 35 years in one individual who used GnRH analogs from age 13.7 years until age 18.6 years before initiating sex hormone treatment (65).

Additional data are available from individuals with late puberty or GnRH analog treatment of other indications. Some studies reported that men with constitutionally delayed puberty have decreased BMD in adulthood (95). However, other studies reported that these men have normal BMD (96, 97). Treating adults with GnRH analogs results in a decrease of BMD (98). In children with central precocious puberty, treatment with GnRH analogs has been found to result in a decrease of BMD during treatment by some (99) but not others (100). Studies have reported normal BMD after discontinuing therapy (69, 72, 73, 101, 102). In adolescents treated with growth hormone who are small for gestational age and have normal pubertal timing, 2-year GnRH analog treatments did not adversely affect BMD (103). Calcium supplementation may be beneficial in optimizing bone health in GnRH analog–treated individuals (104). There are no studies of vitamin D supplementation in this context, but clinicians should offer supplements to vitamin D–deficient adolescents. Physical activity, especially during growth, is important for bone mass in healthy individuals (103) and is therefore likely to be beneficial for bone health in GnRH analog–treated subjects.

GnRH analogs did not induce a change in body mass index standard deviation score in GD/gender-incongruent adolescents (94) but caused an increase in fat mass and decrease in lean body mass percentage (92). Studies in girls treated for precocious puberty also reported a stable body mass index standard deviation score during treatment (72) and body mass index and body composition comparable to controls after treatment (73).

Arterial hypertension has been reported as an adverse effect in a few girls treated with GnRH analogs for precocious/early puberty (105, 106). Blood pressure monitoring before and during treatment is recommended.

Individuals may also experience hot flashes, fatigue, and mood alterations as a consequence of pubertal suppression. There is no consensus on treatment of these side effects in this context.

It is recommended that any use of pubertal blockers (and subsequent use of sex hormones, as detailed below) include a discussion about implications for fertility (see recommendation 1.3). Transgender adolescents may

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want to preserve fertility, which may be otherwise compromised if puberty is suppressed at an early stage and the individual completes phenotypic transition with the use of sex hormones.

Limited data are available regarding the effects of GnRH analogs on brain development. A single cross-sectional study demonstrated no compromise of executive function (107), but animal data suggest there may be an effect of GnRH analogs on cognitive function (108).

Values and preferences

Our recommendation of GnRH analogs places a higher value on the superior efficacy, safety, and reversibility of the pubertal hormone suppression achieved (as compared with the alternatives) and a relatively lower value on limiting the cost of therapy. Of the available alternatives, depot and oral progestin preparations are effective. Experience with this treatment dates back prior to the emergence of GnRH analogs for treating precocious puberty in papers from the 1960s and early 1970s (109–112). These compounds are usually safe, but some side effects have been reported (113–115). Only two recent studies involved transgender youth (116, 117). One of these studies described the use of oral lynestrenol monotherapy followed by the addition of testosterone treatment in transgender boys who were at Tanner stage B4 or further at the start of treatment (117). They found lynestrenol safe, but gonadotropins were not fully suppressed. The study reported metrorrhagia in approximately half of the individuals, mainly in the first 6 months. Acne, headache, hot flashes, and fatigue were other frequent side effects. Another progestin that has been studied in the United States is medroxyprogesterone. This agent is not as effective as GnRH analogs in lowering endogenous sex hormones either and may be associated with other side effects (116). Progestin preparations may be an acceptable treatment for persons without access to GnRH analogs or with a needle phobia. If GnRH analog treatment is not available (insurance denial, prohibitive cost, or other reasons), postpubertal, transgender female adolescents may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see adult section).

Remarks

Measurements of gonadotropin and sex steroid levels give precise information about gonadal axis suppression, although there is insufficient evidence for any specific short-term monitoring scheme in children treated with GnRH analogs (88). If the gonadal axis is not completely suppressed—as evidenced by (for example) menses, erections, or progressive hair growth—the interval of GnRH analog treatment can be shortened or the dose increased. During treatment, adolescents should be monitored for negative effects of delaying puberty, including a halted growth spurt and impaired bone mineral accretion. Table 7 illustrates a suggested clinical protocol.

Anthropometric measurements and X-rays of the left hand to monitor bone age are informative for evaluating growth. To assess BMD, clinicians can perform dual-energy X-ray absorptiometry scans.

2.4. In adolescents who request sex hormone treatment (given this is a partly irreversible treatment), we recommend initiating treatment using a gradually increasing dose schedule (see Table 8) after a multidisciplinary team of medical and MHPs has confirmed the persistence of GD/gender incongruence and sufficient mental capacity to give informed consent, which most adolescents have by age 16 years (Table 5). (1 |⊕⊕OO)

2.5. We recognize that there may be compelling reasons to initiate sex hormone treatment prior to the age of 16 years in some adolescents with GD/gender incongruence, even though there are minimal published studies of gender-affirming hormone treatments administered before age 13.5 to 14 years. As with the care of adolescents ≥16 years of age, we recommend that an expert multidisciplinary team of medical and MHPs manage this treatment. (1 |⊕OOO)

2.6. We suggest monitoring clinical pubertal development every 3 to 6 months and laboratory parameters every 6 to 12 months during sex hormone treatment (Table 9). (2 |⊕⊕OO)

Table 7. Baseline and Follow-Up Protocol During Suppression of Puberty

Every 3–6 mo
Anthropometry: height, weight, sitting height, blood pressure, Tanner stages
Every 6–12 mo
Laboratory: LH, FSH, E2/T, 25OH vitamin D
Every 1–2 y
Bone density using DXA
Bone age on X-ray of the left hand (if clinically indicated)

Adapted from Hembree *et al.* (118).

Abbreviations: DXA, dual-energy X-ray absorptiometry; E2, estradiol; FSH, follicle stimulating hormone; LH, luteinizing hormone; T, testosterone;

Table 8. Protocol Induction of Puberty

Induction of female puberty with oral 17β-estradiol, increasing the dose every 6 mo:
- 5 μg/kg/d
- 10 μg/kg/d
- 15 μg/kg/d
- 20 μg/kg/d
- Adult dose = 2–6 mg/d
- *In postpubertal transgender female adolescents, the dose of 17β-estradiol can be increased more rapidly:*
  - 1 mg/d for 6 mo
  - 2 mg/d

Induction of female puberty with transdermal 17β-estradiol, increasing the dose every 6 mo (new patch is placed every 3.5 d):
- 6.25–12.5 μg/24 h (cut 25-μg patch into quarters, then halves)
- 25 μg/24 h
- 37.5 μg/24 h
- Adult dose = 50–200 μg/24 h
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological estradiol levels (see Table 15).*

Induction of male puberty with testosterone esters increasing the dose every 6 mo (IM or SC):
- 25 mg/m^2/2 wk (or alternatively, half this dose weekly, or double the dose every 4 wk)
- 50 mg/m^2/2 wk
- 75 mg/m^2/2 wk
- 100 mg/m^2/2 wk
- Adult dose = 100–200 mg every 2 wk
- *In postpubertal transgender male adolescents the dose of testosterone esters can be increased more rapidly:*
  - 75 mg/2 wk for 6 mo
  - 125 mg/2 wk
- *For alternatives once at adult dose, see Table 11.*
- *Adjust maintenance dose to mimic physiological testosterone levels (see Table 14).*

Adapted from Hembree *et al.* (118).

Abbreviations: IM, intramuscularly; SC, subcutaneously.

Evidence

Adolescents develop competence in decision making at their own pace. Ideally, the supervising medical professionals should individually assess this competence, although no objective tools to make such an assessment are currently available.

Many adolescents have achieved a reasonable level of competence by age 15 to 16 years (119), and in many countries 16-year-olds are legally competent with regard to medical decision making (120). However, others believe that although some capacities are generally achieved before age 16 years, other abilities (such as good risk assessment) do not develop until well after 18 years (121). They suggest that health care procedures should be divided along a matrix of relative risk, so that younger adolescents can be allowed to decide about low-risk procedures, such as most diagnostic tests and common therapies, but not about high-risk procedures, such as most surgical procedures (121).

Currently available data from transgender adolescents support treatment with sex hormones starting at age 16 years (63, 122). However, some patients may incur potential risks by waiting until age 16 years. These include the potential risk to bone health if puberty is suppressed

Table 9. Baseline and Follow-up Protocol During Induction of Puberty

Every 3–6 mo
- •Anthropometry: height, weight, sitting height, blood pressure, Tanner stages

Every 6–12 mo
- •In transgender males: hemoglobin/hematocrit, lipids, testosterone, 25OH vitamin D
- •In transgender females: prolactin, estradiol, 25OH vitamin D

Every 1–2 y
- •BMD using DXA
- •Bone age on X-ray of the left hand (if clinically indicated)

BMD should be monitored into adulthood (until the age of 25–30 y or until peak bone mass has been reached).
For recommendations on monitoring once pubertal induction has been completed, see Tables 14 and 15.

Adapted from Hembree *et al.* (118).

Abbreviation: DXA, dual-energy X-ray absorptiometry.

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for 6 to 7 years before initiating sex hormones (*e.g.*, if someone reached Tanner stage 2 at age 9-10 years old). Additionally, there may be concerns about inappropriate height and potential harm to mental health (emotional and social isolation) if initiation of secondary sex characteristics must wait until the person has reached 16 years of age. However, only minimal data supporting earlier use of gender-affirming hormones in transgender adolescents currently exist (63). Clearly, long-term studies are needed to determine the optimal age of sex hormone treatment in GD/gender-incongruent adolescents.

The MHP who has followed the adolescent during GnRH analog treatment plays an essential role in assessing whether the adolescent is eligible to start sex hormone therapy and capable of consenting to this treatment (Table 5). Support of the family/environment is essential. Prior to the start of sex hormones, clinicians should discuss the implications for fertility (see recommendation 1.5). Throughout pubertal induction, an MHP and a pediatric endocrinologist (or other clinician competent in the evaluation and induction of pubertal development) should monitor the adolescent. In addition to monitoring therapy, it is also important to pay attention to general adolescent health issues, including healthy life style choices, such as not smoking, contraception, and appropriate vaccinations (*e.g.*, human papillomavirus).

For the induction of puberty, clinicians can use a similar dose scheme for hypogonadal adolescents with GD/gender incongruence as they use in other individuals with hypogonadism, carefully monitoring for desired and undesired effects (Table 8). In transgender female adolescents, transdermal 17β-estradiol may be an alternative for oral 17β-estradiol. It is increasingly used for pubertal induction in hypogonadal females. However, the absence of low-dose estrogen patches may be a problem. As a result, individuals may need to cut patches to size themselves to achieve appropriate dosing (123). In transgender male adolescents, clinicians can give testosterone injections intramuscularly or subcutaneously (124, 125).

When puberty is initiated with a gradually increasing schedule of sex steroid doses, the initial levels will not be high enough to suppress endogenous sex steroid secretion. Gonadotropin secretion and endogenous production of testosterone may resume and interfere with the effectiveness of estrogen treatment, in transgender female adolescents (126, 127). Therefore, continuation of GnRH analog treatment is advised until gonadectomy. Given that GD/gender-incongruent adolescents may opt not to have gonadectomy, long-term studies are necessary to examine the potential risks of prolonged GnRH analog treatment. Alternatively, in transgender male adolescents, GnRH analog treatment can be discontinued once an adult dose of testosterone has been reached and the individual is well virilized. If uterine bleeding occurs, a progestin can be added. However, the combined use of a GnRH analog (for ovarian suppression) and testosterone may enable phenotypic transition with a lower dose of testosterone in comparison with testosterone alone. If there is a wish or need to discontinue GnRH analog treatment in transgender female adolescents, they may be treated with an antiandrogen that directly suppresses androgen synthesis or action (see section 3.0 "Hormonal Therapy for Transgender Adults").

Values and preferences

The recommendation to initiate pubertal induction only when the individual has sufficient mental capacity (roughly age 16 years) to give informed consent for this partly irreversible treatment places a higher value on the ability of the adolescent to fully understand and oversee the partially irreversible consequences of sex hormone treatment and to give informed consent. It places a lower value on the possible negative effects of delayed puberty. We may not currently have the means to weigh adequately the potential benefits of waiting until around age 16 years to initiate sex hormones vs the potential risks/harm to BMD and the sense of social isolation from having the timing of puberty be so out of sync with peers (128).

Remarks

Before starting sex hormone treatment, effects on fertility and options for fertility preservation should be discussed. Adult height may be a concern in transgender adolescents. In a transgender female adolescent, clinicians may consider higher doses of estrogen or a more rapid tempo of dose escalation during pubertal induction. There are no established treatments yet to augment adult height in a transgender male adolescent with open epiphyses during pubertal induction. It is not uncommon for transgender adolescents to present for clinical services after having completed or nearly completed puberty. In such cases, induction of puberty with sex hormones can be done more rapidly (see Table 8). Additionally, an adult dose of testosterone in transgender male adolescents may suffice to suppress the gonadal axis without the need to use a separate agent. At the appropriate time, the multidisciplinary team should adequately prepare the adolescent for transition to adult care.

3.0 Hormonal Therapy for Transgender Adults

The two major goals of hormonal therapy are (1) to reduce endogenous sex hormone levels, and thus reduce

the secondary sex characteristics of the individual's designated gender, and (2) to replace endogenous sex hormone levels consistent with the individual's gender identity by using the principles of hormone replacement treatment of hypogonadal patients. The timing of these two goals and the age at which to begin treatment with the sex hormones of the chosen gender is codetermined in collaboration with both the person pursuing transition and the health care providers. The treatment team should include a medical provider knowledgeable in transgender hormone therapy, an MHP knowledgeable in GD/gender incongruence and the mental health concerns of transition, and a primary care provider able to provide care appropriate for transgender individuals. The physical changes induced by this sex hormone transition are usually accompanied by an improvement in mental well-being (129, 130).

3.1. We recommend that clinicians confirm the diagnostic criteria of GD/gender incongruence and the criteria for the endocrine phase of gender transition before beginning treatment. (1 |⊕⊕⊕○)

3.2. We recommend that clinicians evaluate and address medical conditions that can be exacerbated by hormone depletion and treatment with sex hormones of the affirmed gender before beginning treatment (Table 10). (1 |⊕⊕⊕○)

3.3. We suggest that clinicians measure hormone levels during treatment to ensure that endogenous sex steroids are suppressed and administered sex steroids are maintained in the normal physiologic range for the affirmed gender. (2 |⊕⊕○○)

Evidence

It is the responsibility of the treating clinician to confirm that the person fulfills criteria for treatment. The treating clinician should become familiar with the terms and criteria presented in Tables 1–5 and take a thorough history from the patient in collaboration with the other members of the treatment team. The treating clinician must ensure that the desire for transition is appropriate; the consequences, risks, and benefits of treatment are well understood; and the desire for transition persists. They also need to discuss fertility preservation options (see recommendation 1.3) (67, 68).

Transgender males

Clinical studies have demonstrated the efficacy of several different androgen preparations to induce masculinization in transgender males (Appendix A) (113, 114, 131–134). Regimens to change secondary sex characteristics follow the general principle of hormone replacement treatment of male hypogonadism (135). Clinicians can use either parenteral or transdermal preparations to achieve testosterone values in the normal male range (this is dependent on the specific assay, but is typically 320 to 1000 ng/dL) (Table 11) (136). Sustained supraphysiologic levels of testosterone increase the risk of adverse reactions (see section 4.0 "Adverse Outcome Prevention and Long-Term Care") and should be avoided.

Similar to androgen therapy in hypogonadal men, testosterone treatment in transgender males results in increased muscle mass and decreased fat mass, increased facial hair and acne, male pattern baldness in those genetically predisposed, and increased sexual desire (137).

Table 10. Medical Risks Associated With Sex Hormone Therapy

Transgender female: estrogen
Very high risk of adverse outcomes:
•Thromboembolic disease
Moderate risk of adverse outcomes:
•Macroprolactinoma
•Breast cancer
•Coronary artery disease
•Cerebrovascular disease
•Cholelithiasis
•Hypertriglyceridemia
Transgender male: testosterone
Very high risk of adverse outcomes:
•Erythrocytosis (hematocrit > 50%)
Moderate risk of adverse outcomes:
•Severe liver dysfunction (transaminases > threefold upper limit of normal)
•Coronary artery disease
•Cerebrovascular disease
•Hypertension
•Breast or uterine cancer

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Table 11. Hormone Regimens in Transgender Persons

Transgender females[a]	
Estrogen	
Oral	
Estradiol	2.0–6.0 mg/d
Transdermal	
Estradiol transdermal patch (New patch placed every 3–5 d)	0.025–0.2 mg/d
Parenteral	
Estradiol valerate or cypionate	5–30 mg IM every 2 wk 2–10 mg IM every week
Anti-androgens	
Spironolactone	100–300 mg/d
Cyproterone acetate[b]	25–50 mg/d
GnRH agonist	3.75 mg SQ (SC) monthly 11.25 mg SQ (SC) 3-monthly
Transgender males	
Testosterone	
Parenteral testosterone	
Testosterone enanthate or cypionate	100–200 mg SQ (IM) every 2 wk or SQ (SC) 50% per week
Testosterone undecanoate[c]	1000 mg every 12 wk
Transdermal testosterone	
Testosterone gel 1.6%[d]	50–100 mg/d
Testosterone transdermal patch	2.5–7.5 mg/d

Abbreviations: IM, intramuscularly; SQ, sequentially; SC, subcutaneously.

[a]Estrogens used with or without antiandrogens or GnRH agonist.

[b]Not available in the United States.

[c]One thousand milligrams initially followed by an injection at 6 wk then at 12-wk intervals.

[d]Avoid cutaneous transfer to other individuals.

In transgender males, testosterone will result in clitoromegaly, temporary or permanent decreased fertility, deepening of the voice, cessation of menses (usually), and a significant increase in body hair, particularly on the face, chest, and abdomen. Cessation of menses may occur within a few months with testosterone treatment alone, although high doses of testosterone may be required. If uterine bleeding continues, clinicians may consider the addition of a progestational agent or endometrial ablation (138). Clinicians may also administer GnRH analogs or depot medroxyprogesterone to stop menses prior to testosterone treatment.

Transgender females

The hormone regimen for transgender females is more complex than the transgender male regimen (Appendix B). Treatment with physiologic doses of estrogen alone is insufficient to suppress testosterone levels into the normal range for females (139). Most published clinical studies report the need for adjunctive therapy to achieve testosterone levels in the female range (21, 113, 114, 132–134, 139, 140).

Multiple adjunctive medications are available, such as progestins with antiandrogen activity and GnRH agonists (141). Spironolactone works by directly blocking androgens during their interaction with the androgen receptor (114, 133, 142). It may also have estrogenic activity (143). Cyproterone acetate, a progestational compound with antiandrogenic properties (113, 132, 144), is widely used in Europe. 5α-Reductase inhibitors do not reduce testosterone levels and have adverse effects (145).

Dittrich *et al.* (141) reported that monthly doses of the GnRH agonist goserelin acetate in combination with estrogen were effective in reducing testosterone levels with a low incidence of adverse reactions in 60 transgender females. Leuprolide and transdermal estrogen were as effective as cyproterone and transdermal estrogen in a comparative retrospective study (146).

Patients can take estrogen as oral conjugated estrogens, oral 17β-estradiol, or transdermal 17β-estradiol. Among estrogen options, the increased risk of thromboembolic events associated with estrogens in general seems most concerning with ethinyl estradiol specifically (134, 140, 141), which is why we specifically suggest that it not be used in any transgender treatment plan. Data distinguishing among other estrogen options are less well established although there is some thought that oral routes of administration are more thrombogenic due to the "first pass effect" than are transdermal and parenteral routes, and that the risk of thromboembolic events is dose-dependent. Injectable estrogen and sublingual

estrogen may benefit from avoiding the first pass effect, but they can result in more rapid peaks with greater overall periodicity and thus are more difficult to monitor (147, 148). However, there are no data demonstrating that increased periodicity is harmful otherwise.

Clinicians can use serum estradiol levels to monitor oral, transdermal, and intramuscular estradiol. Blood tests cannot monitor conjugated estrogens or synthetic estrogen use. Clinicians should measure serum estradiol and serum testosterone and maintain them at the level for premenopausal females (100 to 200 pg/mL and <50 ng/dL, respectively). The transdermal preparations and injectable estradiol cypionate or valerate preparations may confer an advantage in older transgender females who may be at higher risk for thromboembolic disease (149).

Values

Our recommendation to maintain levels of gender-affirming hormones in the normal adult range places a high value on the avoidance of the long-term complications of pharmacologic doses. Those patients receiving endocrine treatment who have relative contraindications to hormones should have an in-depth discussion with their physician to balance the risks and benefits of therapy.

Remarks

Clinicians should inform all endocrine-treated individuals of all risks and benefits of gender-affirming hormones prior to initiating therapy. Clinicians should strongly encourage tobacco use cessation in transgender females to avoid increased risk of VTE and cardiovascular complications. We strongly discourage the unsupervised use of hormone therapy (150).

Not all individuals with GD/gender incongruence seek treatment as described (*e.g.*, male-to-eunuchs and individuals seeking partial transition). Tailoring current protocols to the individual may be done within the context of accepted safety guidelines using a multidisciplinary approach including mental health. No evidence-based protocols are available for these groups (151). We need prospective studies to better understand treatment options for these persons.

3.4. We suggest that endocrinologists provide education to transgender individuals undergoing treatment about the onset and time course of physical changes induced by sex hormone treatment. (2 ⊕◯◯◯)

Evidence

Transgender males

Physical changes that are expected to occur during the first 1 to 6 months of testosterone therapy include cessation of menses, increased sexual desire, increased facial and body hair, increased oiliness of skin, increased muscle, and redistribution of fat mass. Changes that occur within the first year of testosterone therapy include deepening of the voice (152, 153), clitoromegaly, and male pattern hair loss (in some cases) (114, 144, 154, 155) (Table 12).

Transgender females

Physical changes that may occur in transgender females in the first 3 to 12 months of estrogen and antiandrogen therapy include decreased sexual desire, decreased spontaneous erections, decreased facial and body hair (usually mild), decreased oiliness of skin, increased breast tissue growth, and redistribution of fat mass (114, 139, 149, 154, 155, 161) (Table 13). Breast development is generally maximal at 2 years after initiating hormones (114, 139, 149, 155). Over a long period of time, the prostate gland and testicles will undergo atrophy.

Although the time course of breast development in transgender females has been studied (150), precise information about other changes induced by sex hormones is lacking (141). There is a great deal of variability among individuals, as evidenced during pubertal development. We all know that a major concern for transgender females is breast development. If we work with estrogens, the result will be often not what the transgender female expects.

Alternatively, there are transgender females who report an anecdotal improved breast development, mood, or sexual desire with the use of progestogens. However, there have been no well-designed studies of the role of progestogens in feminizing hormone regimens, so the question is still open.

Our knowledge concerning the natural history and effects of different cross-sex hormone therapies on breast

Table 12. Masculinizing Effects in Transgender Males

Effect	Onset	Maximum
Skin oiliness/acne	1–6 mo	1–2 y
Facial/body hair growth	6–12 mo	4–5 y
Scalp hair loss	6–12 mo	—[a]
Increased muscle mass/strength	6–12 mo	2–5 y
Fat redistribution	1–6 mo	2–5 y
Cessation of menses	1–6 mo	—[b]
Clitoral enlargement	1–6 mo	1–2 y
Vaginal atrophy	1–6 mo	1–2 y
Deepening of voice	6–12 mo	1–2 y

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157), Wierckx *et al.* (158).

[a]Prevention and treatment as recommended for biological men.

[b]Menorrhagia requires diagnosis and treatment by a gynecologist.

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Table 13. Feminizing Effects in Transgender Females

Effect	Onset	Maximum
Redistribution of body fat	3–6 mo	2–3 y
Decrease in muscle mass and strength	3–6 mo	1–2 y
Softening of skin/decreased oiliness	3–6 mo	Unknown
Decreased sexual desire	1–3 mo	3–6 mo
Decreased spontaneous erections	1–3 mo	3–6 mo
Male sexual dysfunction	Variable	Variable
Breast growth	3–6 mo	2–3 y
Decreased testicular volume	3–6 mo	2–3 y
Decreased sperm production	Unknown	>3 y
Decreased terminal hair growth	6–12 mo	>3 y[a]
Scalp hair	Variable	—[b]
Voice changes	None	—[c]

Estimates represent clinical observations: Toorians *et al.* (149), Asscheman *et al.* (156), Gooren *et al.* (157).

[a]Complete removal of male sexual hair requires electrolysis or laser treatment or both.

[b]Familial scalp hair loss may occur if estrogens are stopped.

[c]Treatment by speech pathologists for voice training is most effective.

development in transgender females is extremely sparse and based on the low quality of evidence. Current evidence does not indicate that progestogens enhance breast development in transgender females, nor does evidence prove the absence of such an effect. This prevents us from drawing any firm conclusion at this moment and demonstrates the need for further research to clarify these important clinical questions (162).

Values and preferences

Transgender persons have very high expectations regarding the physical changes of hormone treatment and are aware that body changes can be enhanced by surgical procedures (*e.g.*, breast, face, and body habitus). Clear expectations for the extent and timing of sex hormone–induced changes may prevent the potential harm and expense of unnecessary procedures.

4.0 Adverse Outcome Prevention and Long-Term Care

Hormone therapy for transgender males and females confers many of the same risks associated with sex hormone replacement therapy in nontransgender persons. The risks arise from and are worsened by inadvertent or intentional use of supraphysiologic doses of sex hormones, as well as use of inadequate doses of sex hormones to maintain normal physiology (131, 139).

4.1. We suggest regular clinical evaluation for physical changes and potential adverse changes in response to sex steroid hormones and laboratory monitoring of sex steroid hormone levels every 3 months during the first year of hormone therapy for transgender males and females and then once or twice yearly. (2 ⊕⊕OO)

Evidence

Pretreatment screening and appropriate regular medical monitoring are recommended for both transgender males and females during the endocrine transition and periodically thereafter (26, 155). Clinicians should monitor weight and blood pressure, conduct physical exams, and assess routine health questions, such as tobacco use, symptoms of depression, and risk of adverse events such as deep vein thrombosis/pulmonary embolism and other adverse effects of sex steroids.

Transgender males

Table 14 contains a standard monitoring plan for transgender males on testosterone therapy (154, 159). Key issues include maintaining testosterone levels in the physiologic normal male range and avoiding adverse events resulting from excess testosterone therapy, particularly erythrocytosis, sleep apnea, hypertension, excessive weight gain, salt retention, lipid changes, and excessive or cystic acne (135).

Because oral 17-alkylated testosterone is not recommended, serious hepatic toxicity is not anticipated with parenteral or transdermal testosterone use (163, 164). Past concerns regarding liver toxicity with testosterone have been alleviated with subsequent reports that indicate the risk of serious liver disease is minimal (144, 165, 166).

Transgender females

Table 15 contains a standard monitoring plan for transgender females on estrogens, gonadotropin suppression, or antiandrogens (160). Key issues include avoiding supraphysiologic doses or blood levels of estrogen that may lead to increased risk for thromboembolic disease, liver dysfunction, and hypertension. Clinicians should monitor serum estradiol levels using laboratories participating in external quality control, as measurements of estradiol in blood can be very challenging (167).

VTE may be a serious complication. A study reported a 20-fold increase in venous thromboembolic disease in a large cohort of Dutch transgender subjects (161). This increase may have been associated with the use of the synthetic estrogen, ethinyl estradiol (149). The incidence decreased when clinicians stopped administering ethinyl estradiol (161). Thus, the use of synthetic estrogens and conjugated estrogens is undesirable because of the inability to regulate doses by measuring serum levels and the risk of thromboembolic disease. In a German gender clinic, deep vein thrombosis occurred in 1 of 60 of transgender females treated with a GnRH analog and oral

Table 14. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Male

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of virilization and for development of adverse reactions.
2. Measure serum testosterone every 3 mo until levels are in the normal physiologic male range:[a]
   a. For testosterone enanthate/cypionate injections, the testosterone level should be measured midway between injections. The target level is 400–700 ng/dL to 400 ng/dL. Alternatively, measure peak and trough levels to ensure levels remain in the normal male range.
   b. For parenteral testosterone undecanoate, testosterone should be measured just before the following injection. If the level is <400 ng/dL, adjust dosing interval.
   c. For transdermal testosterone, the testosterone level can be measured no sooner than after 1 wk of daily application (at least 2 h after application).
3. Measure hematocrit or hemoglobin at baseline and every 3 mo for the first year and then one to two times a year. Monitor weight, blood pressure, and lipids at regular intervals.
4. Screening for osteoporosis should be conducted in those who stop testosterone treatment, are not compliant with hormone therapy, or who develop risks for bone loss.
5. If cervical tissue is present, monitoring as recommended by the American College of Obstetricians and Gynecologists.
6. Ovariectomy can be considered after completion of hormone transition.
7. Conduct sub- and periareolar annual breast examinations if mastectomy performed. If mastectomy is not performed, then consider mammograms as recommended by the American Cancer Society.

[a]Adapted from Lapauw *et al.* (154) and Ott *et al.* (159).

estradiol (141). The patient who developed a deep vein thrombosis was found to have a homozygous C677 T mutation in the methylenetetrahydrofolate reductase gene. In an Austrian gender clinic, administering gender-affirming hormones to 162 transgender females and 89 transgender males was not associated with VTE, despite an 8.0% and 5.6% incidence of thrombophilia (159). A more recent multinational study reported only 10 cases of VTE from a cohort of 1073 subjects (168). Thrombophilia screening of transgender persons initiating hormone treatment should be restricted to those with a personal or family history of VTE (159). Monitoring D-dimer levels during treatment is not recommended (169).

4.2. We suggest periodically monitoring prolactin levels in transgender females treated with estrogens. (2 ⊕⊕◯◯)

Evidence

Estrogen therapy can increase the growth of pituitary lactrotroph cells. There have been several reports of prolactinomas occurring after long-term, high-dose estrogen therapy (170–173). Up to 20% of transgender females treated with estrogens may have elevations in prolactin levels associated with enlargement of the pituitary gland (156). In most cases, the serum prolactin levels will return to the normal range with a reduction or discontinuation of the estrogen therapy or discontinuation of cyproterone acetate (157, 174, 175).

The onset and time course of hyperprolactinemia during estrogen treatment are not known. Clinicians should measure prolactin levels at baseline and then at least annually during the transition period and every 2 years thereafter. Given that only a few case studies reported prolactinomas, and prolactinomas were not reported in large cohorts of estrogen-treated persons, the risk is likely to be very low. Because the major presenting findings of microprolactinomas (hypogonadism and sometimes gynecomastia) are not apparent in transgender females, clinicians may perform radiologic examinations of the pituitary in those patients whose prolactin levels persistently increase despite stable or reduced estrogen levels. Some transgender individuals receive psychotropic medications that can increase prolactin levels (174).

Table 15. Monitoring of Transgender Persons on Gender-Affirming Hormone Therapy: Transgender Female

1. Evaluate patient every 3 mo in the first year and then one to two times per year to monitor for appropriate signs of feminization and for development of adverse reactions.
2. Measure serum testosterone and estradiol every 3 mo.
   a. Serum testosterone levels should be <50 ng/dL.
   b. Serum estradiol should not exceed the peak physiologic range: 100–200 pg/mL.
3. For individuals on spironolactone, serum electrolytes, particularly potassium, should be monitored every 3 mo in the first year and annually thereafter.
4. Routine cancer screening is recommended, as in nontransgender individuals (all tissues present).
5. Consider BMD testing at baseline (160). In individuals at low risk, screening for osteoporosis should be conducted at age 60 years or in those who are not compliant with hormone therapy.

This table presents strong recommendations and does not include lower level recommendations.

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4.3. We suggest that clinicians evaluate transgender persons treated with hormones for cardiovascular risk factors using fasting lipid profiles, diabetes screening, and/or other diagnostic tools. (2 ⊕⊕○○)

Evidence

Transgender males

Administering testosterone to transgender males results in a more atherogenic lipid profile with lowered high-density lipoprotein cholesterol and higher triglyceride and low-density lipoprotein cholesterol values (176–179). Studies of the effect of testosterone on insulin sensitivity have mixed results (178, 180). A randomized, open-label uncontrolled safety study of transgender males treated with testosterone undecanoate demonstrated no insulin resistance after 1 year (181, 182). Numerous studies have demonstrated the effects of sex hormone treatment on the cardiovascular system (160, 179, 183, 184). Long-term studies from The Netherlands found no increased risk for cardiovascular mortality (161). Likewise, a meta-analysis of 19 randomized trials in nontransgender males on testosterone replacement showed no increased incidence of cardiovascular events (185). A systematic review of the literature found that data were insufficient (due to very low–quality evidence) to allow a meaningful assessment of patient-important outcomes, such as death, stroke, myocardial infarction, or VTE in transgender males (176). Future research is needed to ascertain the potential harm of hormonal therapies (176). Clinicians should manage cardiovascular risk factors as they emerge according to established guidelines (186).

Transgender females

A prospective study of transgender females found favorable changes in lipid parameters with increased high-density lipoprotein and decreased low-density lipoprotein concentrations (178). However, increased weight, blood pressure, and markers of insulin resistance attenuated these favorable lipid changes. In a meta-analysis, only serum triglycerides were higher at ≥24 months without changes in other parameters (187). The largest cohort of transgender females (mean age 41 years, followed for a mean of 10 years) showed no increase in cardiovascular mortality despite a 32% rate of tobacco use (161).

Thus, there is limited evidence to determine whether estrogen is protective or detrimental on lipid and glucose metabolism in transgender females (176). With aging, there is usually an increase of body weight. Therefore, as with nontransgender individuals, clinicians should monitor and manage glucose and lipid metabolism and blood pressure regularly according to established guidelines (186).

4.4. We recommend that clinicians obtain BMD measurements when risk factors for osteoporosis exist, specifically in those who stop sex hormone therapy after gonadectomy. (1 ⊕⊕○○)

Evidence

Transgender males

Baseline bone mineral measurements in transgender males are generally in the expected range for their pretreatment gender (188). However, adequate dosing of testosterone is important to maintain bone mass in transgender males (189, 190). In one study (190), serum LH levels were inversely related to BMD, suggesting that low levels of sex hormones were associated with bone loss. Thus, LH levels in the normal range may serve as an indicator of the adequacy of sex steroid administration to preserve bone mass. The protective effect of testosterone may be mediated by peripheral conversion to estradiol, both systemically and locally in the bone.

Transgender females

A baseline study of BMD reported T scores less than −2.5 in 16% of transgender females (191). In aging males, studies suggest that serum estradiol more positively correlates with BMD than does testosterone (192, 193) and is more important for peak bone mass (194). Estrogen preserves BMD in transgender females who continue on estrogen and antiandrogen therapies (188, 190, 191, 195, 196).

Fracture data in transgender males and females are not available. Transgender persons who have undergone gonadectomy may choose not to continue consistent sex steroid treatment after hormonal and surgical sex reassignment, thereby becoming at risk for bone loss. There have been no studies to determine whether clinicians should use the sex assigned at birth or affirmed gender for assessing osteoporosis (*e.g.*, when using the FRAX tool). Although some researchers use the sex assigned at birth (with the assumption that bone mass has usually peaked for transgender people who initiate hormones in early adulthood), this should be assessed on a case-by-case basis until there are more data available. This assumption will be further complicated by the increasing prevalence of transgender people who undergo hormonal transition at a pubertal age or soon after puberty. Sex for comparison within risk assessment tools may be based on the age at which hormones were initiated and the length of exposure to hormones. In some cases, it may be

reasonable to assess risk using both the male and female calculators and using an intermediate value. Because all subjects underwent normal pubertal development, with known effects on bone size, reference values for birth sex were used for all participants (154).

4.5. We suggest that transgender females with no known increased risk of breast cancer follow breast-screening guidelines recommended for those designated female at birth. (2 ⊕⊕◯◯)

4.6. We suggest that transgender females treated with estrogens follow individualized screening according to personal risk for prostatic disease and prostate cancer. (2 ⊕◯◯◯)

Evidence

Studies have reported a few cases of breast cancer in transgender females (197–200). A Dutch study of 1800 transgender females followed for a mean of 15 years (range of 1 30 years) found one case of breast cancer. The Women's Health Initiative study reported that females taking conjugated equine estrogen without progesterone for 7 years did not have an increased risk of breast cancer as compared with females taking placebo (137).

In transgender males, a large retrospective study conducted at the U.S. Veterans Affairs medical health system identified seven breast cancers (194). The authors reported that this was not above the expected rate of breast cancers in cisgender females in this cohort. Furthermore, they did report one breast cancer that developed in a transgender male patient after mastectomy, supporting the fact that breast cancer can occur even after mastectomy. Indeed, there have been case reports of breast cancer developing in subareolar tissue in transgender males, which occurred after mastectomy (201, 202).

Women with primary hypogonadism (Turner syndrome) treated with estrogen replacement exhibited a significantly decreased incidence of breast cancer as compared with national standardized incidence ratios (203, 204). These studies suggest that estrogen therapy does not increase the risk of breast cancer in the short term (<20 to 30 years). We need long-term studies to determine the actual risk, as well as the role of screening mammograms. Regular examinations and gynecologic advice should determine monitoring for breast cancer.

Prostate cancer is very rare before the age of 40, especially with androgen deprivation therapy (205). Childhood or pubertal castration results in regression of the prostate and adult castration reverses benign prostate hypertrophy (206). Although van Kesteren *et al.* (207) reported that estrogen therapy does not induce hypertrophy or premalignant changes in the prostates of transgender females, studies have reported cases of benign prostatic hyperplasia in transgender females treated with estrogens for 20 to 25 years (208, 209). Studies have also reported a few cases of prostate carcinoma in transgender females (210–214).

Transgender females may feel uncomfortable scheduling regular prostate examinations. Gynecologists are not trained to screen for prostate cancer or to monitor prostate growth. Thus, it may be reasonable for transgender females who transitioned after age 20 years to have annual screening digital rectal examinations after age 50 years and prostate-specific antigen tests consistent with U.S. Preventive Services Task Force Guidelines (215).

4.7. We advise that clinicians determine the medical necessity of including a total hysterectomy and oophorectomy as part of gender-affirming surgery. (Ungraded Good Practice Statement)

Evidence

Although aromatization of testosterone to estradiol in transgender males has been suggested as a risk factor for endometrial cancer (216), no cases have been reported. When transgender males undergo hysterectomy, the uterus is small and there is endometrial atrophy (217, 218). Studies have reported cases of ovarian cancer (219, 220). Although there is limited evidence for increased risk of reproductive tract cancers in transgender males, health care providers should determine the medical necessity of a laparoscopic total hysterectomy as part of a gender-affirming surgery to prevent reproductive tract cancer (221).

Values

Given the discomfort that transgender males experience accessing gynecologic care, our recommendation for the medical necessity of total hysterectomy and oophorectomy places a high value on eliminating the risks of female reproductive tract disease and cancer and a lower value on avoiding the risks of these surgical procedures (related to the surgery and to the potential undesirable health consequences of oophorectomy) and their associated costs.

Remarks

The sexual orientation and type of sexual practices will determine the need and types of gynecologic care required following transition. Additionally, in certain countries, the approval required to change the sex in a birth certificate for transgender males may be dependent on having a complete hysterectomy. Clinicians should help patients research nonmedical administrative criteria and

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provide counseling. If individuals decide not to undergo hysterectomy, screening for cervical cancer is the same as all other females.

5.0 Surgery for Sex Reassignment and Gender Confirmation

For many transgender adults, genital gender-affirming surgery may be the necessary step toward achieving their ultimate goal of living successfully in their desired gender role. The type of surgery falls into two main categories: (1) those that directly affect fertility and (2) those that do not. Those that change fertility (previously called sex reassignment surgery) include genital surgery to remove the penis and gonads in the male and removal of the uterus and gonads in the female. The surgeries that effect fertility are often governed by the legal system of the state or country in which they are performed. Other gender-conforming surgeries that do not directly affect fertility are not so tightly governed.

Gender-affirming surgical techniques have improved markedly during the past 10 years. Reconstructive genital surgery that preserves neurologic sensation is now the standard. The satisfaction rate with surgical reassignment of sex is now very high (187). Additionally, the mental health of the individual seems to be improved by participating in a treatment program that defines a pathway of gender-affirming treatment that includes hormones and surgery (130, 144) (Table 16).

Surgery that affects fertility is irreversible. The World Professional Association for Transgender Health Standards of Care (222) emphasizes that the "threshold of 18 should not be seen as an indication in itself for active intervention." If the social transition has not been satisfactory, if the person is not satisfied with or is ambivalent about the effects of sex hormone treatment, or if the person is ambivalent about surgery then the individual should not be referred for surgery (223, 224).

Gender-affirming genital surgeries for transgender females that affect fertility include gonadectomy, penectomy, and creation of a neovagina (225, 226). Surgeons often invert the skin of the penis to form the wall of the vagina, and several literatures reviews have reported on outcomes (227). Sometimes there is inadequate tissue to form a full neovagina, so clinicians have revisited using intestine and found it to be successful (87, 228, 229). Some newer vaginoplasty techniques may involve autologuous oral epithelial cells (230, 231).

The scrotum becomes the labia majora. Surgeons use reconstructive surgery to fashion the clitoris and its hood, preserving the neurovascular bundle at the tip of the penis as the neurosensory supply to the clitoris. Some surgeons are also creating a sensate pedicled-spot adding a G spot to the neovagina to increase sensation (232). Most recently, plastic surgeons have developed techniques to fashion labia minora. To further complete the feminization, uterine transplants have been proposed and even attempted (233).

Neovaginal prolapse, rectovaginal fistula, delayed healing, vaginal stenosis, and other complications do sometimes occur (234, 235). Clinicians should strongly remind the transgender person to use their dilators to maintain the depth and width of the vagina throughout the postoperative period. Genital sexual responsivity and other aspects of sexual function are usually preserved following genital gender-affirming surgery (236, 237).

Ancillary surgeries for more feminine or masculine appearance are not within the scope of this guideline. Voice therapy by a speech language pathologist is available to transform speech patterns to the affirmed gender (148). Spontaneous voice deepening occurs during testosterone treatment of transgender males (152, 238). No studies have compared the effectiveness of speech therapy, laryngeal surgery, or combined treatment.

Breast surgery is a good example of gender-confirming surgery that does not affect fertility. In all females, breast size exhibits a very broad spectrum. For transgender females to make the best informed decision, clinicians should delay breast augmentation surgery until the patient has completed at least 2 years of estrogen therapy, because the breasts continue to grow during that time (141, 155).

Another major procedure is the removal of facial and masculine-appearing body hair using either electrolysis or

Table 16. Criteria for Gender-Affirming Surgery, Which Affects Fertility

1. Persistent, well-documented gender dysphoria
2. Legal age of majority in the given country
3. Having continuously and responsibly used gender-affirming hormones for 12 mo (if there is no medical contraindication to receiving such therapy)
4. Successful continuous full-time living in the new gender role for 12 mo
5. If significant medical or mental health concerns are present, they must be well controlled
6. Demonstrable knowledge of all practical aspects of surgery (*e.g.*, cost, required lengths of hospitalizations, likely complications, postsurgical rehabilitation)

laser treatments. Other feminizing surgeries, such as that to feminize the face, are now becoming more popular (239–241).

In transgender males, clinicians usually delay gender-affirming genital surgeries until after a few years of androgen therapy. Those surgeries that affect fertility in this group include oophorectomy, vaginectomy, and complete hysterectomy. Surgeons can safely perform them vaginally with laparoscopy. These are sometimes done in conjunction with the creation of a neopenis. The cosmetic appearance of a neopenis is now very good, but the surgery is multistage and very expensive (242, 243). Radial forearm flap seems to be the most satisfactory procedure (228, 244). Other flaps also exist (245). Surgeons can make neopenile erections possible by reinervation of the flap and subsequent contraction of the muscle, leading to stiffening of the neopenis (246, 247), but results are inconsistent (248). Surgeons can also stiffen the penis by imbedding some mechanical device (*e.g.*, a rod or some inflatable apparatus) (249, 250). Because of these limitations, the creation of a neopenis has often been less than satisfactory. Recently, penis transplants are being proposed (233).

In fact, most transgender males do not have any external genital surgery because of the lack of access, high cost, and significant potential complications. Some choose a metaoidioplasty that brings forward the clitoris, thereby allowing them to void in a standing position without wetting themselves (251, 252). Surgeons can create the scrotum from the labia majora with good cosmetic effect and can implant testicular prostheses (253).

The most important masculinizing surgery for the transgender male is mastectomy, and it does not affect fertility. Breast size only partially regresses with androgen therapy (155). In adults, discussions about mastectomy usually take place after androgen therapy has started. Because some transgender male adolescents present after significant breast development has occurred, they may also consider mastectomy 2 years after they begin androgen therapy and before age 18 years. Clinicians should individualize treatment based on the physical and mental health status of the individual. There are now newer approaches to mastectomy with better outcomes (254, 255). These often involve chest contouring (256). Mastectomy is often necessary for living comfortably in the new gender (256).

5.1. We recommend that a patient pursue genital gender-affirming surgery only after the MHP and the clinician responsible for endocrine transition therapy both agree that surgery is medically necessary and would benefit the patient's overall health and/or well-being. (1 ⊕⊕◯◯)

5.2. We advise that clinicians approve genital gender-affirming surgery only after completion of at least 1 year of consistent and compliant hormone treatment, unless hormone therapy is not desired or medically contraindicated. (Ungraded Good Practice Statement)

5.3. We advise that the clinician responsible for endocrine treatment and the primary care provider ensure appropriate medical clearance of transgender individuals for genital gender-affirming surgery and collaborate with the surgeon regarding hormone use during and after surgery. (Ungraded Good Practice Statement)

5.4. We recommend that clinicians refer hormone-treated transgender individuals for genital surgery when: (1) the individual has had a satisfactory social role change, (2) the individual is satisfied about the hormonal effects, and (3) the individual desires definitive surgical changes. (1 ⊕◯◯◯)

5.5. We suggest that clinicians delay gender-affirming genital surgery involving gonadectomy and/or hysterectomy until the patient is at least 18 years old or legal age of majority in his or her country. (2 ⊕⊕◯◯).

5.6. We suggest that clinicians determine the timing of breast surgery for transgender males based upon the physical and mental health status of the individual. There is insufficient evidence to recommend a specific age requirement. (2 ⊕◯◯◯)

Evidence

Owing to the lack of controlled studies, incomplete follow-up, and lack of valid assessment measures, evaluating various surgical approaches and techniques is difficult. However, one systematic review including a large numbers of studies reported satisfactory cosmetic and functional results for vaginoplasty/neovagina construction (257). For transgender males, the outcomes are less certain. However, the problems are now better understood (258). Several postoperative studies report significant long-term psychological and psychiatric pathology (259–261). One study showed satisfaction with breasts, genitals, and femininity increased significantly and showed the importance of surgical treatment as a key therapeutic option for transgender females (262). Another analysis demonstrated that, despite the young average age at death following surgery and the relatively larger number of individuals with somatic morbidity, the study does not allow for determination of

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causal relationships between, for example, specific types of hormonal or surgical treatment received and somatic morbidity and mortality (263). Reversal surgery in regretful male-to-female transsexuals after sexual reassignment surgery represents a complex, multistage procedure with satisfactory outcomes. Further insight into the characteristics of persons who regret their decision postoperatively would facilitate better future selection of applicants eligible for sexual reassignment surgery. We need more studies with appropriate controls that examine long-term quality of life, psychosocial outcomes, and psychiatric outcomes to determine the long-term benefits of surgical treatment.

When a transgender individual decides to have gender-affirming surgery, both the hormone prescribing clinician and the MHP must certify that the patient satisfies criteria for gender-affirming surgery (Table 16).

There is some concern that estrogen therapy may cause an increased risk for venous thrombosis during or following surgery (176). For this reason, the surgeon and the hormone-prescribing clinician should collaborate in making a decision about the use of hormones before and following surgery. One study suggests that preoperative factors (such as compliance) are less important for patient satisfaction than are the physical postoperative results (56). However, other studies and clinical experience dictate that individuals who do not follow medical instructions and do not work with their physicians toward a common goal do not achieve treatment goals (264) and experience higher rates of postoperative infections and other complications (265, 266). It is also important that the person requesting surgery feels comfortable with the anatomical changes that have occurred during hormone therapy. Dissatisfaction with social and physical outcomes during the hormone transition may be a contraindication to surgery (223).

An endocrinologist or experienced medical provider should monitor transgender individuals after surgery. Those who undergo gonadectomy will require hormone replacement therapy, surveillance, or both to prevent adverse effects of chronic hormone deficiency.

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City of Birmingham's LGBTQ+ Advisory Board Issues Statement on HB1/SB10

The following is a statement from the LGBTQ+ Advisory Board, which advises the Mayor's Office and the city's LGBTQ+ liaison on issues affecting the LGBTQ+ community in the city of Birmingham. Mayor Woodfin established the board in 2018.

Statement

Birmingham is a welcoming community for all and that includes transgender and gender-diverse youth. We pride ourselves on being a place for world-class medical care and human rights activism. In just one year, we will welcome people from all over the world as we host the World Games 2022. It would be a shame to dim the light that is shining so brightly on our city by restricting essential healthcare to an oppressed segment of our community. The "Vulnerable Child Compassion and *Protection Act*." – known as House bill-1 and companion Senate bill-10 – has passed through committees, the full Senate, and is heading to the Alabama House.

The legislation would criminalize physicians and pharmacists who provide lifesaving healthcare for transgender and gender-diverse youth, care that is the expert standard of care. The bill further demands that school personnel out students who are trans or gender-diverse to their parents or guardians, compromising the health and wellbeing of the students they are meant to support. Inserting the state into these medical decisions is not only intrusive but also dangerous for the very children this bill claims to defend. In fact, the American Psychological Association (APA) just recently reaffirmed that gender diversity is real and a natural part of the human experience.

As a community of youth-serving professionals, educators, and community members whose lived experience reflect those affected by this legislation, we condemn these bills with a unified voice. Politics have no place in the private, trusting, space where doctors work with their patients. The medicine in question follows a standardized evidence-based gender affirmative model of pediatric care endorsed by the American Academy of Pediatrics and it's 67,000 members nationwide, including the Alabama Chapter of the American Academy of Pediatrics. This bill invades the sacred communication between physicians, parents and patients, as well as school personnel and students, which protects and enriches the well-being of all youth. We urge all those across the political spectrum to use their voice to oppose this incredibly harmful legislation.

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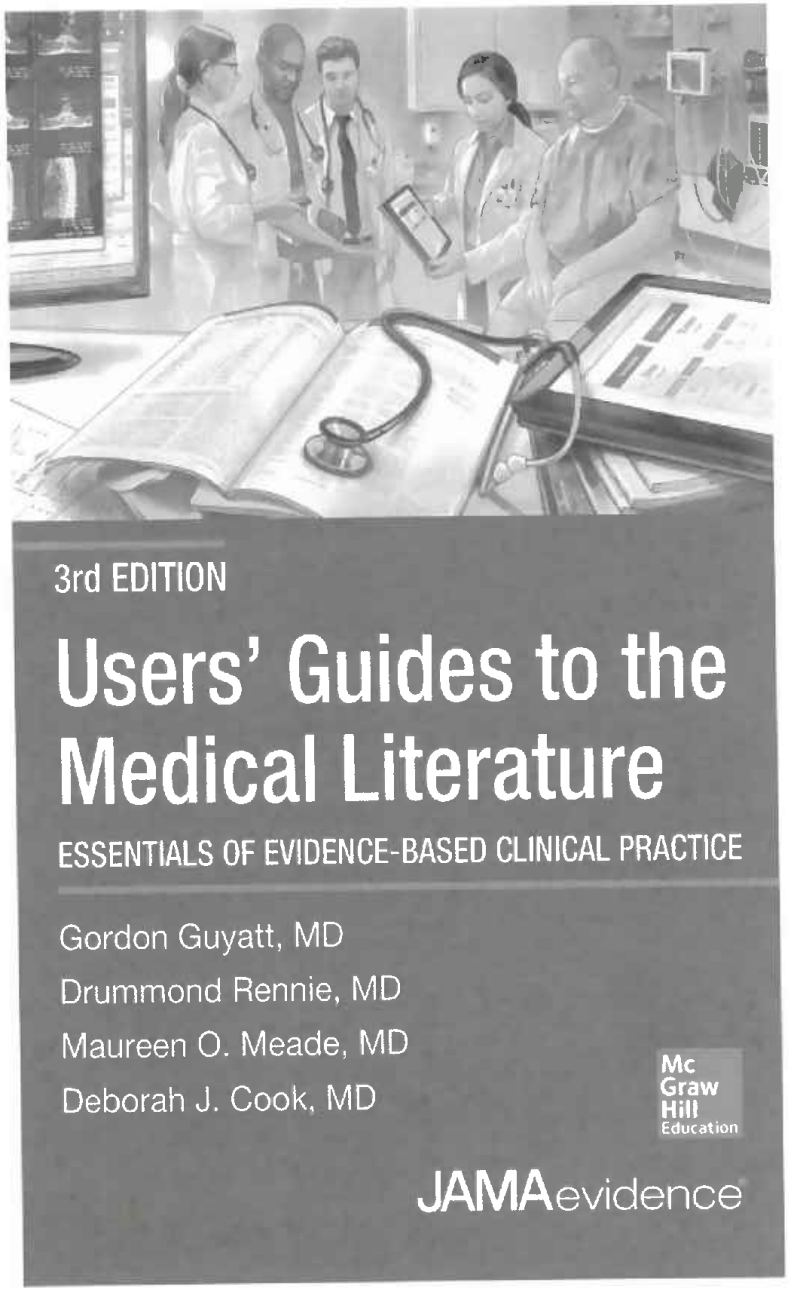

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To our students, in many countries, whose interest, passion, and probing questions made possible the development of the methods we use to communicate the concepts of evidence-based medicine.

GG, MOM, and DJC

To Deb, who has watched over and tended me while I have watched over and tended this wonderful group, with gratitude for her love and her good humor.

DR

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FOREWORD

When I was attending school in wartime Britain, staples of the curriculum, along with cold baths, mathematics, boiled cabbage, and long cross-country runs, were Latin and French. It was obvious that Latin was a theoretical exercise—the Romans were dead, after all. However, although France was clearly visible just across the Channel, for years it was either occupied or inaccessible, so learning the French language seemed just as impractical and theoretical an exercise. It was unthinkable to me and my teachers that I would ever put it to practical use—that French was a language to be spoken.

This is the relationship too many practitioners have with the medical literature—clearly visible but utterly inaccessible. We recognize that practice should be based on discoveries announced in the medical journals. But we also recognize that every few years the literature doubles in size, and every year we seem to have less time to weigh it,[1] so every day the task of taming the literature becomes more hopeless. The translation of those hundreds of thousands of articles into everyday practice appears to be an obscure task left to others, and as the literature becomes more inaccessible, so does the idea that the literature has any utility for a particular patient become more fanciful.

This book, now in its third edition, is intended to change all that. It is designed to make the clinician fluent in the language of the medical literature in all its forms. To free the clinician from practicing medicine by rote, by guesswork, and by their variably integrated experience. To put a stop to clinicians being ambushed by drug company representatives, or by their patients, telling them of new therapies the clinicians are unable to evaluate. To end their dependence on out-of-date authority. To enable the practitioner to work from the patient and use the literature as a tool to solve the patient's problems. To provide the clinician access to what is relevant and the ability to assess its validity and whether it applies to a specific patient. In other

words, to put the clinician in charge of the single most powerful resource in medicine.

The Users' Guides Series in *JAMA*

I have left it to Gordon Guyatt, MD, MSc, the moving force, principal editor, and most prolific coauthor of the Users' Guides to the Medical Literature series in *JAMA*, to describe the history of this series and of this book in the accompanying preface. But where did *JAMA* come into this story?

In the late 1980s, at the invitation of my friend David Sackett, MD, I visited his department at McMaster University to discuss a venture with *JAMA*—a series that examined the evidence behind the clinical history and examination. After these discussions, a series of articles and systematic reviews was developed and, with the enthusiastic support of then *JAMA* Editor in Chief George Lundberg, MD, *JAMA* began publishing The Rational Clinical Examination series in 1992.[2] By that time, I had formed an excellent working relationship with the brilliant group at McMaster. Like their leader, Sackett, they tended to be iconoclastic, expert at working together and forming alliances with new and talented workers, and intellectually exacting. Like their leader, they delivered on their promises.

So, when I heard that they were thinking of updating the wonderful little series of Readers' Guides published in 1981 in the *Canadian Medical Association Journal* (*CMAJ*), I took advantage of this working relationship to urge them to update and expand the series for *JAMA*. Together with Sackett, and first with Andy Oxman, MD, and then with Gordon Guyatt taking the lead (when Oxman left to take a position in Oslo), the Users' Guides to the Medical Literature series was born. We began publishing articles in the series in *JAMA* in 1993.[3]

At the start, we thought we might have 8 or 10 articles, but the response from readers was so enthusiastic and the variety of types of article in the literature so great that ever since I have found myself receiving, sending for review, and editing new

articles for the series. Just before the first edition of this book was published in 2002, Gordon Guyatt and I closed this series at 25, appearing as 33 separate journal articles.

The passage of years during the preparation of the original *JAMA* series and the publication of the first edition of this book had a particularly useful result. Some subjects that were scarcely discussed in the major medical journals in the early 1990s but that had burgeoned years later could receive the attention that had become their due. For instance, in 2000, *JAMA* published 2 Users' Guides[4,5] on how readers should approach reports of qualitative research in health care. To take another example, systematic reviews and meta-analyses, given a huge boost by the activities of the Cochrane Collaboration, had become prominent features of the literature, and as Gordon Guyatt points out in his preface, the change in emphasis in the Users' Guides to preappraised resources continues.

The Book

From the start, readers kept urging us to put the series together as a book. That had been our intention right from the start, but each new article delayed its implementation. How fortunate! When the original Readers' Guides appeared in the *CMAJ* in 1981, Gordon Guyatt's phrase "evidence-based medicine" had never been coined, and only a tiny proportion of health care workers possessed computers. The Internet did not exist and electronic publication was only a dream. In 1992, the Web—for practical purposes—had scarcely been invented, the dot-com bubble had not appeared, let alone burst, and the health care professions were only beginning to become computer literate. But at the end of the 1990s, when Guyatt and I approached my colleagues at *JAMA* with the idea of publishing not merely the standard printed book but also Web-based and CD-ROM formats of the book, they were immediately receptive. Putting the latter part into practice has been the notable achievement of Rob Hayward, MD, of the Centre for Health Evidence of the University of Alberta.

The science and art of evidence-based medicine, which this book does so much to reinforce, has developed remarkably during the past 25 years, and this is reflected in every page of this book. Encouraged by the immediate success of the first and second editions of the *Users' Guides to the Medical Literature*, Gordon Guyatt and the Evidence-Based Medicine Working Group have once again brought each chapter up to date for this third edition. They have also added 6 completely new chapters: Evidence-Based Medicine and the Theory of Knowledge, How to Use a Noninferiority Trial, How to Use an Article About Quality Improvement, How to Use an Article About Genetic Association, Understanding and Applying the Results of a Systematic Review and Meta-analysis, and Network Meta-analysis. Some of these chapters appear in the larger Manual version of this book.

An updated Web version of the *Users' Guides to the Medical Literature* will accompany the new edition. As part of the online educational resource, JAMAevidence, the *Users' Guides to the Medical Literature* online is intertwined with the online edition of *The Rational Clinical Examination: Evidence-Based Clinical Diagnosis*. Together they serve as the cornerstones of a comprehensive online educational resource for teaching and learning evidence-based medicine. Interactive calculators and worksheets provide practical complements to the content, and downloadable PowerPoint presentations serve as invaluable resources for instructors. Finally, podcast presentations bring the foremost minds behind evidence-based medicine to medical students, residents, and faculty around the world.

Once again, I thank Gordon Guyatt for being an inspired author, a master organizer, and a wonderful teacher, colleague, and friend. I know personally and greatly admire a good number of his colleagues in the Evidence-Based Medicine Working Group, but it would be invidious to name them, given the huge collective effort this has entailed. This is an enterprise that came about only because of the strenuous efforts of many individuals. On the *JAMA* side, I must thank Annette Flanagin, RN, MA, a wonderfully efficient, creative, and diplomatic colleague

at *JAMA*. All of this was coordinated and kept up to schedule by the energy and meticulous efficiency of Kate Pezalla, MA. My colleague, Edward Livingston, MD, a surgeon and a perceptive critic, is taking over the *Users' Guides to the Medical Literature* series at *JAMA*, and I am confident it will prosper in his hands. In addition, I acknowledge the efforts of our partners at McGraw-Hill Education—James Shanahan, Scott Grillo, Michael Crumsho, and Robert Pancotti.

Finally, I thank my friends Cathy DeAngelis, MD, MPH, and her successor, Howard Bauchner, MD, MPH, former and current Editors in Chief of The JAMA Network, for their strong backing of me, my colleagues, and this project. Howard inherited this project. Once I found out that his immediate and enthusiastic acceptance of it was based on his regular use of early articles in the Users' Guides series, any concern about its reception vanished. Indeed, Howard was the instigator of Evidence-Based Medicine—An Oral History,[2,3] a video series of personal views on the birth and early growth of evidence-based medicine that has helped put the Users' Guides into perspective. Howard's infectious good spirits and sharp intelligence bode well for further editions of this book.

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PREFACE

Evidence-based medicine (EBM)—as a concept with that particular moniker—is now almost 25 years old. Looking back, periods of infancy, childhood, adolescence,[1] and now a mature adulthood are evident.[2] This third edition of the *Users' Guides to the Medical Literature* firmly establishes the maturity of the EBM movement.

The first articulation of the world view that was to become EBM appeared in 1981 when a group of clinical epidemiologists at McMaster University, led by David Sackett, MD, published the first of a series of articles that advised clinicians on how to read clinical journals.[3] Although a huge step forward, the series had its limitations. After teaching what they then called *critical appraisal* for a number of years, the group became increasingly aware of both the necessity and the challenges of going beyond reading the literature in a browsing mode and instead using research studies to solve patient management problems on a day-to-day basis.

In 1990, I assumed the position of residency director of the Internal Medicine Program at McMaster. Through Dave Sackett's leadership, critical appraisal had evolved into a philosophy of medical practice based on knowledge and understanding of the medical literature supporting each clinical decision. We believed that this represented a fundamentally different style of practice and required a term that would capture this difference.

My mission as residency director was to train physicians who would practice this new approach to medicine. In the spring of 1990, I presented our plans for changing the program to the members of the Department of Medicine, many of whom were unsympathetic. The term suggested to describe the new approach was *scientific medicine*. Those already hostile were incensed at the implication that they had previously been "unscientific." My second try at a name for our philosophy of medical practice,

evidence-based medicine, became extremely popular in a very short time. To use the current vernacular, it went viral.[4]

After that fateful Department of Medicine meeting at McMaster, the term *EBM* first appeared in the autumn of 1990 in an information document for residents entering, or considering application to, the residency program. The relevant passage follows:

> Residents are taught to develop an attitude of "enlightened scepticism" towards the application of diagnostic, therapeutic, and prognostic technologies in their day-to-day management of patients. This approach . . . has been called "evidence-based medicine." . . . The goal is to be aware of the evidence on which one's practice is based, the soundness of the evidence, and the strength of inference the evidence permits. The strategy employed requires a clear delineation of the relevant question(s); a thorough search of the literature relating to the questions; a critical appraisal of the evidence and its applicability to the clinical situation; a balanced application of the conclusions to the clinical problem.

The first published appearance of the term was in the American College of Physicians' *Journal Club* in 1991.[5] Meanwhile, our group of enthusiastic evidence-based medical educators at McMaster were refining our practice and teaching of EBM. Believing that we were on to something important, we linked up with a larger group of academic physicians, largely from the United States, to form the first Evidence-Based Medicine Working Group and published an article in *JAMA* that defined and expanded on the description of EBM, labeling it as a "paradigm shift."[6]

This working group then addressed the task of producing a new set of articles, the successor to the Readers' Guides, to present a more practical approach to applying the medical literature to clinical practice. With the unflagging support and wise counsel of *JAMA* Deputy Editor Drummond Rennie, MD, the Evidence-Based Medicine Working Group created a 25-part series called the *Users' Guides to the Medical Literature*, published in *JAMA* between 1993 and 2000.[7] The series continues

to be published in *JAMA*, with articles that address new concepts and applications.

The first edition of the *Users' Guides to the Medical Literature* was a direct descendant of the *JAMA* series. By the time of the book's publication in 2002, EBM had already undergone its first fundamental evolution, the realization that evidence was never sufficient for clinical decision making. Rather, management decisions always involve trade-offs between desirable and undesirable consequences and thus require value and preference judgments. Indeed, in the first edition of the *Users' Guide to the Medical Literature*, the first principle of EBM was presented as Clinical Decision Making: Evidence Is Never Enough, joining the previously articulated principle of a hierarchy of evidence.

It did not take long for people to realize that the principles of EBM were equally applicable for other health care workers, including nurses, dentists, orthodontists, physiotherapists, occupational therapists, chiropractors, and podiatrists. Thus, terms such as *evidence-based health care* and *evidence-based practice* are appropriate to cover the full range of clinical applications of the evidence-based approach to patient care. Because our *Users' Guides* are directed primarily at physicians, we have continued with the term *EBM*.

The second edition incorporated 2 new EBM developments in EBM thinking. First, we had realized that only a few clinicians would become skilled at critically appraising original journal articles and that preappraised evidence would be crucial for evidence-based clinical practice. Second, our knowledge of how best to ensure that clinical decisions were consistent with patient values and preferences was rudimentary and would require extensive study.

This third edition of the *Users' Guides to the Medical Literature* builds on these realizations, most substantially in the revised guide to finding the evidence. The emphasis is now on preappraised resources and particularly on the successor to medical texts: electronic publications that produce updated

evidence summaries as the data appear and provide evidence-based recommendations for practice.

Awareness of the importance of preappraised evidence and evidence-based recommendations is reflected in other changes in the third edition. We have added a fundamental principle to the hierarchy of evidence and the necessity for value and preference judgments: that optimal clinical decision making requires systematic summaries of the best available evidence.

This principle has led to a fundamental revision of the *Users' Guide* to systematic reviews, which now explicitly includes the meta-analyses and acknowledges 2 core considerations. The first is how well the systematic review and meta-analysis were conducted. The second, inspired by the contributions of the GRADE (Grading of Recommendations Assessment, Development and Evaluation) Working Group,[8] demands an assessment of the confidence that one can place in the estimates of effect emerging from the review and meta-analysis. However well done the review, if the primary evidence on which it is based warrants little confidence, inferences from the review will inevitably be very limited.

The third edition of the *Users' Guides to the Medical Literature* incorporates the lessons we have learned in more than 20 years of teaching the concepts of EBM to students with a wide variety of backgrounds, prior preparation, clinical interest, and geographic location. Indeed, among our many blessings is the opportunity to travel the world, helping to teach at EBM workshops. Participating in workshops in Thailand, Saudi Arabia, Egypt, Pakistan, Oman, Kuwait, Singapore, the Philippines, Japan, India, Peru, Chile, Brazil, Germany, Spain, France, Belgium, Norway, the United States, Canada, and Switzerland—the list goes on—provides us with an opportunity to try out and refine our teaching approaches with students who have a tremendous heterogeneity of backgrounds and perspectives. At each of these workshops, the local EBM teachers share their own experiences,

struggles, accomplishments, and EBM teaching tips that we can add to our repertoire.

We are grateful for the extraordinary privilege of sharing, in the form of the third edition of *Users' Guides to the Medical Literature*, what we have learned.

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McMaster University

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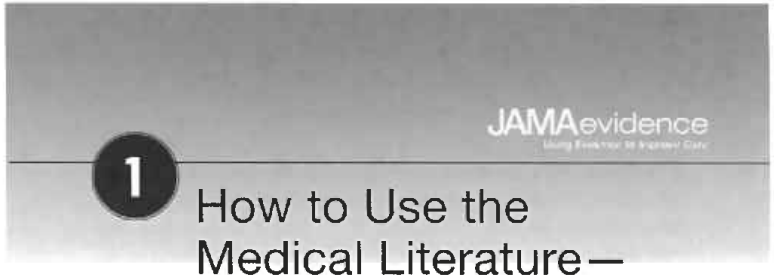


How to Use the Medical Literature—and This Book—to Improve Your Patient Care

Gordon Guyatt and Maureen O. Meade

IN THIS CHAPTER

The objective of this book is to help you make efficient use of the published literature in guiding your patient care. What does the published literature comprise? Our definition is broad. You may find *evidence*[a] in a wide variety of sources, including original journal articles, *reviews* and *synopses* of *primary studies*, *clinical practice guidelines*, and traditional and innovative medical textbooks. Increasingly, clinicians can most easily access many of these sources through the Internet.

THE STRUCTURE OF THE *USERS' GUIDES TO THE MEDICAL LITERATURE*: THE FOUNDATIONS

This book is not like a novel that you read from beginning to end. Indeed, the *Users' Guides* are designed so that each part is largely self-contained. Thus, we anticipate that clinicians may be selective in their reading of the core content chapters and will certainly be selective when they move beyond the essentials. On the first reading, you may choose only a few advanced areas that interest you. If, as you use the medical literature, you find the need to expand your understanding of, for instance, studies addressing *screening* tests or the use of *surrogate outcomes*, you can consult the relevant chapters to familiarize or reacquaint yourself with the issues. You may also find the glossary a useful reminder of the formal definitions of terms used herein. Finally, we rely heavily on examples to make our points. You will find examples identified by their blue background.

The Essentials version of this book comprises 18 chapters in 7 sections: The Foundations, Therapy, Harm, Diagnosis, Prognosis, Summarizing the Evidence, and Moving From Evidence to Action (Box 1-1). A larger Manual version of this book includes additional chapters in each section.

[a]The italicization, here and in every other chapter, represents the first occurrence in the chapter of a word defined in the glossary.

BOX 1-1

Sections of This Book

The Foundations
Therapy
Harm
Diagnosis
Prognosis
Summarizing the Evidence
Moving From Evidence to Action

The first section of this book introduces the foundations of *evidence-based practice*. Two chapters in this section, What Is Evidence-Based Medicine? and Evidence-Based Medicine and the Theory of Knowledge, present the 3 guiding principles of *evidence-based medicine* (EBM), and place EBM in the context of a humanistic approach to medical practice. The subsequent chapters in this section deal with defining your clinical question, locating the best evidence to address that question, and distinguishing *bias* from *random error* (a key principle of critical appraisal).

Clinicians are primarily interested in making accurate diagnoses and selecting optimal treatments for their patients. They also must avoid exposing patients to *harm* and offer patients prognostic information. Thus, chapters in 4 sections of this book (Therapy, Harm, Diagnosis, and Prognosis) begin by outlining what every medical student, intern and resident, and practicing physician and other clinicians will need to know to use articles that present primary data that address these 4 principal issues in providing patient care.

Increasingly, we have become aware that individual studies are often unrepresentative of all relevant studies (ie, showing larger or smaller *treatment effects* than *pooled estimates* of all relevant

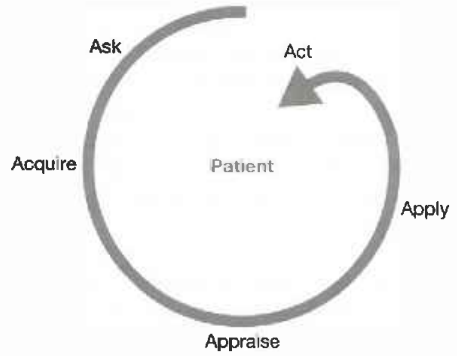
studies), imprecise, or limited in their applicability—so much so that, since the previous edition of this book, we have added the need for systematic summaries of all relevant studies as a core principle of EBM. This has major implications for clinicians looking to use the literature to provide optimal patient care. Efficient and optimally effective evidence-based practice dictates bypassing the critical assessment of primary studies and, if they are available, moving straight to the evaluation of rigorous *systematic reviews*. Even more efficient than using a systematic review is moving directly to an evidence-based recommendation. Ideally, management recommendations—summarized in clinical practice guidelines or *decision analyses*—will incorporate the best evidence and make explicit the value judgments used in moving from evidence to recommendations for action. Unfortunately, many clinical practice guidelines sometimes provide recommendations that are inconsistent with the best evidence or with typical patient *values and preferences*. The last 2 sections of the book, Summarizing the Evidence and Moving From Evidence to Action, provide clinicians with guides for using systematic reviews (with and without *meta-analyses*) and recommendations to optimize their patient care.

Our approach to addressing diagnosis, therapy, harm, and *prognosis* begins when the clinician faces a clinical question (Figure 1-1). Having identified the problem, the clinician then formulates a structured clinical question (the "Ask," Figure 1-1) (see Chapter 3, What Is the Question?) and continues with finding the best relevant evidence (the "Acquire," Figure 1-1) (see Chapter 4, Finding Current Best Evidence).

Many chapters of this book include an example of a search for the best evidence. These searches were accurate at the time they were done, but you are unlikely to get exactly the same results if you replicate the searches now. The reasons for this include additions to the literature and occasional structural changes in databases. Thus, you should view the searches as illustrations of searching principles, rather than as currently definitive searches that address the clinical question. Having identified the best evidence, the clinician then proceeds

FIGURE 1-1

Using the Medical Literature to Provide Optimal Patient Care



through the next 3 steps in evaluating that evidence: appraisal, considering how to apply the results, and acting (Figure 1-1). The appraisal includes 2 questions, "How serious is the *risk of bias*?" and "What are the results?" The first question, "How serious is the risk of bias?" deals with the extent to which the results represent an unbiased estimate of the truth. In the first 2 editions of this book, we referred to risk of bias as *validity* and used the question, "Are the results valid?" We have made this change because "risk of bias" is a more explicit and transparent term. In Chapter 7, How to Use a Noninferiority Trial, limitations of study design related to these topics include issues beyond risk of bias. Therefore, in Chapter 7, we continue to use the term validity and the question "Are the results valid?" to capture the risk of bias and these additional issues.

The second question in the appraisal step is, "What are the results?" For issues of therapy or harm, this will involve assessing the magnitude and precision of the impact of the intervention (a treatment or possible harmful exposure) (see Chapter 6,

Therapy [Randomized Trials]; Chapter 7, How to Use a Noninferiority Trial; Chapter 8, Does Treatment Lower Risk? Understanding the Results; Chapter 9, Confidence Intervals: Was the Single Study or Meta-analysis Large Enough? and Chapter 10, Harm [Observational Studies]). For issues of diagnosis, this will involve generating *pretest probabilities* and then *posttest probabilities* on the basis of test results (see Chapter 11, The Process of Diagnosis, and Chapter 12, Diagnostic Tests). For issues of prognosis, this will involve determining the likelihood of events occurring over time and the precision of those estimates (see Chapter 13, Prognosis).

Once we understand the results, we move to dealing with applicability (Figure 1-1) and ask ourselves the third question: "How can I apply these results to patient care?" This question has 2 parts. First, can you *generalize* (or, to put it another way, particularize) the results to your patient? For instance, your confidence in estimates of treatment effect decreases if your patient is too dissimilar from those who participated in the *trial* or trials. Second, what is the significance of the results for your patient? Have the investigators measured all *patient-important outcomes*? What is the tradeoff among the benefits, *risks*, and *burdens* of alternative management strategies?

Often, you will find a systematic review that, if it is done well and includes a meta-analysis (see Chapter 14, The Process of a Systematic Review and Meta-analysis), will have conducted the search and risk of bias appraisals and, further, summarized the results and suggested the confidence you can place in estimates (see Chapter 15, Understanding and Applying the Results of a Systematic Review and Meta-analysis). In addition, you often will find a recommendation that, if developed rigorously, is based on trustworthy systematic reviews of the evidence and explicitly considers patient values and preferences (see Chapter 17, How to Use a Patient Management Recommendation: Clinical Practice Guidelines and Decision Analyses) and provides guidance on the issue of applying the results to your patient. In our discussions of systematic reviews and guidelines, we introduce the

GRADE (*Grading of Recommendations Assessment, Development and Evaluation*) approach to summarizing evidence and developing recommendations, an approach that we believe represents a major advance in EBM (see Chapter 15, Understanding and Applying the Results of a Systematic Review and Meta-analysis).

The final step in using the evidence is action (Figure 1-1). Often, this will involve shared decision making with your patients (see Chapter 18, Decision Making and the Patient), a key part of the EBM process.

We have kept the initial chapters of each part of this book simple and succinct. From an instructor's point of view, these core chapters constitute a curriculum for a short course in using the literature for medical students, resident physicians, or students of other health professions. They also are appropriate for a continuing education program for practicing physicians and other clinicians.

ADVANCED TOPICS

Moving beyond the foundations, the advanced topics in this book will interest clinicians who want to practice EBM at a more sophisticated level. They are organized according to the core issues addressed in the sections on Therapy, Harm, Diagnosis, and Prognosis.

The presentations of advanced topics will deepen your understanding of study methods, statistical issues, and use of the numbers that emerge from medical research. We wrote the advanced chapters mindful of an additional audience: those who teach evidence-based practice. Many advanced entries read like guidelines for an interactive discussion with a group of learners in a tutorial or on the ward. That is natural enough because the material was generated in such small-group settings. Indeed, the Evidence-Based Medicine Working Group has produced materials that specifically discuss the challenges that arise when these concepts are presented in small-group

settings, including a series of 5 articles published in the *Canadian Medical Association Journal*[1] and another 5 articles in the *Journal of General Internal Medicine*.[2]

Experience on the wards and in outpatient clinics, and with the first 2 editions of the *Users' Guides to the Medical Literature*, has taught us that this approach is well suited to the needs of any clinician who is eager to achieve an evidence-based practice.

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JAMA evidence

2 What Is Evidence-Based Medicine?

Gordon Guyatt, Roman Jaeschke, Mark C. Wilson, Victor M. Montori, and W. Scott Richardson

IN THIS CHAPTER

Evidence-based medicine (EBM) involves conscientiously working with patients to help them resolve (sometimes) or cope with (often) problems related to their physical, mental, and social health. The EBM approach necessitates awareness and understanding of clinical research *evidence*. For those involved in making health care decisions, EBM encompasses creating implementation strategies to ensure practice evidence that is well grounded in best evidence research summaries.

At the core of EBM is a care and respect for patients who will suffer if clinicians fall prey to muddled clinical reasoning and to neglect or misunderstanding of research findings. Practitioners of EBM strive for a clear and comprehensive understanding of the evidence underlying their clinical care and work with each patient to ensure that chosen courses of action are in that patient's best interest. Practicing EBM requires clinicians to understand how uncertainty about clinical research evidence intersects with an individual patient's predicament and preferences. In this chapter, we outline how EBM proposes to achieve these goals and, in so doing, define the nature of EBM.

THREE FUNDAMENTAL PRINCIPLES OF EBM

Conceptually, EBM involves 3 fundamental principles. First, optimal clinical decision making requires awareness of the best available evidence, which ideally will come from systematic summaries of that evidence. Second, EBM provides guidance to decide whether evidence is more or less trustworthy—that is, how confident can we be of the properties of diagnostic tests, of our patients' *prognosis*, or of the impact of our therapeutic options? Third, evidence alone is never sufficient to make a clinical decision. Decision makers must always trade off the benefits and *risks*, *burden*, and costs associated with alternative management strategies and, in doing so, consider their patients' unique predicament and *values and preferences*.[1]

Best Evidence Summaries

In 1992, Antman et al[2] published an article that compared the recommendations of experts for management of patients with myocardial infarction to the evidence that was available at the time the recommendations were made. Figures 2-1 and 2-2 summarize their results in *forest plots*. Both are cumulative *meta-analyses*: the first of thrombolytic therapy for myocardial infarction and the second for lidocaine antiarrhythmic therapy. In both cases, the line in the center represents an *odds ratio* of 1.0 (treatment is neither beneficial nor harmful). As in any forest plot, the dots represent the best estimates of treatment effect (often from individual studies; in this case from the totality of accumulated evidence), and the associated lines represent the 95% *confidence intervals* (CIs).

The "Patients" column presents the total number of patients enrolled in all *randomized clinical trials* (RCTs) conducted to the date specified in the "Year" column—the reason we call it a cumulative meta-analysis. In both figures, early on, with relatively few patients, the CIs are wide, but they progressively narrow as new trials were reported.

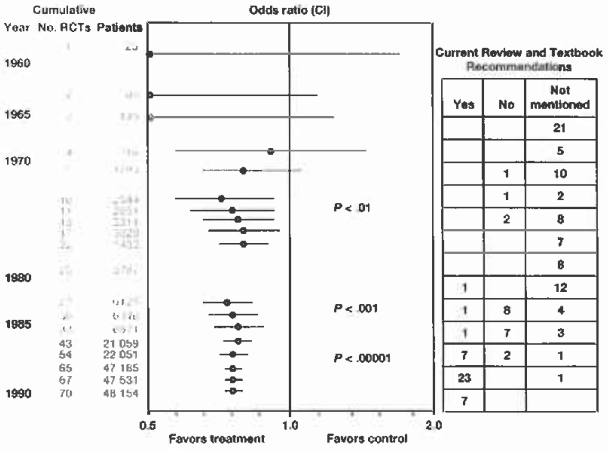
For the thrombolytic example, by 10 trials and approximately 2500 patients, it appears that thrombolytic therapy reduces mortality, but the CIs are still wide enough to permit residual uncertainty. By 30 trials and more than 6000 patients, the reduction in odds of death of approximately 25% seems secure.

Despite this apparently definitive result, additional trials that enrolled 40 000 patients—half of whom did not receive the benefits of life-prolonging thrombolytic therapy—were conducted. Why was this necessary?

The right side of each figure, which presents the guidance expressed in then-current reviews and textbooks as the data were accumulating, provides the answer to this question. Until approximately a decade after the answer was in, there was considerable disagreement among experts, with many recommending against, or not mentioning, thrombolytic therapy. To the detriment of patients who did not receive thrombolytic

FIGURE 2-1

Thrombolytic Therapy in Acute Myocardial Infarction



Abbreviations: CI, confidence interval; RCTs, randomized clinical trials.

This is a cumulative meta-analysis of thrombolytic therapy for myocardial infarction. The line down the center, the odds ratio, equals 1.0. The dots represent best estimates, and the lines around the dots are 95% CIs. The numbers on the left side of the figure are trials and patient totals across trials.

Early on, the CIs are very wide. By 10 trials, it appears therapy reduces mortality, but the effect is still uncertain. By 30 trials, the effect seems secure. However, 40 000 more patients were enrolled after the answer was in. Why?

The right side of the figure displays current reviews and textbook recommendations as data accumulated. Recommendations are in favor ("Yes"), against ("No"), or "Not mentioned." Two key points: (1) at the same time, experts disagreed, and (2) it took 10 years for experts to catch up with evidence.

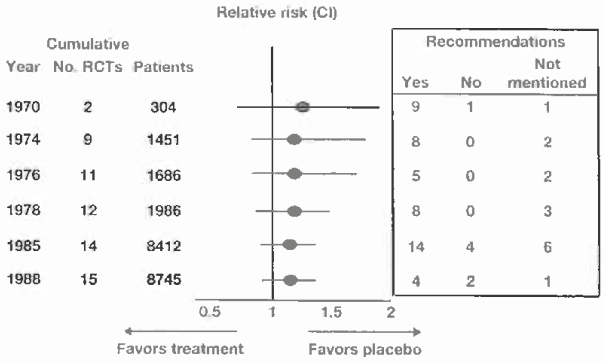
Reproduced from Antman et al.[2]

therapy during this period, it took a decade for the experts to catch up with the evidence.

Figure 2-2 tells a perhaps even more disturbing story. This cumulative meta-analysis reveals that there was never any RCT

FIGURE 2-2

Prophylactic Lidocaine in Acute Myocardial Infarction



Abbreviations: CI, confidence interval; RCTs, randomized clinical trials.

This figure shows a cumulative meta-analysis of the effect of prophylactic lidocaine in preventing death from myocardial infarction. In this case, there is never any evidence of benefit. Ultimately, harm is not proved, but there clearly is no benefit. Most experts, however, were recommending therapy despite RCT evidence. Also, as in Figure 2-1, there was a lot of disagreement among experts.

Reproduced from Antman et al.[2]

evidence that suggested a lower mortality with prophylactic lidocaine after myocardial infarction—indeed, *point estimates* suggested an increase in death rate. Nevertheless, although we once again see widespread disagreement among the experts, most texts and reviews were recommending prophylactic lidocaine during the 2 decades during which the RCT evidence was accumulating.

Why the expert disagreement, the lag behind the evidence, and the recommendations inconsistent with the evidence? These stories come from the era before *systematic reviews* and meta-analyses were emerging in the late 1980s. If the evidence

summaries presented in the forest plots had been available to the experts, they would have grasped the benefits of thrombolytic therapy far earlier than they did and abandoned prophylactic lidocaine far earlier. Indeed, following EBM principles that limit reliance on biologic rationale and place far more emphasis on empirical evidence, the experts may never have started using lidocaine.

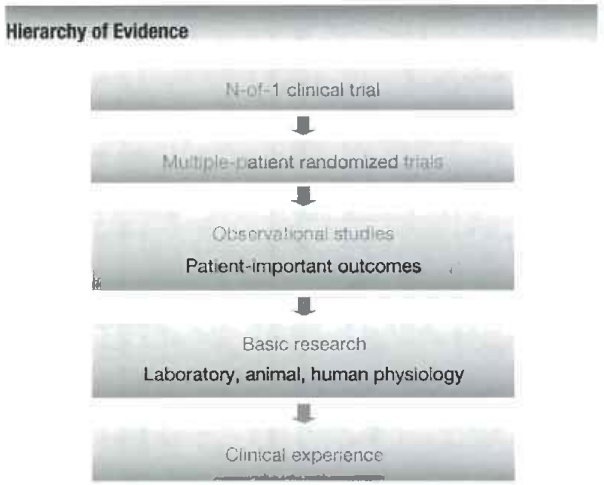
Rational clinical decisions require systematic summaries of the best available evidence. Without such summaries, clinicians—expert or otherwise—will be unduly influenced by their own preconceptions and by unrepresentative and often lower-quality evidence. This, the first principle of EBM, immediately raises another question: "How does one recognize the best evidence?"

Guides to Confidence in Estimates

Summaries of the best evidence for diagnosis, prognosis, or treatment present evidence, respectively, for how to interpret test results, predict patients' likely fate, or understand the impact of alternative management strategies. Sometimes, such evidence is trustworthy—we have high confidence in estimates of test properties, patients' prognosis, or treatment effects. At other times, limitations in evidence leave us uncertain. Evidence-based medicine provides guidance to distinguish between these situations and the range of confidence between them.

Historically, EBM answered the question, "What is the best evidence?" with *hierarchies of evidence*, the most prominent of which was the hierarchy related to evidence that supported therapeutic interventions (Figure 2-3). Issues of diagnosis or prognosis require different hierarchies. For studies of the accuracy of diagnostic tests, the top of the hierarchy includes studies that enrolled patients about whom clinicians had diagnostic uncertainty and that undertook a *blind* comparison between the candidate test and a *criterion standard* (see Chapter 12, Diagnostic Tests, and Chapter 13, Prognosis). For prognosis, prospective observational studies accurately documenting *exposures* and outcomes and

FIGURE 2-3



Because we would like to optimally individualize patient care, n-of-1 randomized clinical trials are at the top of the hierarchy of study designs, followed by conventional randomized trials. Next in the hierarchy are observational studies; we should try to find studies that focus on outcomes important to the patient. Next, if there are no clinical studies available, we may look at basic scientific research, although caution must be used in extrapolating the results to the clinical setting. Clinical experience is at the bottom of the hierarchy, either your own or that of colleagues or experts.

following up all patients during relevant periods would sit atop the hierarchy.

Returning to the hierarchy of therapy, noting the limitations of human intuition,[3] EBM places the unsystematic observations of individual clinicians lowest on the hierarchy. Noting that predictions based on physiologic experiments are often right but sometimes disastrously wrong, EBM places such experiments at the next step up in the hierarchy. Observational studies

that measure the apparent impact on *patient-important outcomes* and RCTs constitute the next 2 steps up the hierarchy of evidence.

All of the sources of evidence mentioned thus far involve generalizations from groups of patients to an individual, and all are limited in this regard. The same strategies that minimize *bias* in conventional therapeutic trials that involve multiple patients, however, can guard against misleading results in studies that involve single patients.[4] In the *n-of-1 RCT*, a patient and clinician are blind to whether that patient is receiving active or *placebo* medication. The patient makes quantitative ratings of troublesome symptoms during each period, and the n-of-1 RCT continues until both the patient and the clinician conclude that the patient is or is not obtaining benefit from the target intervention. An n-of-1 RCT can provide definitive evidence of treatment effectiveness in individual patients[5,6] and is thus at the top of the evidence hierarchy. Unfortunately, n-of-1 RCTs are restricted to chronic conditions with treatments that act and cease acting quickly and are subject to considerable logistic challenges. We therefore must usually rely on studies of other patients to make inferences regarding our patient.

This hierarchy is far from absolute, and a more sophisticated framework has emerged for judging confidence in estimates of effect. Table 2-1 summarizes that framework, formulated by the *GRADE* (*Grading of Recommendations Assessment, Development and Evaluation*) Working Group, originally to provide an approach to the development of *clinical practice guidelines*.[7,8] The GRADE approach involves rating our confidence in estimates of the effects of health care interventions (also referred to as quality of evidence) as high, moderate, low, or very low. Consistent with the previous hierarchy approach, in the GRADE guidance, RCTs begin as high confidence and observational studies begin as low confidence. We lose confidence in a body of RCT evidence, however, if studies have major problems in design and execution (*risk of bias*); results are imprecise, inconsistent, or indirect (eg, the population of interest differs from the population studied); or we have a high suspicion of publication bias (see Chapter 15, Understanding and Applying the Results of a Systematic Review and Meta-analysis). When a body of RCT evidence suffers from a number of these limitations, the confidence in estimates may be low or even very low.

Similarly, if treatment effects are sufficiently large and consistent, the GRADE approach allows for moderate or even high confidence ratings from carefully conducted observational studies.

TABLE 2-1

Confidence Assessment Criteria[a]

Study Design	Confidence in Estimates	Lower If[a]	Higher If[a]
Randomized trial	High	Risk of bias –1 Serious –2 Very serious	Large effect +1 Large +2 Very large Dose response +1 Evidence of a gradient
	Moderate	Inconsistency –1 Serious –2 Very serious	
Observational study	Low	Indirectness –1 Serious –2 Very serious	
	Very low	Imprecision –1 Serious –2 Very serious Publication bias –1 Likely –2 Very likely	

[a]Minus and plus signs refer, respectively, to rating down and rating up confidence in estimates. The 1 refers to rating down or up by 1 level (eg, from high to moderate or moderate to high), and the 2 refers to rating down or up by 2 levels (eg, high to low or low to high).

For example, observational studies have allowed extremely strong inferences about the efficacy of insulin in diabetic ketoacidosis or that of hip replacement in patients with debilitating hip osteoarthritis.

The EBM approach implies a clear course of action for clinicians addressing patient problems. They should seek the highest-quality evidence available to guide their clinical decisions. This approach makes it clear that any claim that there is no evidence for the effect of a particular treatment is a non sequitur. The available evidence may warrant very low confidence—it may be the unsystematic observation of a single clinician or physiologic studies that point to mechanisms of action that are only indirectly related—but there is always evidence.

Evidence Is Never Enough to Drive Clinical Decision Making

First, picture a woman with chronic pain from terminal cancer. She has come to terms with her condition, resolved her affairs, said her good-byes, and wishes to receive only palliative care. She develops severe pneumococcal pneumonia. Evidence that antibiotic therapy reduces morbidity and mortality from pneumococcal pneumonia warrants high confidence. This evidence does not, however, dictate that this patient should receive antibiotics. Her values—emerging from her comorbidities, social setting, and beliefs—are such that she would prefer to forgo treatment.

Now picture a second patient, an 85-year-old man with severe dementia who is mute and incontinent, is without family or friends, and spends his days in apparent discomfort. This man develops pneumococcal pneumonia. Although many clinicians would argue that those responsible for his decision making should elect not to administer antibiotic therapy, others would suggest that they should. Again, evidence of treatment effectiveness does not automatically imply that treatment should be administered.

Finally, picture a third patient, a healthy 30-year-old mother of 2 children who develops pneumococcal pneumonia. No clinician would doubt the wisdom of administering antibiotic therapy to this patient. This does not mean, however, that an underlying value judgment has been unnecessary. Rather, our values are sufficiently concordant, and the benefits so overwhelm the risk of treatment that the underlying value judgment is unapparent.

By values and preferences, we mean the collection of goals, expectations, predispositions, and beliefs that individuals have for certain decisions and their potential outcomes. The explicit enumeration and balancing of benefits and risks that are central to EBM bring the underlying value judgments involved in making management decisions into bold relief.

Acknowledging that values play a role in every important patient care decision highlights our limited understanding of how to ensure that decisions are consistent with individual and, where appropriate, societal values. As we discuss further in the final section of this chapter, developing efficient processes for helping patients and clinicians work together toward optimal decisions consistent with patient values and preferences remains a frontier for EBM.

Next, we comment on additional skills that clinicians must master for optimal patient care and the relation of those skills to EBM.

CLINICAL SKILLS, HUMANISM, AND EBM

In summarizing the skills and attributes necessary for *evidence-based practice*, Box 2-1 highlights how EBM complements traditional aspects of clinical expertise. One of us, an intensive care specialist, developed a lesion on his lip shortly before an important presentation. He was concerned and, wondering whether he should take acyclovir, proceeded to spend the next 30 minutes searching for and evaluating the highest-quality evidence. When he began to discuss his remaining uncertainty

BOX 2-1

Knowledge and Skills Necessary for Optimal Evidence-Based Practice

- Diagnostic expertise
- In-depth background knowledge
- Effective searching skills
- Effective critical appraisal skills
- Ability to define and understand benefits and risks of alternatives
- In-depth physiologic understanding that allows application of evidence to the individual
- Sensitivity and communication skills required for full understanding of patient context
- Ability to elicit and understand patient values and preferences and work with patients in shared decision making

with his partner, an experienced dentist, she cut short the discussion by exclaiming, "But, my dear, that isn't herpes!"

This story illustrates the necessity of obtaining the correct diagnosis before seeking and applying research evidence regarding optimal treatment. After making the diagnosis, the clinician relies on experience and background knowledge to define the relevant management options. Having identified those options, the clinician can search for, evaluate, and apply the best evidence regarding patient management.

In applying evidence, clinicians rely on their expertise to define features that affect the applicability of the results to the individual patient. The clinician must judge the extent to which differences in treatment (for instance, local surgical expertise or the possibility of patient *nonadherence*) or patient characteristics (such as age, comorbidity, or the patient's

personal circumstances) may affect estimates of benefit and risk that come from the published literature.

We note that some of these skills—the sensitivity to the patient's unique predicament and the communication skills necessary for shared decision making—are often not typically associated with EBM. We believe they are, in fact, at the core of EBM. Understanding the patient's personal circumstances is of particular importance and requires advanced clinical skills, including listening skills and compassion. For some patients, incorporation of patient values for major decisions will mean a full enumeration of the possible benefits, risks, and inconveniences associated with alternative management strategies. For some patients and problems, this discussion should involve the patient's family. For other problems—the discussion of *screening* with prostate-specific antigen with older male patients, for instance—attempts to involve family members might violate cultural norms.

Some patients are uncomfortable with an explicit discussion of benefits and risk and object to clinicians placing what they perceive as excessive responsibility for decision making on their shoulders. In such cases, it is the physician's responsibility to develop insight to ensure that choices will be consistent with the patient's values and preferences while remaining sensitive to the patient's preferred role in decision making.

ADDITIONAL CHALLENGES FOR EBM

Busy clinicians—particularly those early in their development of the skills needed for *evidence-based practice*—will find that they often perceive time limitations as the biggest challenge to evidence-based practice. This perception may arise from having inadequate access to various evidence-based resources. Fortunately, a tremendous array of sophisticated evidence-based information is now available for clinicians working in high-income countries, and the pace of innovation remains extremely rapid (see Chapter 4, Finding Current Best Evidence).

Access to preprocessed information cannot, however, address other skills required for efficient evidence-based practice. These skills include formulating focused clinical questions, matching prioritized questions to the most appropriate resources, assessing confidence in estimates, and understanding how to apply results to clinical decision making. Although these skills take time to learn, the reward in terms of efficient and effective practice can more than compensate.

Another challenge for evidence-based practice is ensuring that management strategies are consistent with patients' values and preferences. In a time-constrained environment, how can we ensure that patients' involvement in decision making has the form and extent that they desire and that the outcome reflects their needs and desires? Evidence-based medicine leaders are now making progress in addressing these challenges.[9,10]

This book deals primarily with decision making at the level of the individual patient. Evidence-based approaches can also inform health care policy making, day-to-day decisions in public health, and systems-level decisions, such as those facing hospital managers. In each of these areas, EBM can support the appropriate goal of gaining the greatest health benefit from limited resources.

In the policy arena, dealing with differing values poses even more challenges than in the arena of individual patient care. Should we restrict ourselves to alternative resource allocation within a fixed pool of health care resources, or should we consider expanding health care services at the cost, for instance, of higher tax rates for individuals or corporations? How should we deal with the large body of observational studies that suggest that social and economic factors may have a larger influence on the health of populations than health care provision? How should we deal with the tension between what may be best for a person and what may be optimal for the society of which that person is a member? The debate about such issues is at the core of evidence-based policy making in health care; it also has implications for decision making at the individual patient level.

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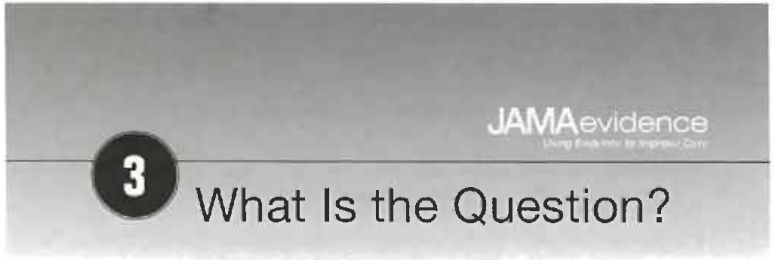

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IN THIS CHAPTER

THREE WAYS TO USE THE MEDICAL LITERATURE

Consider a medical student, early in her training, seeing a patient with newly diagnosed type 2 diabetes mellitus. She will ask questions such as the following: "What is type 2 diabetes mellitus?" "Why does this patient have polyuria?" "Why does this patient have numbness and pain in his legs?" "What treatment options are available?" These questions address normal human physiology and the pathophysiology associated with a medical condition.

Traditional medical textbooks, whether in print or online, that describe underlying pathophysiology or epidemiology of a disorder provide an excellent resource for addressing these *background questions*. In contrast, the sorts of *foreground questions* that experienced clinicians usually ask require different resources. Formulating a question is a critical and generally unappreciated skill for *evidence-based practice*. The following ways to use the medical literature provide opportunities to practice that skill.

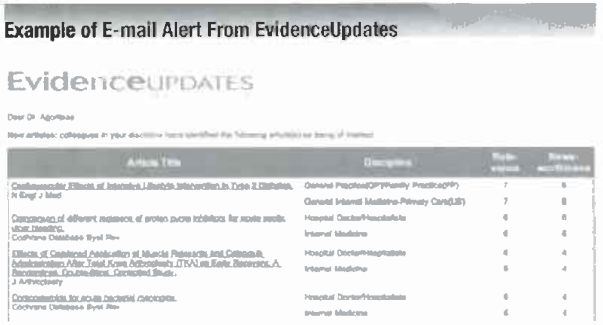
Staying Alert to Important New Evidence

A general internist is checking e-mails on a smartphone while riding public transit to work. While screening a weekly e-mail alert from EvidenceUpdates (http://plus.mcmaster.ca/EvidenceUpdates, Figure 3-1), the internist sees an article titled, Cardiovascular Effects of Intensive Lifestyle Intervention in Type 2 Diabetes,[1] recently published and rated by internist colleagues as newsworthy and highly relevant for practice.

This internist is in the process of addressing a question that clinicians at all stages of training and career development are constantly posing: "What important new evidence should I know to optimally treat patients?" Clinicians traditionally addressed this question by attending rounds and conferences

FIGURE 3-1

Example of E-mail Alert From EvidenceUpdates


EvidenceUPDATES

and by subscribing to target medical journals in which articles relevant to their practice appear. They kept up-to-date by skimming the table of contents and reading relevant articles.

This traditional approach to what we might call the browsing mode of using the medical literature has major limitations of inefficiency and its resulting frustration. Many screened articles may prove of little relevance or newsworthiness or fail to meet the critical appraisal criteria that are presented in this book. To make matters worse, the volume of research is markedly increasing,[2] and relevant studies appear in a large variety of journals.[3] *Evidence-based medicine* offers solutions to these problems.

The most efficient strategy for ensuring you are aware of recent developments relevant to your practice is to subscribe to e-mail alerting systems, such as EvidenceUpdates, used by the internist in this example. This free service has research staff screening approximately 45 000 articles per year in more than 125 clinical journals for methodologic quality and a worldwide panel of practicing physicians rating them for clinical relevance and newsworthiness.[4] You can tailor alerting systems to your information needs (clinical disciplines and frequency of alerts)

and identify the 20 to 50 articles per year that will influence your practice.[5] Several other free or subscription-based alerting systems are available, both for a wide scope of disciplines (eg, NEJM Journal Watch, http://www.jwatch.org) and for specific subspecialties (eg, OrthoEvidence, http://www.myorthoevidence.com).

An alternative to alerting systems are *secondary evidence-based journals*. For example, in internal and general medicine, *ACP Journal Club* (http://acpjc.acponline.org) publishes *synopses* of articles that meet criteria of both high clinical relevance and methodologic quality. We describe such secondary journals in more detail in Chapter 4, Finding Current Best Evidence. If you prefer browsing to receiving alerts, such preappraised sources of *evidence* may increase your efficiency.

Some specialties (primary care and mental health care) and subspecialties (cardiology, oncology, and obstetrics and gynecology) already have specialty-devoted secondary journals; others do not. The New York Academy of Medicine keeps a current list of available secondary journals in many health care disciplines (http://www.nyam.org/fellows-members/ebhc/eb_publications.html). If your specialty does not yet have its own journal, you can apply your own relevance and methodologic screening criteria to articles in your target specialty or subspecialty journals. When you have learned the skills, you will be surprised at the small proportion of studies to which you need attend and the efficiency with which you can identify them.

Problem Solving

Experienced clinicians managing a patient with type 2 diabetes mellitus will ask questions such as "In patients with new-onset type 2 diabetes mellitus, which clinical features or test results predict the development of diabetic complications?" "In patients with type 2 diabetes mellitus requiring drug therapy, does starting with metformin treatment yield improved diabetes control and reduce long-term complications better than other initial treatments?" Here, clinicians are defining specific

questions raised in caring for patients and then consulting the literature to resolve these questions.

Asking Background and Foreground Questions

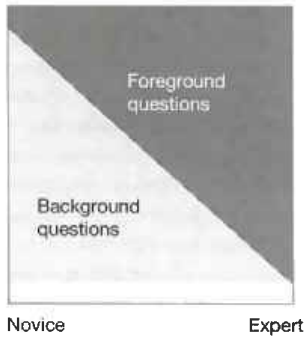
One can think of the first set of questions, those of the medical student, as background questions and of the browsing and problem-solving sets as foreground questions. In most situations, you need to understand the background thoroughly before it makes sense to address foreground issues.

Experienced clinicians may occasionally require background information when a new condition or medical *syndrome* (eg, Middle East respiratory syndrome coronavirus), a new diagnostic test (eg, molecular diagnosis), or a new treatment modality (eg, dipeptidyl peptidase 4 inhibitors) appears in their clinical arena.

Figure 3-2 represents the evolution of the questions we ask as we progress from being novices posing background questions to experts posing foreground questions. This book explores how clinicians can use the medical literature to solve their foreground questions.

FIGURE 3-2

Background and Foreground Questions



CLARIFYING YOUR QUESTION

The Structure: Patients, Exposures, Outcome

Clinical questions often spring to mind in a form that makes finding answers in the medical literature a challenge. Dissecting the question into its component parts to facilitate finding the best evidence is a fundamental skill. One can divide questions of therapy or *harm* into 4 parts following the *PICO* framework: patients or population, intervention(s) or exposure(s), comparator, and outcome (Box 3-1). For questions of *prognosis*, you can use 1 of 2 alternative structures. One has only 3 elements: patients, exposure (time), and outcome. An alternative focuses on patient-related factors, such as age and sex, that can modify prognosis: patients, exposure (eg, older age or male), comparison (eg, younger age or female), and outcome. For diagnostic tests, the structure we suggest is patients, exposure (test), and outcome (*criterion standard*).[6]

BOX 3-1

Framing Clinical Questions: PICO

Patients or Population: Who are the relevant patients?

Intervention(s) or Exposure(s): For example, diagnostic tests, foods, drugs, surgical procedures, time, or risk factors. What are the management strategies we are interested in comparing or the potentially harmful exposures about which we are concerned?

Comparator: For issues of therapy, prevention, or harm, there will always be both an experimental intervention or putative harmful exposure and a control, alternative, or comparison intervention.

Outcome: What are the patient-relevant consequences of the exposures in which we are interested? We may also be interested in the consequences to society, including cost or resource use. It may also be important to specify the period of interest.

Five Types of Foreground Clinical Questions

In addition to clarifying the population, intervention or exposure, and outcome, it is productive to label the nature of the question that you are asking. There are 5 fundamental types of clinical questions:

1. Therapy: determining the effect of interventions on *patient-important outcomes* (*symptoms*, function, morbidity, mortality, and costs)
2. Harm: ascertaining the effects of potentially harmful agents (including therapies from the first type of question) on patient-important outcomes
3. *Differential diagnosis*: in patients with a particular clinical presentation, establishing the frequency of the underlying disorders
4. Diagnosis: establishing the *power* of a test to differentiate between those with and without a *target condition* or disease
5. Prognosis: estimating a patient's future course

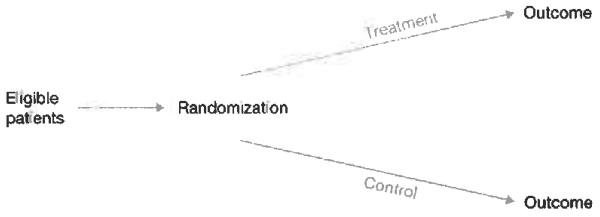
Finding a Suitably Designed Study for Your Question Type

You need to correctly identify the category of study because, to answer your question, you must find an appropriately designed study. If you look for a *randomized trial* to inform the properties of a diagnostic test, you will not find the answer you seek. We will now review the study designs associated with the 5 major types of questions.

To answer questions about a therapeutic issue, we seek studies in which a process analogous to flipping a coin determines participants' receipt of an *experimental treatment* or a control or standard treatment: a randomized trial (see Chapter 6, Therapy [Randomized Trials]). Once investigators allocate participants to treatment or *control groups*, they follow them forward in time to determine whether they have, for instance, a stroke or

FIGURE 3-3

Structure of Randomized Trials



myocardial infarction—what we call the outcome of interest (Figure 3-3). When randomized trials are not available, we look to *observational studies* in which—rather than randomization—clinician or patient preference, or happenstance, determines whether patients receive an intervention or alternative (see Chapter 5, Why Study Results Mislead: Bias and Random Error).

Ideally, we would also look to randomized trials to address issues of harm. For most potentially harmful exposures, however, randomly allocating patients is neither practical nor ethical. For instance, one cannot suggest to potential study participants that an investigator will decide by the flip of a coin whether or not they smoke during the next 20 years. For exposures such as smoking, the best one can do is identify observational studies (often subclassified as *cohort* or *case-control studies*) that provide less trustworthy evidence than randomized trials (see Chapter 10, Harm [Observational Studies]).

Figure 3-4 depicts a common observational study design in which patients with and without the exposures of interest are followed forward in time to determine whether they experience the outcome of interest. For smoking, an important outcome would likely be the development of cancer.

For sorting out differential diagnosis, we need a different study design (Figure 3-5). Here, investigators collect a group of patients with a similar presentation (eg, painless jaundice,

FIGURE 3-4

Structure of Observational Cohort Studies

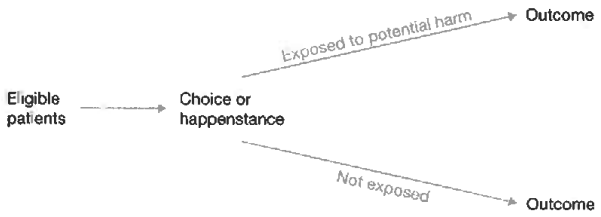
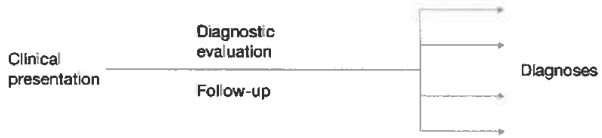


FIGURE 3-5

Structure of Studies of Differential Diagnosis



syncope, or headache), conduct an extensive battery of tests, and, if necessary, follow patients forward in time. Ultimately, for each patient the investigators hope to establish the underlying cause of the symptoms and *signs* with which the patient presented.

Establishing the performance of a diagnostic test (ie, the test's properties or operating characteristics) requires a slightly different design (Figure 3-6). In diagnostic test studies, investigators identify a group of patients among whom they suspect a disease or condition of interest exists (such as tuberculosis, lung cancer, or iron deficiency anemia), which we call the target condition. These patients undergo the new diagnostic test and a *reference standard* (also referred to as *gold standard* or criterion standard). Investigators evaluate the diagnostic test by comparing its classification of patients with that of the reference standard (Figure 3-6).

A final type of study examines a patient's prognosis and may identify factors that modify that prognosis. Here, investigators identify patients who belong to a particular group (such as pregnant women, patients undergoing surgery, or patients with cancer) with or without factors that may modify their prognosis (such as age or *comorbidity*). The exposure here is time, and investigators follow up patients to determine whether they experience the *target outcome*, such as an adverse obstetric or neonatal event at the end of a pregnancy, a myocardial infarction after surgery, or survival in cancer (Figure 3-7).

FIGURE 3-6

Structure of Studies of Diagnostic Test Properties

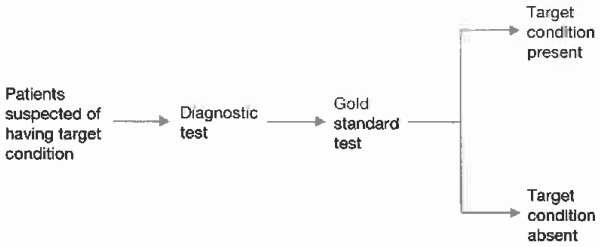
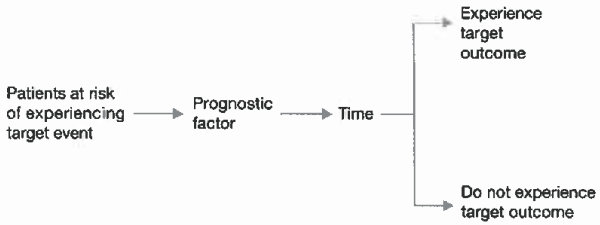


FIGURE 3-7

Structure of Studies of Prognosis



Three Examples of Question Clarification

We will now provide examples of the transformation of unstructured clinical questions into the structured questions that facilitate the use of the medical literature.

Example 1: Diabetes and Target Blood Pressure

A 55-year-old white woman presents with type 2 diabetes mellitus and hypertension. Her glycemic control is excellent with metformin, and she has no history of complications. To manage her hypertension, she takes a small daily dose of a thiazide diuretic. During a 6-month period, her blood pressure is near 155/88 mm Hg.

Initial Question: When treating hypertension, at what target blood pressure should we aim?

Digging Deeper: One limitation of this formulation of the question is that it fails to specify the population in adequate detail. The benefits of tight control of blood pressure may differ among patients with diabetes vs those without diabetes, in type 1 vs type 2 diabetes, and among patients with and without diabetic complications.

The detail in which we specify the patient population is a double-edged sword. On the one hand, being very specific (middle-aged women with uncomplicated type 2 diabetes) will ensure that the answer we get is applicable to our patient. We may, however, fail to find any studies that restrict themselves to this population. The solution is to start with a specific patient population but be ready to remove specifications to find a relevant article. In this case, we may be ready to remove the "female," "middle-aged," "uncomplicated," and "type 2," in that order. If we suspect that the optimal target blood pressure may be similar among patients

with and without diabetes, and if it proves absolutely necessary, we might remove "diabetes" from the question.

The order in which we remove the patient specifications depends on how likely it is that those characteristics will influence response to treatment. We suggest removing "female" first because we think it likely that optimal target blood pressure will be similar in men and women. Similarly, younger, middle-aged, and elderly individuals are likely to have the same optimal targets (although here we are not quite so sure). As our doubts about the same optimal targets across populations becomes progressively greater (uncomplicated vs complicated diabetes, type 1 vs type 2, or patients with diabetes vs those without), we become increasingly reluctant to remove the particular patient characteristic from the question.

We may wish to specify that we are interested in the addition of a specific antihypertensive agent. Alternatively, the intervention of interest may be any antihypertensive treatment. Furthermore, a key part of the intervention will be the target for blood pressure control. For instance, we might be interested in knowing whether it makes any difference if our target diastolic blood pressure is less than 80 mm Hg vs less than 90 mm Hg. Another limitation of the initial question formulation is that it fails to specify the criteria (the outcomes of interest) by which we will judge the appropriate target for our hypertensive treatment.

Improved (Searchable) Question: A Question About Therapy

- *Patients:* Patients with hypertension and type 2 diabetes without diabetic complications.
- *Intervention/Exposure:* Any antihypertensive agent that aims at a target diastolic blood pressure of 90 mm Hg.

- *Comparator:* Target diastolic blood pressure of 80 mm Hg.
- *Outcomes:* Stroke, myocardial infarction, cardiovascular death, and total mortality.

Example 2: Transient Loss of Consciousness

A previously well, although a heavy drinker, 55-year-old man presents to the emergency department with an episode of transient loss of consciousness. On the evening of presentation, he had his usual 5 beers and started to climb the stairs at bedtime. The next thing he remembers is being woken by his son, who found him lying near the bottom of the stairs. The patient took about a minute to regain consciousness and remained confused for another 2 minutes. His son did not witness any shaking, and there had not been any incontinence. Physical examination findings were unremarkable; the electrocardiogram revealed a sinus rhythm with a rate of 80/min and no abnormalities. Glucose, sodium, and other laboratory results were normal, and a blood alcohol test result was negative.

Initial Question: How extensively should I investigate this patient?

Digging Deeper: The initial question gives us little idea of where to look in the literature for an answer. As it turns out, there are a host of questions that could be helpful in choosing an optimal investigational strategy. We could, for instance, pose a question of differential diagnosis: If we knew the distribution of ultimate diagnoses in such patients, we could choose to investigate the more common and omit investigations targeted at remote possibilities.

Other information that would help us would be the properties of individual diagnostic tests. If an electroencephalogram were extremely accurate for diagnosing a

seizure or a 24-hour Holter monitor for diagnosing arrhythmia, we would be far more inclined to order these tests than if they missed patients with the underlying problems or falsely identified patients as not having the problems.

Alternatively, we could ask a question of prognosis. If patients had benign prognoses, we might be much less eager to investigate extensively than if patients tended to have poor outcomes. Finally, the ultimate answer to how intensively we should investigate might come from a randomized trial in which patients similar to this man were allocated to more vs less intensive investigation.

Improved (Searchable) Questions: A Question About Differential Diagnosis

- *Patients:* Middle-aged patients presenting with transient loss of consciousness.
- *Intervention/Exposure:* Thorough investigation and *follow-up* for common and less common diagnoses.
- *Comparator:* Minimal investigation and follow-up.
- *Outcomes:* Frequency of underlying disorders, such as vasovagal syncope, seizure, arrhythmia, and transient ischemic attack.

A Question About Diagnosis

- *Patients:* Middle-aged patients presenting with transient loss of consciousness.
- *Intervention/Exposure:* Electroencephalogram.
- *Outcomes:* Reference standard investigation (probably long-term follow-up).

A Question About Prognosis

- *Patients:* Middle-aged patients presenting with transient loss of consciousness.

- *Exposure/Comparison:* Time.
- *Outcomes:* Morbidity (complicated arrhythmias or seizures, strokes, or serious accidents) and mortality in the year after presentation.

A Question About Diagnostic Impact

You can think of this also as a question of therapy; the principles of critical appraisal are the same.

- *Patients:* Middle-aged patients presenting with loss of consciousness.
- *Intervention/Exposure:* Comprehensive investigation.
- *Comparator:* Minimal investigation.
- *Outcomes:* Morbidity and mortality in the year after presentation.

Example 3: Squamous Cell Carcinoma

A 60-year-old man with a 40-pack-year smoking history presents with hemoptysis. A chest radiograph shows a parenchymal mass with a normal mediastinum, and a fine-needle aspiration and biopsy of the mass reveals non–small cell carcinoma. Aside from hemoptysis, the patient is asymptomatic, and the physical examination results are normal.

Initial Question: What investigations should we undertake before deciding whether to offer this patient surgery?

Digging Deeper: The key defining features of this patient are his non–small cell carcinoma and the fact that his medical history, physical examination, and chest radiograph indicate no evidence of intrathoracic or extrathoracic metastatic disease. Alternative investigational strategies address 2 issues: Does the patient have occult mediastinal disease, and does he have occult extrathoracic metastatic

disease? Investigational strategies for addressing the possibility of occult mediastinal disease include undertaking a mediastinoscopy or performing computed tomography (CT) of the chest and proceeding according to the results of this investigation. Investigational strategies for extrathoracic disease include brain and abdominal CT and bone scanning. Positron emission tomography–CT (PET-CT) represents an alternative approach for both intrathoracic and extrathoracic disease.

What outcomes are we trying to influence in our choice of investigational approach? We would like to prolong the patient's life, but the extent of his underlying tumor is likely to be the major determinant of survival, and our investigations cannot change that. We wish to detect occult mediastinal metastases if they are present because, if the cancer has spread, resectional surgery is unlikely to benefit the patient. Thus, in the presence of mediastinal metastatic disease, patients will usually receive palliative approaches and avoid an unnecessary thoracotomy.

We could frame our structured clinical question in 2 ways. One would be asking about the usefulness of the PET-CT scan for identifying metastatic disease. More definitive would be to ask a question of diagnostic impact, analogous to a therapy question: What investigational strategy would yield superior patient-important outcomes?

Improved (Searchable) Questions: A Question About Diagnosis

- *Patients:* Newly diagnosed non–small cell lung cancer with no evidence of extrapulmonary metastases.
- *Intervention:* PET-CT scan of the chest.
- *Outcome:* Mediastinal spread at mediastinoscopy.

A Question About Diagnostic Impact (Therapy)

- *Patients:* Newly diagnosed non–small cell lung cancer with no evidence of extrapulmonary metastases.
- *Intervention:* PET-CT.
- *Comparator:* Alternative diagnostic strategies.
- *Outcome:* Unnecessary thoracotomy.

CONCLUSION: DEFINING THE QUESTION

Constructing a searchable and answerable question that allows you to use the medical literature to solve problems is no simple matter. It requires a detailed understanding of the clinical issues involved in patient management. The 3 examples in this chapter illustrate that each patient encounter may trigger a number of clinical questions and that you must give careful thought to what you really want to know. Bearing the structure of the question in mind—patient or population, intervention or exposure, outcome, and, for therapy or harm questions, comparison—is helpful in arriving at an answerable question. Identifying the type of questions—therapy, harm, differential diagnosis, diagnosis, and prognosis—will not only ensure you choose the right question structure but also ensure that you are looking for a study with an appropriate design.

Careful definition of the question will provide another benefit: you will be less likely to be misled by a study that addresses a question related to that in which you are interested, but with 1 or more important differences. For instance, making sure that the study compares experimental treatment to current optimal care may highlight the limitations of trials that use a *placebo* comparator rather than an alternative

active agent. Specifying that you are interested in patient-important outcomes (such as long bone fractures) identifies the limitations of studies that focus on *substitute* or *surrogate end points* (such as bone density). Specifying that you are primarily interested in avoiding progression to dialysis will make you appropriately wary of a *composite end point* of progression to dialysis or doubling of serum creatinine level. You will not reject such studies out of hand, but the careful definition of the question will help you to critically apply the results to your patient care.

A final crucial benefit from careful consideration of the question is that it sets the stage for efficient and effective literature searching to identify and retrieve the current best evidence (see Chapter 4, Finding Current Best Evidence). Specifying a structured question and identifying an appropriate study design to answer it will allow you to select and use searching resources efficiently and thus enhance your evidence-based practice.

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4 Finding Current Best Evidence

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IN THIS CHAPTER

(continued on following page)

INTRODUCTION

Searching for Evidence: A Clinical Skill

Searching for current best evidence in the medical literature has become a central skill in clinical practice.[1,2] On average, clinicians have 5 to 8 questions about individual patients per daily shift[3-5] and regularly use online *evidence-based medicine* (EBM) resources to answer them.[6-9] Some now even consider that "the use of search engines is as essential as the stethoscope."[10]

However, because of the increasing volume of new literature and speed of new research, finding useful evidence efficiently remains challenging. Approximately 2000 new articles are indexed in PubMed every day,[10] and although few of them directly inform clinical practice, as many as 75 are *randomized clinical trials* and 11 are *systematic reviews*.[11] These numbers explain why searching in PubMed is not the most efficient way to look for evidence-based answers. For example, when typing "stroke prevention in atrial fibrillation" in PubMed, you will see that current best evidence is literally lost in an output of almost 4000 citations, with a mix of trials, reviews, guidelines, and editorials that are impossible to screen for relevance during your daily practice.

Fortunately, numerous EBM resources now provide shorter and more efficient paths. These resources select, process, and organize the evidence; some, however, are more trustworthy than others. This chapter will help you navigate through existing EBM resources, distinguish the trustworthy from the less trustworthy, and maximize your chances of quickly finding answers based on current best evidence.

Start by Clarifying the Question

As we have seen in Chapter 3, What Is the Question? framing the question appropriately is an important prerequisite to any search. An initial distinction to make is whether you are asking a *background question* (eg, definition or pathophysiology

of a syndrome or mechanism of a treatment modality) or a *foreground question* (eg, targeted questions of therapy, *harm*, diagnosis, or *prognosis* that provide the evidentiary basis for decision making). Although some EBM resources also answer background questions, this chapter, and the *Users' Guides to the Medical Literature* overall, focuses on efficiently finding answers to foreground questions.

Foreground questions often arise in a form that does not facilitate finding an answer (see Chapter 3, What Is the Question?). A first step is to translate and structure the question into its components, using the *PICO* framework, which accounts for the patient or population, the intervention or exposure, the comparator, and the outcomes (see Chapter 3, Box 3-1). When framing your question, remember to consider all *patient-important outcomes*. Doing so will guide you in selecting the body of evidence that adequately addresses your patient's dilemma between benefits and harms that matter to your patient's decision.

Structuring the question will not only clarify what you are looking for but also help you formulate relevant search terms and combine them into search strategies, adapted to each type of EBM resource. We explore, toward the end of this chapter (see Translating a Question Into Search Terms), how the issues of question formulation and choice of search strategies become particularly crucial when evidence is harder to find using preappraised resources and you need to search in larger databases, such as PubMed. Finally, clarifying your question will help you search for appropriate study designs (see Chapter 3, What Is the Question?) and select corresponding search filters (eg, Clinical Queries) to reduce the number of citations in search outputs and enhance your chances of finding the best relevant evidence.

Searching the Medical Literature Is Sometimes Futile

Consider the following clinical question: "In patients with pulmonary embolism, to what extent do those with pulmonary

infarction have a poorer *health outcome* than those without pulmonary infarction?"

Before beginning your search to answer this question, you should think about how investigators would differentiate between those with and without infarction. Because there is no definitive method, short of autopsy, to make this differentiation, our literature search is doomed before we begin.

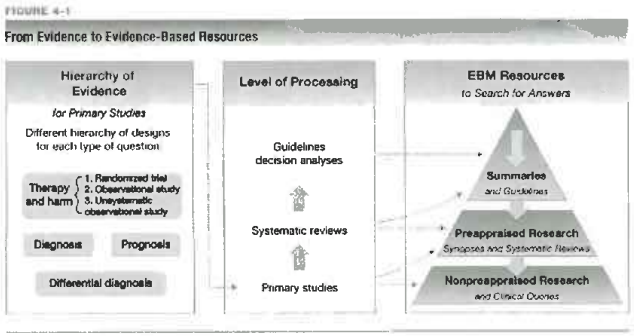
This example illustrates that the medical literature will not help you when no feasible study design or measurement tools exist that investigators could use to resolve an issue. Your search also will be futile if no one has conducted and published the necessary study. Before embarking on a search, carefully consider whether the yield is likely to be worth the time expended.

HOW EVIDENCE IS PROCESSED AND ORGANIZED INTO EBM RESOURCES

Evidence-based medicine resources are rapidly evolving and provide innovative solutions to deal with the production, summary, and appraisal of the evidence.[1] Numerous EBM resources are currently available. To clearly see how to navigate across available resources, we offer 3 classification systems: (1) *hierarchy of evidence* in primary studies, (2) level of processing of the evidence, and (3) categories of EBM resources (Figure 4-1). Together, these 3 classification systems describe the flow of evidence from primary studies to existing EBM resources.

Hierarchy of Evidence

At the level of *primary studies*, our first classification relates to the hierarchy of evidence (Figure 4-1, left box). For each type of question, EBM suggests a hierarchy of research designs to minimize the *risk of bias*. For questions regarding therapy or harm, well-conducted randomized clinical trials are superior



to *observational studies*, which are superior to unsystematic clinical observations. Questions of diagnostic test properties, *differential diagnosis*, or prognosis require different hierarchies of study design (see Chapter 2, What Is Evidence-Based Medicine?).

Furthermore, within each type of design, some studies provide evidence of higher quality than others. The ideal EBM resource should facilitate access to studies with the most appropriate design and lowest risk of bias.

Levels of Processing

A second classification refers to the level of processing of the evidence (Figure 4-1, middle box). Primary studies can stand alone or be processed into systematic reviews. On the basis of clear eligibility criteria, authors of a systematic review conduct a comprehensive search for all primary studies, critically appraise their quality, and, when it is considered appropriate, provide a summary estimate of effects across studies. Well-conducted systematic reviews are far more useful than single primary studies because they represent the entire body of relevant evidence (see Chapter 14, The Process of a Systematic Review and Meta-analysis). Searching for systematic reviews instead of primary studies will save you substantial time and effort.

A further level of processing is to move from evidence (ideally systematic reviews) to recommendations for practice, as in *clinical practice guidelines* (see Moving From Evidence to Action). Providing recommendations requires judging the relative desirability of alternative courses of action. Therefore, this level of processing requires looking at the entire body of evidence, integrating and appraising the evidence from systematic reviews for each patient-important outcome, taking into account patient *values and preferences*, and being mindful of resource considerations. *Decision analyses* (see Chapter 17, How to Use a Patient Management Recommendation: Clinical Practice Guidelines and Decision Analyses) and health technology assessment

reports also may provide a similar level of processing of the evidence. As for primary studies, some guidelines are more trustworthy than others, and the ideal EBM resources should provide access to the more trustworthy ones.

Pyramid of EBM Resources

Although the 2 previous classifications—the hierarchy of evidence and level of processing—help you decide what type of evidence is likely to answer your question, they do not inform you of where to search for the evidence. For example, you may wonder where to search for high-quality systematic reviews. Should you start your search in the Cochrane Library, use review filters in PubMed, or look in the reference list of an online summary such as UpToDate? To make that choice, you need to understand how evidence is organized into a third classification: the *pyramid of EBM resources* (Figure 4-1, right box). From a practical perspective, resources can be viewed in 3 broad categories: summaries and guidelines, preappraised research, and nonpreappraised research.

Table 4-1 outlines these categories of EBM resources. Box 4-1 and the subsequent paragraph provide a fuller description of each category with examples of resources.

You can navigate efficiently across these different types of resources, as well as search all 3 categories simultaneously, using *federated search engines*, such as ACCESSSS (http://plus.mcmaster.ca/accessss), Trip (http://www.tripdatabase.com), Sum Search (http://sumsearch.org), or Epistemonikos (http://www.epistemonikos.org). Before we describe these search engines in detail, we will look at general criteria that will help clinicians choose which EBM resources to select given their question and which to avoid.

To complement resources that help you answer clinical questions, additional resources can link the evidence with your daily practice, such as *clinical decision support systems*[15] or context-specific access to online resources within electronic

TABLE 4-1
Categories of EBM Resources

Category	Layers*	Description	Examples
Summaries and guidelines	Online summary resources Databases of clinical practice guidelines	Summary of the body of evidence at a topic-level (not limited to a question, intervention, or outcome) Often with actionable recommendations for clinical decision making Regularly updated	UpToDate DynaMed Clinical Evidence Best Practice US National Guidelines Clearinghouse
Preappraised research	Synopses of systematic reviews Systematic reviews Synopses of studies	Structured abstracts or 1-page summaries of selected systematic reviews or studies Various degrees of preappraisal – Selection according to methodologic criteria – Clinicians' ratings – Clinicians' comments – Experts' structured appraisal Continuously updated Source of evidence alerts	 ACP Journal Club McMaster *PLUS* DARE Cochrane Evidence Updates

(Continued)

TABLE 4-1

Categories of EBM Resources *(Continued)*

Category	Layers*	Description	Examples
Nonpreappraised research	Filtered studies	All primary studies with no preappraisal	PubMed (MEDLINE) CINAHL CENTRAL
	Unfiltered studies	Automatic filtering of databases for specific study designs or clinical content	Filters Clinical Queries in PubMed
Federated searches	All layers of resources searched at once	Search engines that retrieve evidence from summaries and preappraised and nonpreappraised research, and organize the results accordingly	ACCESSSS Trip SumSearch Epistimonikos

Abbreviations: ACCESSSS, ACCess to Evidence-based Summaries, Synopses, Systematic Reviews and Studies; CENTRAL, Cochrane Central Register of Controlled Trials; CINAHL, Cumulative Index to Nursing and Allied Health Literature; DARE, Database of Abstracts of Reviews of Effects

*These layers correspond to the 6-S pyramid from Haynes et al.[17]

BOX 4-1

Overview of EBM Resources

1. Summaries and guidelines.

Summaries are regularly updated online resources that aim to integrate the body of evidence at a topic level for several related questions. For example, a topic such as "treatment of type 2 diabetes mellitus in the elderly patient" will usually summarize evidence for drug therapy, strategies to control glycemic levels and avoid hypoglycemia, and lifestyle modification and the reduction of cardiovascular risk. These summaries often provide actionable recommendations for practice. Current examples widely used by clinicians include UpToDate (http://www.uptodate.com), DynaMed (https://dynamed.ebscohost.com), and Best Practice (http://bestpractice.bmj.com).

Guidelines follow a similar approach, usually focused on a specific topic or disease (eg, "antithrombotic therapy and prevention of thrombosis"[12]). Even more than summaries, guidelines are focused on providing recommendations for optimal patient management. Searching for available guidelines is more challenging because they are scattered across specialty journals and organization websites. A useful resource to search for guidelines is the US National Guideline Clearinghouse (http://www.guideline.gov), which includes guidelines from many countries.

2. Preappraised research.

When summaries or guidelines do not provide a satisfactory answer (eg, they provide an answer that is apparently not based on current best evidence or do not provide an answer at all), you must look directly at research findings, first from systematic reviews and then, if necessary, from primary studies. Many resources can prevent the unpleasant experience of searching the whole medical literature (at the risk of getting lost) or having to screen and read articles as PDFs. These resources select only

systematic reviews and studies that meet defined methodologic criteria and provide synopses—a 1-page structured abstract or description of reviews or studies. The degree and quality of preappraisal vary across resources. Some provide clinicians' ratings or short comments on relevance or newsworthiness, whereas others include a structured appraisal from experts. An example of the former is McMaster *PLUS* (Premium LiteratUre Service[13,14]; http://plus.mcmaster.ca/evidenceupdates), and examples of the latter are *ACP Journal Club* (http://acpjc.acponline.org) and DARE (Database of Abstracts of Reviews of Effects; www.crd.york.ac.uk/crdweb). You can access preappraised research in 2 complementary ways: by searching these specific databases for a given question and, for some of them, by subscribing to an e-mail alerting system. Personalized alerts are an efficient way to remain up-to-date on important new research in your area of interest (see, for example, BMJ EvidenceUpdates; http://plus.mcmaster.ca/evidenceupdates).

3. Nonpreappraised research.

Only when other sources have failed to provide an answer should you search for primary studies in the larger databases, such as MEDLINE (http://www.ncbi.nlm.nih.gov/pubmed) or CINAHL (http://www.cinahl.com). Because these databases include millions of articles, using them efficiently requires more advanced searching skills. Limiting your search with filters, such as Clinical Queries (http://www.ncbi.nlm.nih.gov/pubmed/clinical), provides a useful way to reduce the number of abstracts you need to review to identify the best evidence to address your clinical question.

medical records.[16] However, although some clinical decision support systems have the potential to improve processes of care or patient outcomes,[17] most cover only a limited range of clinical problems, are not necessarily based on current best evidence, and are often "homebuilt" so that their use is questionable.[1]

THREE CRITERIA FOR CHOOSING AN EBM RESOURCE

All EBM resources are not equally trustworthy, and none provide answers to all questions. Efficient searching involves choosing the appropriate resources for your clinical question—in much the same way you choose diagnostic tests appropriate for your patient's symptoms. Table 4-2 offers an initial guideline for making resource choices.

Based on Current Best Evidence

Many online summaries and guideline websites promote themselves as "evidence-based," but few have explicit links to research

TABLE 4-2

Selection Criteria for Choosing or Evaluating EBM Resources

Criterion	Description of Criterion
On the basis of current best evidence	How strong is the commitment to evidence to support inference?
	Does it have citations to references to all evidence summaries and recommendations?
	Is the process for keeping it up-to-date transparent and trustworthy?
	Is the quality of the evidence assessed?
	Is the strength of recommendations reported?
	Are numerical effect estimates reported for patient important outcomes?
Coverage and specificity	Does the resource cover my discipline and specific area of practice adequately?
	Does it cover questions of the type I am asking (eg, therapy, diagnosis, prognosis, harm)?
Availability and access	Is it readily available in all locations in which I would use it?
	Can I easily afford it?

findings. To judge the strength of the commitment to evidence to support inference, check whether you can distinguish statements that are based on high-quality vs low-quality evidence. If you cannot make this distinction, dismiss the resource altogether. Resources should provide citations to references to relevant research findings. Currency is important, and a simple way to judge whether the evidence is up-to-date is to look for the date of the most recent reference cited: if it is more than 2 years old, it is possible that future studies lead to a different conclusion.[1,18,19] Generally, the process for keeping a resource up-to-date should be transparent and trustworthy. A date stamp should accompany each summarized topic or piece of evidence (eg, "This topic last updated: Sep 17, 2013"), along with access to the explicit mechanism used to screen for related new findings. An opaque process should raise a red flag that the evidence may be partial, biased, or already outdated.

A summary or guideline should use a rating system to assess the risk of bias of cited studies and the quality of reviews. Resources that provide recommendations should be based on the entire body of existing evidence, ideally summarized in systematic reviews, and provide the benefits and harms of available options. The resources also should use an appropriate system to grade strength of recommendations and provide explicit judgments concerning underlying values and preferences (see Moving From Evidence to Action). Finally, to be actionable, the recommendations should report numerical effect estimates for patient-important outcomes to support clinical judgment and shared decision making at the point of care. For example, the ninth edition of the Antithrombotic Therapy and Prevention of Thrombosis guideline issued a weak recommendation for aspirin for primary prevention of cardiovascular events in people older than 50 years, based on moderate confidence in estimates of effect (grade 2B).[20] The authors provide numerical estimates: for example, in people at moderate risk of cardiovascular events, prophylactic aspirin resulted in 19 fewer myocardial infarctions per 1000 (from 26 fewer to 12 fewer) but 16 more major extracranial bleeds per 1000 (from 7 more to 20 more).

Coverage and Specificity

An ideal resource will cover most of the questions relevant to your practice—and not much more. However, few, if any, resources are sufficient as such a one-stop shop for the evidence you need,[18] and resources from the 3 levels of the pyramid of EBM resources are often complementary. The higher you look in the pyramid, the more time it takes for the resource developers to process and summarize the evidence at a topic level, making these resources potentially out of date. To be comprehensive in your searching, you will need to look for preappraised research for more recent evidence. Conversely, the lower you look in the pyramid, the larger, and often less specific, the resource. Thus, preappraised research limited to your area of practice, such as collections of synopses designed to help you keep up with information on the latest developments in a specific field or specialty—eg, *Evidence-Based Mental Health* (http://ebmh.bmj.com) or *Evidence-Based Nursing* (http://ebn.bmj.com)—may serve your needs efficiently.

The type of question also will affect your choice of a specific resource. For example, resources that focus on management issues informed mainly by randomized clinical trials, such as the Cochrane Database of Systematic Reviews, may not be ideal to answer questions of harm or rare adverse events. Similarly, background questions are more likely to be answered by summaries (eg, UpToDate or DynaMed) than preappraised research (eg, systematic reviews or synopses). For example, if you have background questions about the Middle East respiratory syndrome coronavirus, both UpToDate and DynaMed have a dedicated entry on the topic that summarizes its case definition and the incidence of recent clusters.

Availability and Access

The most trustworthy and efficient resources are frequently expensive, particularly those at the top of the pyramid of EBM resources. For example, an individual subscription to an online

summary often costs more than $250 annually. To establish your information resource regimen, you can map the EBM resources that are accessible to you through your university, school, or clinical institution and check whether they meet your information needs. Academic clinicians typically have access to the resources of their academic institution or hospital libraries, including the full texts of many studies and reviews.

Clinicians in private practice in high-income countries may have access to some resources through their professional associations but otherwise may be burdened by the cost of subscriptions. Some countries have national libraries that centralize access to many resources. Often, the institutional choice of resources is not made by practicing clinicians and may be guided by financial constraints. If an important resource is not available, make the case for it to your librarian (and suggest which other resources are less useful in practice).[1] If your institution is not willing to pay a license, consider subscribing individually. Health professionals in lower-income countries may have institutional access to information resources through the World Health Organization's Health InterNetwork Access to Research Initiative (http://www.who.int/hinari/en) or other organizations but otherwise face even greater financial obstacles to information resources. Additional strategies include seeking open-access journals, writing to authors for a reprint or e-print of their article, and contacting colleagues in academic centers who have access to more extensive library facilities.

Preappraised resources are sometimes expensive as well, and therefore we further describe how searching federated search engines, such as ACCESSSS or Trip, can give you an overview of the clinical content of various resources to help you make subscription decisions.

Free e-mail systems, such as BMJ EvidenceUpdates (http://plus.mcmaster.ca/evidenceupdates), can alert you to important new findings, although access to full texts will vary according to your institutional or personal licenses. An increasing number of full-text articles are accessible through PubMed or Google Scholar or directly via open-access journals (eg, *CMAJ*, PLOS journals, and BioMed Central journals; see http://www.doaj.org for a directory of open-access journals). Many other journals provide free access to full-text articles 6 to 12 months after publication (eg, *BMJ*, *JAMA*, and *Mayo Clinic Proceedings*) or a portion of their content at the time of publication. However, focusing on free full-text articles and free Internet resources may give a partial and potentially biased view of current best evidence.[21]

Finally, ask your institution or professional organization how to access EBM resources at the point of care and obtain proxy server permission or remote access at home (eg, using a VPN connection). This will give you direct access to evidence on your smartphone and tablets and considerably enhance your *evidence-based practice.*

USING THE PYRAMID OF EBM RESOURCES TO ANSWER YOUR QUESTIONS

Numerous EBM resources are available, including many providers of summaries at the top level of the pyramid. Each has a different clinical scope, as well as different methodologic and editorial processes. No single portal lists them all, but many can be found through the New York Academy of Medicine (http://www.nyam.org/fellows-members/ebhc/eb_resources.html) or the Cochrane Collaboration (http://www.cochrane.org/about-us/webliography-evidence-based-health-care-resources) websites.

It is beyond the scope of this chapter to discuss the pros and cons of each resource. Instead, we will focus on how to navigate across the pyramid of EBM resources and discuss how these resources can complement each other. We provide examples of resources to illustrate important aspects both from research on evidence retrieval and from our own practice but do not aim to be comprehensive or prescriptive on which resource to use.

Summaries and Guidelines

Start your searches by using resources at the top of the pyramid for summaries and guidelines that address your question. These resources can provide a comprehensive view of the body of evidence at a topic level. Imagine, for example, that you are looking for antithrombotic therapies most appropriate for prevention of stroke in patients with atrial fibrillation. Available options include aspirin; other antiplatelet agents, such as clopidogrel; a combination of aspirin plus other antiaggregants; warfarin; or new anticoagulants, such as direct thrombin inhibitors or factor Xa inhibitors. To fully address your question from lower levels of the pyramid, you would need to retrieve, read, and integrate several systematic reviews or trials that cover all of the relevant comparisons and important outcomes. Summaries and guidelines aim to integrate this body of evidence and also often provide actionable recommendations for practice.

Table 4-3 lists examples of 10 widely used online summaries and their corresponding URLs. A recent analytical survey compared them on 3 aspects: the timeliness of updates, coverage of clinical topics, and quality of processing and reporting of the evidence.[19] At the time of this assessment (2011), the mean time since update ranged from 3.5 months (DynaMed) to 29 months (First Consult), and the percentage of clinical topics covered ranged from 25% (Clinical Evidence) to 83% (UpToDate). Quality substantially varied across the resources. For example, despite its limited coverage, the authors rated Clinical Evidence as the highest-quality resource. Because EBM resources continuously evolve, these numbers may be outdated but illustrate that online summaries can be complementary. Summaries also differ on their methods and commitment to providing actionable recommendations (eg, UpToDate now formulates recommendations using the *GRADE* [*Grading of Recommendations Assessment, Development and Evaluation*] framework, whereas

TABLE 4-3
Rank Orderings of 10 Online Summaries Compared on 3 Aspects[19]

Summary Resource	URL	Updates	Coverage, No. (%)	Quality
DynaMed	https://dynamed.ebscohost.com	1	3 (70)	2
UpToDate	http://www.uptodate.com	5	1 (83)	2
Micromedex	http://www.micromedex.com	2	8 (47)	2
Best Practice	http://bestpractice.bmj.com	3	4 (63)	7
Essential Evidence Plus	http://www.essentialevidenceplus.com	7	7 (48)	2
First Consult	http://www.firstconsult.com	9	5 (60)	2
Medscape Reference	http://reference.medscape.com	6	2 (82)	9
Clinical Evidence	http://clinicalevidence.bmj.com	8	10 (25)	1
ACP PIER	http://acpjc.acponline.org	4	9 (33)	7
PEPID	http://www.pepidonline.com	NA	6 (58)	10

Abbreviation: NA, data not available.
Reproduced with permission from the *Journal of Clinical Epidemiology*.[19]

Clinical Evidence focuses more on the summary of evidence, also using GRADE) and their editorial style (eg, structured bullet points in DynaMed and Best Practice vs textbook-like structured chapters in UpToDate).

Unlike summaries, most guidelines are scattered across journals or websites from individual countries or health organizations. One of the most comprehensive portals to search for guidelines is the US National Guideline Clearinghouse (http://www.guideline.gov). It includes the full text of many US guidelines and thousands of international guidelines. Searching is easy, although initial retrievals are often relatively large. Other international guidelines can be found through the UK National Institute for Health and Care Excellence (https://www.evidence.nhs.uk) or the Guideline International Network (http://www.g-i-n.net/library/international-guidelines-library).

Perhaps even more than other types of preappraised evidence, practice guidelines are extremely variable in their trustworthiness.[22,23] When you conduct your search, look for guidelines that are transparent in how they process the evidence and formulate recommendations (see Chapter 17, How to Use a Patient Management Recommendation: Clinical Practice Guidelines and Decision Analyses). The US National Guideline Clearinghouse website also allows side-by-side comparisons of the guideline process and components for guidelines on the same topic.

Finally, the top of the EBM pyramid also includes decision analyses, which process a body of evidence in a similar way to guidelines, map out the options with outcomes and probabilities, and help you judge the benefits and harms of different treatment options for a specific patient (see Chapter 17, How to Use a Patient Management Recommendation: Clinical Practice Guidelines and Decision Analyses). These decision analyses often can be found in stand-alone studies, *economic evaluation* reports, and health technology assessment reports. An efficient way to locate decision analyses is through the Centre for Reviews and Dissemination at the UK University of York (http://www.crd.york.ac.uk/crdweb) by selecting the search filters "HTA" and "NHS EED" (for economic evaluation).

Preappraised Research

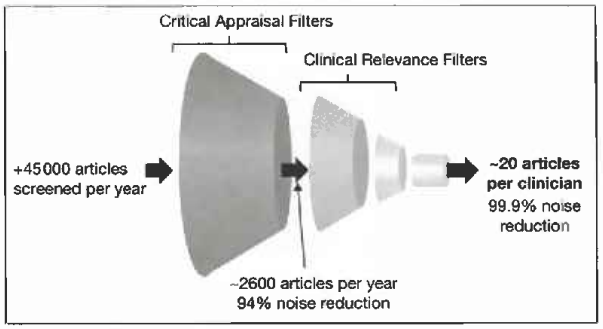
If you do not find a satisfactory answer in summaries or guidelines, either because your question is not covered or because you have reasons to doubt what you found, you may need to look for preappraised research. You also might search preappraised research to look for more recent evidence published since the summary or guideline was last updated.[24] You might wonder how often this additional searching would be worth the trouble. A recent study of the quality of online summaries found that, on average, new high-quality evidence providing potentially different conclusions than existing summaries was available for approximately 52% of the topics evaluated in UpToDate, 60% in Best Practice, and 23% in DynaMed.[18] This potential discrepancy between newly published evidence and existing recommendations would occur more frequently, and likely with greater adverse consequences, for most clinical practice guidelines, which are usually updated every 2 to 8 years.[25]

Consider, for example, the question of whether cardiac resynchronization therapy (CRT) reduces mortality in patients with heart failure and a narrow QRS complex. An initial search in mid-September 2013 in DynaMed or UpToDate provided an excellent summary of available evidence on the efficacy of CRT according to the degree of heart failure and the QRS duration but did not yet identify a more recent trial published in the *New England Journal of Medicine*.[26] This trial found that CRT did not reduce the composite rate of death or hospitalization for heart failure and actually may increase mortality. This important new evidence will of course be included in subsequent updates, but this process typically takes a couple of months to up to 29 months, depending on the online summary.[19]

A quick and efficient way to find preappraised research is to search specific databases, which include only studies and reviews that are more likely to be methodologically sound and clinically relevant. Figure 4-2 shows a typical example of this improved selection process from McMaster *PLUS* (Premium

FIGURE 4-2

Example of Preappraised Research: McMaster PLUS



Reproduced with permission of the Health Information Research Unit, McMaster University.

LiteratUre Service), a large database created by the McMaster Health Knowledge Refinery (http://hiru.mcmaster.ca/hiru/HIRU_McMaster_PLUS_Projects.aspx). The selection process used is as follows: trained research staff continually critically appraise more than 45 000 articles per year, from more than 125 empirically selected, high-quality clinical journals, and identify studies and systematic reviews that meet prespecified methodologic standards. For example, studies of prevention or therapy must have random allocation, a follow-up rate of at least 80%, and at least 1 patient-important outcome. These selected articles are then rated for relevance and newsworthiness by frontline clinicians from around the globe.[27] McMaster *PLUS* is thus a continuously updated database of more than 32 000 highly selective articles (with approximately 3300 added every year) that also feeds several other EBM resources and journals (eg, *ACP Journal Club*, Clinical Evidence, and DynaMed). A simple way to access McMaster *PLUS* is through the free search

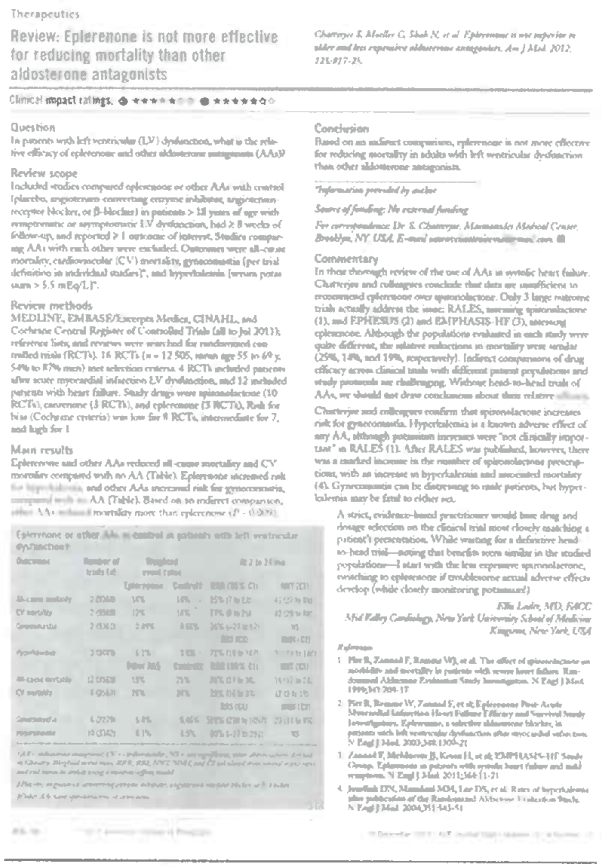
engine of BMJ EvidenceUpdates (http://plus.mcmaster.ca/EvidenceUpdates/QuickSearch.aspx) or through the McMaster search engine, ACCESSSS, which we discuss further below (see Searching All Levels of the Pyramid at the Same Time). McMaster *PLUS* also has distinct databases for nursing (http://plus.mcmaster.ca/np) and rehabilitation studies (http://plus.mcmaster.ca/rehab).

In a further level of preappraisal, the more clinically relevant studies and systematic reviews are selected to become *synopses* (<1% of the initial selection). These synopses are usually a 1-page, structured summary of the research findings, along with a brief commentary from an expert in the field. You can find various types of synopses in specialized evidence-based *secondary evidence-based journals*. Figure 4-3 shows an example of a synopsis of a systematic review from *ACP Journal Club* (http://acpjc.acponline.org) on the impact of eplerenone on mortality compared with other aldosterone antagonists in heart failure. The abstract summarizes salient elements of the methods and results and an expert provides a commentary. This appraisal is not always systematic or as thorough as a full critical appraisal, but it usually provides the gist of the strengths and weaknesses of a study. Similar resources include *Evidence-Based Medicine* (http://ebm.bmj.com), *Evidence-Based Mental Health* (http://ebmh.bmj.com), *Evidence-based Oncology* (www.sciencedirect.com/science/journal/13634054), or POEMs (Patient-Oriented Evidence that Matters) (www.essentialevidenceplus.com/content/poems). The New York Academy of Medicine keeps a current list of specialized EBM journals in many health care disciplines (www.nyam.org/fellows-members/ebhc/eb_publications.html).

When searching preappraised research, make synopses of systematic reviews your first priority because they summarize the body of evidence on a question. In addition to evidence-based journals, you can find synopses of systematic reviews in DARE (Database of Abstracts of Reviews of Effects) (http://www.cochrane.org/editorial-and-publishing-policy-resource/database-abstracts-reviews-effects-dare). If no synopses answer

FIGURE 4-3

Example of Synopsis of a Systematic Review From *ACP Journal Club*



Therapeutics

Review: Eplerenone is not more effective for reducing mortality than other aldosterone antagonists

Clinical impact ratings.

Question

Review scope

Review methods

Main results

Conclusion

Commentary

Reproduced with permission of *ACP Journal Club*.[28]

your question, move to a direct search for other systematic reviews. A useful resource is the Cochrane Library (http://www.thecochranelibrary.com).

Regardless of the resources you use, remember that preappraisal and the collection of these synopses can only increase the likelihood of finding sound evidence efficiently. It does not guarantee it. You should also apply your own critical appraisal to the research findings that are summarized, as explained throughout the *Users' Guides to the Medical Literature*.

Alerts to Important New Evidence

In addition to building continuously updated databases of preappraised research, an increasing number of resources offer e-mail *alerting services*. To make the volume of new evidence manageable, these alerts are usually tailored to your information needs when you register (eg, clinical disciplines, quality choices, and frequency of alerts).

For example, the whole process leading to McMaster *PLUS*, including clinicians' ratings for relevance and newsworthiness, results in up to a 99.9% noise (non–clinically relevant) reduction and produces a manageable stream of approximately 20 to 50 key articles per year in a clinical area that may influence your practice (Figure 4-2).[28] You can receive these alerts by subscribing to BMJ EvidenceUpdates or ACCESSSS. Several other free or fee-based alerting systems are available for both a wide scope of disciplines (eg, NEJM Journal Watch, http://www.jwatch.org) and specific subspecialties (eg, OrthoEvidence, http://www.myorthoevidence.com). When using any of these alerting resources, check whether their process of selecting and appraising the evidence is explicit, trustworthy, and meeting your needs.

Nonpreappraised Research

Only when summaries, guidelines, and preappraised research have failed to provide an answer should you search among the

tens of millions of nonpreappraised research articles. They are stored in many different databases (the ones usually searched in systematic reviews), such as PubMed's MEDLINE, EMBASE, CINAHL, or Web of Science. These databases can be accessed directly or through different search engines. Some search engine companies, such as Ovid (http://www.ovid.com), are designed to facilitate complex search strategies, such as those done by medical librarians or authors of systematic reviews. For clinical purposes, PubMed is the most popular search engine, providing free access to the entire MEDLINE database (http://www.ncbi.nlm.nih.gov/pubmed).

Consider, for example, the question of whether statins can prevent dementia. Summaries and preappraised research provide limited or selected evidence to answer that question. Because of its volume, searching PubMed to find relevant evidence requires more advanced searching skills, particularly in the choice and combination of search terms. Simple searches typically yield large outputs with few easily identified relevant studies in the first pages.

To limit irrelevant studies in the outputs, use methodologic filters, such as Clinical Queries. As shown in Figure 4-4, instead of typing your search terms on the main page of PubMed, select Clinical Queries or go directly to http://www.ncbi.nlm.nih.gov/pubmed/clinical. Empirically validated "methods" search terms are added to your search, according to your type of question. For example, Table 4-4 lists the filters used for questions of therapy that facilitate the retrieval of randomized clinical trials.[29] Two filters are available for each search category, 1 broad (sensitive) and 1 narrow (specific), the latter being more adapted to clinical practice. Use of a filter will increase the proportion of relevant studies from approximately 2% to 30% in the first 2 pages of PubMed's output (first 40 citations).[2] Similar filters are available for questions of diagnosis, etiology, prognosis, and *clinical prediction rules*.

Table 4-5 lists similar broad and narrow filters to find systematic reviews from PubMed.[30] In contrast with Clinical Queries,

FIGURE 4-4

Clinical Queries in PubMed. Accessing From Main Page and Choosing of Filter (Category and Scope)

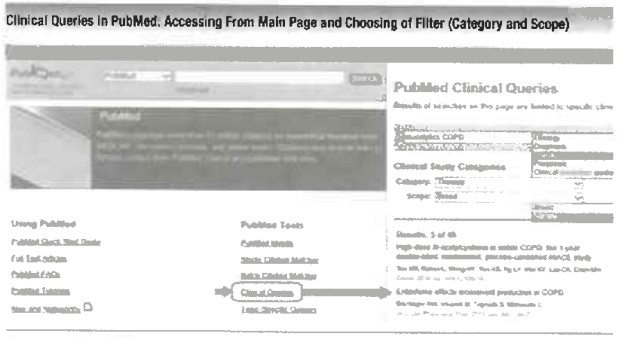


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TABLE 4-4

Clinical Queries "Therapy" Filter: Performance and Strategy Used[a]

	Sensitivity, %	Specificity, %	PubMed Equivalent
Broad filter	99	70	((clinical[Title/Abstract] AND trial[Title/Abstract]) OR clinical trials[MeSH Terms] OR clinical trial[Publication Type] OR random*[Title/Abstract] OR random allocation[MeSH Terms] OR therapeutic use[MeSH Subheading])
Narrow filter	93	97	(randomized controlled trial[Publication Type] OR (randomized[Title/Abstract] AND controlled[Title/Abstract] AND trial[Title/Abstract]))

Abbreviation: MeSH, medical subject headings.

[a]Reproduced with permission of the US National Library of Medicine and PubMed.

these filters are not implemented in PubMed; the search strategy needs to be copied and pasted right after your search. Going back to our example of the search phrase "statins for the prevention of dementia," an unfiltered search retrieves hundreds of citations that cannot be reliably screened in clinical practice. When adding the narrow filter of Table 4-5 to your search, the output shrinks to 19 citations (in October 2013), and a quick review will identify 6 systematic reviews, including 1 Cochrane Review, updated in 2009, and the most recent review, published in *Mayo Clinic Proceedings* in September 2013, Statins and Cognition: A Systematic Review and Meta-analysis of Short- and Long-term Cognitive Effects. The University of York keeps a comprehensive list of available filters and the publications that describe

TABLE 4-5

Filters to Retrieve Systematic Reviews From PubMed[a30]

	Sensitivity, %	Specificity, %	PubMed Equivalent
Broad filter	99.9	52	search*[Title/Abstract] OR meta analysis[Publication Type] OR meta analysis[Title/Abstract] OR meta analysis[MeSH Terms] OR review[Publication Type] OR diagnosis[MeSH Subheading] OR associated[Title/Abstract]
Narrow filter	71	99	MEDLINE[Title/Abstract] OR (systematic[Title/Abstract] AND review[Title/Abstract]) OR meta analysis[Publication Type]

Abbreviation: MeSH, medical subject headings.

[a]These filters are not implemented in PubMed; the search strategy needs to be copied and pasted right after the search to optimally filter systematic reviews. Reproduced with permission from the *BMJ*.

their development and validations. For example, in addition to the ones we have already discussed, you will find filters for adverse events, economic evaluation, observational studies, and even qualitative studies (https://sites.google.com/a/york.ac.uk/issg-search-filters-resource/home/search-filters-by-design).

Another useful database for clinical practice is the Cochrane Controlled Trials Registry, the largest electronic compilation of controlled trials, built from MEDLINE, EMBASE, and other sources, including hand searches of most major health care journals. Because it includes only trials, this registry is the fastest, most reliable method of determining whether a controlled trial has been published on any topic. You can search the registry

in the Cochrane Library's advanced search function (http://onlinelibrary.wiley.com/cochranelibrary/search; select "Search Limits," then "Trials"). However, to access the full text of articles, you will need a subscription to the Cochrane Library or several Ovid Evidence-Based Medicine Review packages of databases (http://www.ovid.com/site/catalog/DataBase/904.jsp).

Searching All Levels of the Pyramid at the Same Time

At this point, you may wonder if you can search across all levels of the pyramid of resources, instead of having sequential searches in different resources to get the current best evidence. Federated search engines do this easily. One of the most comprehensive and transparent federated resources is ACCESSSS (http://plus.mcmaster.ca/accessss). Typing a single question in ACCESSSS will run parallel searches in major resources from each level of the pyramid, from summaries to all types of preappraised research and all Clinical Queries filters in PubMed. Table 4-6 presents the resources searched by ACCESSSS. Results are given in 1 page organized by level in the pyramid of EBM resources, with the most relevant and useful for clinical practice on the top (see Figure 4-5). Subscribing to ACCESSSS is free, although access to the full text of some resources will depend on institutional or personal subscriptions. To directly link your own subscriptions to all features of ACCESSSS, you can ask to add your institution to its list.

Other interesting and free federated searches that similarly search multiple resources at more or less each level of the pyramid are available. Instead of looking into summaries at the top, Trip (http://www.tripdatabase.com) has an algorithm to retrieve clinical practice guidelines, classified by country, along with many sources of synopses and other preappraised and nonpreappraised research. Its navigation is easy, and additional interesting features include the ability to structure your search with PICO (patient, intervention, comparator, outcome) and tailor your search to issues in developing countries. SumSearch (http://sumsearch.org) shares similar

TABLE 4-6

Example of a Federated Search: EBM Resources Searched in Parallel in ACCESSSS[a]

Summaries	DynaMed
	UpToDate
	Best Practice
	ACP PIER
Preappraised research	
Synopses of systematic reviews	*ACP Journal Club* DARE
	McMaster *PLUS* (including Cochrane reviews)
Systematic reviews	
Synopses of studies	McMaster *PLUS*
Nonpreappraised research	
Filtered studies	Clinical Queries in PubMed
Unfiltered studies	PubMed (MEDLINE)

Abbreviations: ACCESSSS, ACCess to Evidence-based Summaries, Synopses, Systematic Reviews and Studies; DARE, Database of Abstracts of Reviews of Effects; EBM, evidence-based medicine.

[a]Reproduced with permission of the Health Information Research Unit, McMaster University.

features, particularly for the retrieval of practice guidelines, but it organizes output according to level of processing (original studies, systematic reviews, and guidelines; Figure 4-1, middle box). SumSearch is linked to alerts from NEJM JournalWatch (http://www.jwatch.org). Finally, Epistemonikos (http://www.epistemonikos.org) is innovative both in simultaneously searching multiple resources and in indexing and interlinking relevant evidence. For example, Epistemonikos connects systematic reviews and their included studies and thus allows clustering of systematic reviews based on the primary studies they have in common. Epistemonikos is also unique in offering an appreciable multilingual user interface, multilingual search, and translation of abstracts in more than 9 languages.

FIGURE 4-5

Output of a Federated Search in ACCESSSS

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When to Use Google

Google (http://www.google.com) has brought a revolution in the way we search the Internet. Its powerful algorithm retrieves answers to any type of question. Many factors seem to influence its output, including the relevance to your query but also

the number of times a specific website has been previously accessed or cited, the computer IP and server from which you conduct your search, your nationality, and possibly other financial and nonfinancial interests. Because of its lack of transparency, Google is not a reliable way to filter current best evidence from unsubstantiated or nonscientifically supervised sources. When searching the Web, be aware that you are not searching defined databases but rather surfing the constantly shifting seas of electronic communications. The material you need that is supported by evidence may not float to the surface at any particular time.

On the other hand, "Googling" can be useful for defined purposes. It is often the fastest way to answer general background questions, often through multilingual resources such as Wikipedia (http://www.wikipedia.org), or research new topics, conditions, or treatments that have attracted media attention before being included in any EBM resources (eg, at the time of viral outbreaks around the globe, you may have wondered what Middle East respiratory syndrome coronavirus is). Google also can help you refine the wording of your search terms by rapidly finding 1 relevant citation. For example, you might want to learn whether incretins are associated with pancreatic cancer, but you are unclear about the different types of incretins. By searching Google and Wikipedia, you will rapidly remember how to spell (or copy and paste) dipeptidyl peptidase 4 inhibitor or glucagon-like peptide 1 analogs. Finally, Google can be a surprisingly powerful tool to search for uncommon patterns of symptoms and findings by simply typing them together as a query. These uncommon combinations would usually retrieve little or no information in most medical databases. Google can sometimes find the rare citation that would give you a clue about that syndrome.

A better alternative to Google for answering foreground questions is Google Scholar, which applies Google algorithms to scholarly literature (http://www.google.com/scholar). Although Google Scholar's search algorithms are not transparent,

comparisons have found Google Scholar to be comparable to other databases,[31] and an analysis has found increasing evidence that Google Scholar retrieves twice as many relevant articles as PubMed, with almost 3 times greater access to free full-text articles,[32] as well as access to conference abstracts that might be useful for rare topics. Google Scholar has a complex searching system, and the help feature provides useful guidance in refining your searches (http://scholar.google.com/intl/en/scholar/help.html).

TRANSLATING A QUESTION INTO SEARCH TERMS

How to Choose and Combine Search Terms

Table 4-7 illustrates how you can break down a question into its PICO components and corresponding search terms. You next choose and combine search terms into a variety of search strategies, adapted to each resources. One advantage of searching the top EBM resources is that you can keep searches simple because the databases are highly selective and relatively small. One or 2 search terms for the population or problem and for your intervention or exposure will find most relevant topics. For example, if you are interested in the impact of mucolytics on patients with chronic obstructive pulmonary disease (COPD) who are stable, simply searching with the terms "COPD mucolytic" in summaries (eg, UpToDate) and preappraised research (eg, DARE) will usually suffice. Being too specific in your search can cause you to lose important information. In contrast, searching nonpreappraised research (eg, PubMed) usually requires more specific and structured searches.

To find the evidence you need in large databases, your search terms should closely relate to the components of your PICO question (see Chapter 3, What Is the Question?). For some components, the corresponding search terms are straightforward.

TABLE 4-7

Combining Search Terms Into Different Search Strategies

PICO Components		Potential Search Terms
P	Patients with stable chronic bronchitis	COPD OR (chronic bronchitis)
I	Any mucolytic agent	Mucolytic
C	Placebo (and current best care)	Placebo
O	Number of exacerbation, mortality	Exacerbation OR mortality
Level of the Pyramid		**Examples of Search Strategies[a]**
Summaries and preappraised research		Chronic bronchitis mucolytic
		COPD mucolytic
Nonpreappraised research		COPD mucolytic exacerbation
		(COPD OR (chronic bronchitis)) AND mucolytic
		(COPD OR (chronic bronchitis)) AND mucolytic AND exacerbation
		(COPD OR (chronic bronchitis)) AND mucolytic AND (exacerbation OR mortality)

Abbreviation: COPD, chronic obstructive pulmonary disease; PICO, patient or population, intervention or exposure, comparator, and outcome.
[a]OR and AND are Boolean operators in these searches.

For example, if your population is patients with diabetes, you may simply use "diabetes" or "diabetic." Other components of PICO may prove more challenging, such as "antithyroid drug therapy" as an intervention. Indeed, you might choose "antithyroid" as a single term or consider combining several drugs, such as "carbimazole OR propylthiouracil OR methimazole." Notice that the latter example combines search terms with "OR" in capital letters to signify this is a *Boolean operator*: the search

will retrieve studies for either of these treatments. In contrast, adding no operator actually corresponds to linking search terms with "AND." For example, typing "neuraminidase inhibitors" is equivalent to typing "neuraminidase AND inhibitors" and will retrieve only studies that include both terms, instead of all studies that include any type of inhibitor.

Efficient wording of search terms is based in part on your familiarity with the topic but is also based on trial and error. The *Medical Subject Headings* (MeSH) Thesaurus (http://www.nlm.nih.gov/mesh/MBrowser.html) can help you find words generally used by indexers for a given medical concept. A quick Google search often can give you a sense of appropriate wording in a faster way. If you are surprised that a search yields little relevant evidence, ask yourself if you misspelled a term or were too specific (eg, adding too many words that will automatically be linked with "AND"). Definitions also can differ. For example, in MeSH, "ventilation" refers to "supplying a building or house, their rooms and corridors, with fresh air." "Pulmonary ventilation" is the preferred term for clinicians because it indicates "the total volume of gas inspired or expired per unit of time, usually measured in liters per minute."

Broad vs Narrow Searches

Table 4-8 indicates how to refine your search. If you initially found little evidence, you can broaden your search (eg, increase its sensitivity) by adding synonyms for each concept or using truncated terms (eg, diabet* will retrieve diabetes, diabetic, and many other similar terms with different endings). Conversely, if your initial search retrieved too many citations to be screened, you can narrow your search (eg, increase its specificity) by linking more PICO components with "AND" or by adding limits and methodologic filters (eg, narrow Clinical Queries; http://www.ncbi.nlm.nih.gov/pubmed/clinical). More sophisticated approaches include entering PICO components sequentially

TABLE 4-8

Refining the Search Strategy[1,19,30,34]

Ways to Increase Sensitivity	Ways to Increase Specificity
Many search terms for a similar PICO component, linked with "OR"	More PICO concepts linked with "AND": (P) AND (I) AND (C) AND (O)
Truncated terms, wildcards (eg, diabet*, wom?n)	Use of NOT to exclude irrelevant terms
Synonyms (pressure sore, decubitus ulcer)	Use of NOT as Boolean operator
Variant spelling (tumour, tumor)	Limits (date, age group, etc)
Explosion of MeSH terms	Methodologic filters (Clinical Queries)
Use of PubMed "Related citations" or bibliography of relevant articles	Content filters (topic or disease specific)

Abbreviation: MeSH, medical subject headings; PICO, patient or population, intervention or exposure, comparator, and outcome.

according to their importance to obtain a manageable number of articles in large databases, such as PubMed.[33]

Finding Related Articles

When your PubMed search seems laborious, a useful trick is to find at least 1 potentially relevant article to your question and use the "Related citations" feature, as highlighted in Figure 4-6. It will automatically look for other articles that are similar in their titles, abstracts, and index terms. You then can screen the new output and select "Related citations" for each potentially relevant article you find. To keep track of potentially relevant citations, send them to the PubMed clipboard as you screen, and they will be labeled as items in the clipboard (Figure 4-6). This strategy may help you gather relevant articles rapidly in a snowball sampling.

Getting Help

Finally, because of the complexity and interconnections of medical databases, some searches simply require the help of information specialists. In anticipation of such cases in your clinical practice, befriend your medical librarians. They can be a great resource to help answer difficult questions or those that require elaborate search strategies.

FIGURE 4-6

Features in PubMed: Related Citations and Clipboard

A, Link to "Related citations" from a relevant article. B, Dialogue box allowing user to send relevant articles to the clipboard. C, After having sent an article to the clipboard, it is labeled so in the output.

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BOX 4-2

Tips to Help Improve Searching Skills

With the pyramid of EBM resources in mind, map the EBM resources that are accessible to you through your affiliations or personal subscriptions.

Choose which resources you would like to explore next, according to your information needs and the criteria described in this chapter.

Bookmark these resources in the browsers of all of your devices—your desktop computer, smartphone, or tablet. Find out if you can get remote access from your institution and implement it so that access is automatic.

Subscribe to an e-mail alerting system for newly published evidence that is transparent and trustworthy.

Train yourself on questions that are familiar to you and compare EBM resources.

Keep track of your questions. It can enhance your learning and help you reflect back on your evidence-based practice.

Finally, always keep the patient perspective. This will help you focus on the appropriate body of evidence that informs all patient important outcomes, instead of being driven by the evidence that is first presented to you.

CONCLUSION: IMPROVING YOUR SEARCHING SKILLS IN DAILY PRACTICE

Box 4-2 presents a few practical tips to help you improve your searching skills in daily practice. Because of the continuous flow of new research findings of variable quality, finding current best evidence is challenging. However, this process has been greatly facilitated by the development of numerous EBM resources that can provide fast answers at the point of care. No resource is sufficient for all information needs, and you will need to use several in combination to find current best evidence. This chapter provides guidance on how to navigate across the pyramid of resources efficiently, ideally by using federated search engines.

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5 Why Study Results Mislead: Bias and Random Error

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IN THIS CHAPTER

Our clinical questions have correct answers that correspond to an underlying reality or truth. For instance, there is a true underlying magnitude of the impact of β-blockers on mortality in patients with heart failure, the impact of inhaled corticosteroids on exacerbations in patients with asthma, the impact of reamed vs unreamed nailing of tibial fractures, the *prognosis* of patients with hip osteoarthritis, and the diagnostic properties of a pregnancy test. Research studies attempt to estimate that underlying truth. Unfortunately, however, we will never know the exact truth. Studies may be flawed in their design or conduct and introduce *systematic error* (or *bias*). Even if a study could be perfectly designed and executed, the estimated *treatment effect* may miss the mark because of *random error*. The next section explains why.

RANDOM ERROR

Consider a perfectly balanced coin. Every time we flip the coin, the *probability* of it landing with its head up or tail up is equal—50%. Assume, however, that we as investigators do not know that the coin is perfectly balanced—in fact, we have no idea how well balanced it is, and we would like to find out. We can state our question formally: What is the true underlying probability of a resulting head or tail on any given coin flip? Our first experiment addressing this question is a series of 10 coin flips; the result: 8 heads and 2 tails. What are we to conclude? Taking our result at face value, we infer that the coin is very unbalanced (ie, biased in such a way that it yields heads more often than tails) and that the probability of heads on any given flip is 80%.

Few would be happy with this conclusion. The reason for our discomfort is that we know that the world is not constructed so that a perfectly balanced coin will always yield 5 heads and 5 tails in any given set of 10 coin flips. Rather, the result is subject to the play of chance, otherwise

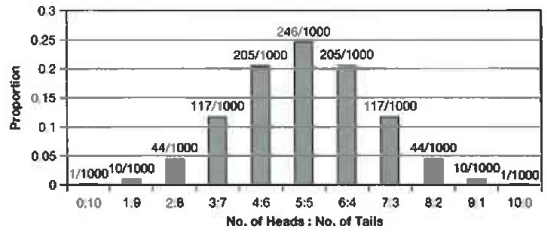
known as random error. Some of the time, 10 flips of a perfectly balanced coin will yield 8 heads. On occasion, 9 of 10 flips will turn up heads. On rare occasions, we will find heads on all 10 flips. Figure 5-1 shows the actual distribution of heads and tails in repeated series of coin flips.

What if the 10 coin flips yield 5 heads and 5 tails? Our awareness of the play of chance leaves us uncertain that the coin is balanced: a series of 10 coin flips of a very biased coin (a true probability of heads of 0.8, for instance) could, by chance, yield 5 heads and 5 tails.

Let us say that a funding agency, intrigued by the results of our first small experiment, provides us with resources to conduct a larger study. This time, we increase the sample size of our experiment markedly, conducting a series of 1000 coin flips. If we end up with 500 heads and 500 tails, are we ready to conclude that we are dealing with a true coin? We are much more confident but still not completely sure. The reason for our remaining uncertainty is that we know that, were the true underlying probability of heads 51%, we would sometimes see 1000 coin flips yield the result we have just observed.

FIGURE 5-1

Theoretical Distribution of Results of an Infinite Number of Repetitions of 10 Flips of an Unbiased Coin



We can apply the above logic to the results of studies that address questions of prognosis, diagnosis, and *harm*, and also to *randomized clinical trials* (RCTs) that address treatment issues. For instance, an RCT finds that 10 of 100 treated patients die during treatment, as do 20 of 100 control patients. Does treatment really reduce the death rate by 50%? Maybe, but awareness of chance will leave us with some degree of uncertainty about the magnitude of the *treatment effect*—and perhaps about whether treatment helps at all.

In a study of congestive heart failure, 228 of 1320 patients (17%) with moderate to severe heart failure allocated to receive *placebo* died, as did 156 of 1327 (12%) allocated to receive bisoprolol.[1] Although the true underlying reduction in the *relative risk* of dying is likely to be in the vicinity of the 32% suggested by the study, we must acknowledge that appreciable uncertainty remains about the true magnitude of the effect (see Chapter 9, Confidence Intervals: Was the Single Study or Meta-analysis Large Enough?).

We have now addressed the question with which we started: "Why is it that no matter how powerful and well designed a study, we will never be sure of the truth?" The answer is that chance is directionless, and it is equally likely, for instance, to overestimate or underestimate treatment effects.

BIAS

Bias is the term we use for the other reason study results may be misleading. In contrast to random error, bias leads to systematic deviations (ie, the error has direction) from the underlying truth. In studies of prognosis, bias leads us to falsely optimistic or pessimistic conclusions about a patient's fate. In studies of diagnosis, bias leads us to an overly optimistic (usually) or

pessimistic assessment of a test's value in differentiating between those with and without a target condition. In treatment or harm studies, bias leads to either an underestimate or an overestimate of the underlying benefit or harm (Box 5-1).

Bias may intrude as a result of differences, other than the *experimental intervention*, between patients in treatment and *control groups* at the time they enter a study. At the start of a study, each patient, if left untreated, is destined to do well—or poorly. To do poorly means to have an adverse event (eg, a stroke) during the study. We often refer to the adverse event that is the focus of a study as the *target outcome* or *target event*. Bias will result if treated and control patients differ in their prognosis (ie, their likelihood of experiencing the target outcome) at the start of the study. For instance, if patients in the control group have more severe atherosclerosis or are older than their counterparts, their destiny will be to have a greater proportion of adverse events than those in the intervention or treatment group, and the results of the study will be biased in favor of the treatment group; that is, the study will yield a larger treatment

BOX 5-1

How Can a Study of an Intervention (Treatment) Be Biased?

Intervention and control groups may be different at the start
- Example: patients in control group are sicker or older

Intervention and control groups may, independent of the experimental treatment, become different as the study proceeds
- Example: patients in the intervention group receive effective additional medication

Intervention and control groups may differ, independent of treatment, at the end
- Example: more sick patients lost to follow-up in the intervention group

effect than would be obtained were the study groups prognostically similar at baseline.

Even if patients in the intervention and control groups begin the study with the same prognosis, the result may still be biased. This will occur if, for instance, effective interventions are differentially administered to treatment and control groups. For instance, in a study of a novel agent for the *prevention* of complications of atherosclerosis, the intervention group might receive more intensive statin therapy than the control group.

Finally, patients may begin prognostically similar, and stay prognostically similar, but the study may end with a biased result. This could occur if, for example, the study loses patients to *follow-up* (see Chapter 6, Therapy [Randomized Trials]) or because a study is *stopped early* because of an apparent large treatment effect.

STRATEGIES FOR REDUCING THE RISK OF BIAS

This book teaches you how to recognize *risk of bias* not only in studies that address issues of therapy and harm but also in studies of prognosis and diagnosis. In studies of prognosis, investigators can reduce bias by enrolling a representative sample and ensuring they are completely followed up. In studies of diagnosis, investigators can ensure that they have chosen an appropriate *criterion* or *gold standard* for diagnosis and that those interpreting test results are unaware of the gold standard findings. In the remainder of this chapter, however, we focus on issues of therapy and harm.

We have noted that bias arises from differences in *prognostic factors* in treatment and control groups at the start of a study or from differences in prognosis that arise as a study proceeds. What can investigators do to reduce these biases? Table 5-1 summarizes the available strategies to reduce biases in RCTs and *observational studies*.

TABLE 5-1
Ways of Reducing Bias in Studies of Therapy and Harm

Source of Bias	Therapy: Strategy for Reducing Bias	Harm: Strategy for Reducing Bias
Differences Observed at the Start of the Study		
Treatment and control patients differ in prognosis	Randomization	Statistical adjustment for prognostic factors in the analysis of data
	Randomization with stratification	Matching
Differences That Arise as the Study Proceeds		
Placebo effects	Blinding of patients	Choice of outcomes (such as mortality) less subject to placebo effects
Cointervention	Blinding of caregivers	Documentation of treatment differences and statistical adjustment
Bias in assessment of outcome	Blinding of assessors of outcome	Choice of outcomes (such as mortality) less subject to observer bias

(Continued)

TABLE 5-1

Ways of Reducing Bias in Studies of Therapy and Harm *(Continued)*

Source of Bias	Therapy: Strategy for Reducing Bias	Harm: Strategy for Reducing Bias
Differences at the Completion of the Study		
Loss to follow-up	Ensuring complete follow-up	Ensuring complete follow-up
Stopping study early because of large effect	Completing study as initially planned by sample size calculation	Not applicable
Omitting patients who did not receive assigned treatment	Including all patients for whom data are available in the arm to which they were randomized	Not applicable

When studying new treatments, investigators can implement a large of number of strategies to limit the risk of bias. They can reduce the likelihood of differences in the prognostic features in treated and untreated patients at baseline by *randomly allocating* patients to the 2 groups. They can balance placebo effects by administering identical-appearing but biologically inert treatments—placebos—to patients in the control group. *Blinding* clinicians to whether patients are receiving active or placebo therapy can eliminate the risk of important *cointerventions*, and blinding outcome assessors minimizes bias in the assessment of event rates.

Investigators studying either treatment effects or harm using observational study designs have far less control over the risk of bias. They must be content to compare patients whose *exposure* is determined by their choice or circumstances, and they can address potential differences in patients' fate only by statistical adjustment for known prognostic factors. Blinding is impossible, so their best defense against placebo effects and bias in outcome assessment is to choose *end points*, such as death, that are less subject to these biases. Investigators who address both sets of questions can reduce bias by minimizing loss to follow-up (Table 5-1).

Note that when investigators choose observational study designs to study treatment issues, clinicians must apply the risk of bias criteria developed primarily for questions of harm. Similarly, if the potentially harmful exposure is a drug with beneficial effects, investigators may be able to randomize patients to intervention and control groups. In this case, clinicians can apply the risk of bias criteria designed primarily for therapy questions. Whether for issues of therapy or harm, the strength of inference from RCTs will almost invariably be greater than the strength of inference from observational studies.

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