IN THE UNITED STATES DISTRICT COURT
FOR THE WESTERN DISTRICT OF WISCONSIN

ALINA BOYDEN and
SHANNON ANDREWS,

Plaintiffs, Case No. 17-cv-264

v.

STATE OF WISCONSIN DEPARTMENT
OF EMPLOYEE TRUST FUNDS, et al.,

Defendants.

DECLARATION OF CAROLYN M. WALD

I, Carolyn M. Wald, certify under penalty of perjury that the following is true and correct to the best of my knowledge and recollection:

1. I am an attorney licensed to practice in the State of Illinois and have been admitted to practice in the Western District of Wisconsin.

2. I am one of the attorneys representing the Plaintiffs in the above-captioned matter.

3. Attached to this Declaration are true and correct copies of the following documents:

   a. Attached hereto as **Exhibit A** is a true and correct copy of the website *About EPPC*, Ethics & Public Policy Center, https://eppc.org/about/.

b. Attached hereto as **Exhibit B** is a true and correct copy of the letter published on the website *Expert LGBTI Consensus Letter,* Vanderbilt University Medical Center, https://www.vumc.org/lgbti/files/lgbti/publication_files/ExpertLGBTIConcensusLetter.pdf

c. Attached hereto as **Exhibit C** is a true and correct copy of the Advocate Article: *New 'Scientific' Study on Sexuality, Gender is Neither New nor Scientific*.

d. Attached hereto as **Exhibit D** is a true and correct copy of the faculty biography of Paul W. Hruz. M.D., Ph.D. from Washington University in St. Louis School of Medicine.

e. Attached hereto as **Exhibit E** is a true and correct copy of the Amicus Brief in *Gloucester County School Board v. G.G.*

f. Attached hereto as **Exhibit F** is a true and correct copy of the Southern Poverty Law Center Article: Meet the *Anti-LGBT Hate Group that Filed an Amicus Brief with the Alabama Supreme Court*.

g. Attached hereto as **Exhibit G** is a true and correct copy of the Memorandum from the American College of Pediatricians: *A Medical Response to DOE and DOJ Guidance for Schools*.

h. Attached hereto as **Exhibit H** is a true and correct copy of the Proto Magazine Article: *Crossing Over*.

i. Attached hereto as **Exhibit I** is a true and correct copy of the City Pages Article: *University of Minnesota Professor's Research Hijacked*.

j. Attached hereto as **Exhibit J** is a true and correct copy of the Medicare *Decision Memo for Gender Dysphoria and Gender Reassignment Surgery*.

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

Executed this 7th day of September, 2018.

/s/ Carolyn M. Wald
Carolyn M. Wald

Exhibit A

About EPPC

Founded in 1976 by Dr. Ernest W. Lefever, the Ethics and Public Policy Center is Washington, D.C.'s premier institute dedicated to applying the Judeo-Christian moral tradition to critical issues of public policy. From the Cold War to the war on terrorism, from disputes over the role of religion in public life to battles over the nature of the family, EPPC and its scholars have consistently sought to defend and promote our nation's founding principles—respect for the inherent dignity of the human person, individual freedom and responsibility, justice, the rule of law, and limited government.

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>
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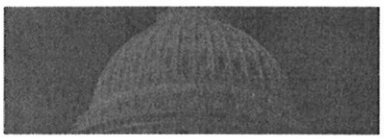

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Exhibit B

March 22, 2017

To Whom It May Concern,

Dr. Paul McHugh and Dr. Lawrence Mayer's Fall 2016 report, "Sexuality and Gender: New Findings from the Biological, Psychological and Social Sciences," published in the 50th issue of the non-peer reviewed bioethics magazine The New Atlantis, misleads readers about the state of scientific research and evidence-based clinical practice guidelines addressing the health of people who are lesbian, gay, bisexual, transgender and queer (LGBTQ).

As researchers with expertise in gender and sexuality, and/or as clinicians who serve LGBTQ people, we are called to correct the record. A substantial body of research points to stigma and its consequences as contributing to the mental and physical health disparities among LGBTQ people.[1-16] Based on scientific consensus, many major medical associations have issued guidelines and policy statements calling for clinicians to affirm and support the sexual orientation, gender identity and gender expression of their patients as part of a standard, evidence-based approach to high quality, patient-centered healthcare.[17-25]

Although the “Sexuality and Gender” report cites many peer-reviewed scientific articles, the interpretation, analysis, and summary of the scientific evidence in the report has not been peer-reviewed. As scientific and medical experts, we affirm that the report's conclusions do not reflect current scientific or medical consensus about sexual orientation or gender identity research findings or clinical care recommendations. As such, the report's conclusions should not be viewed as a source of scientific or medical justification to support any legislation, judicial action, policymaking or clinical decision-making affecting the lives of LGBTQ people or their families.

In summary, as researchers and clinicians with expertise in gender and sexuality, we affirm that the “Sexuality and Gender” report does not represent prevailing expert consensus opinion about sexual orientation or gender identity related research or clinical care.

Signed,

Lauren Abern, MD

Shayna Abraham, MA

Mere Abrams, MSW
Gender Specialist

Sheila Addison, PhD

Licensed Marriage and Family Therapist

Deanna Adkins, MD
Assistant Professor of Pediatrics

Leonard Alberts, MD

Vicki Allen, MSW, LCSW-C
Therapist

Brittany Allen, MD
Assistant Professor
Co-Medical Director, Pediatric and Adolescent Transgender Health (PATH) Clinic, American Family Children's Hospital

Heather Kramer Almquist, LPC
Psychotherapist

Juan Luis Alvarez Gayou, MD, PhD

Ilana Ambrogi, MD

Jean Amoura, MD

Joel Anderson, PhD

Eva Angeli, MD

Y. Gavriel Ansara, PhD

Sascha Arbouet, MD

Jon Arcelus, MD, PhD
Full Professor, Mental Health and Transgender Health

Dani Archie, PhD

Tyler Arguello, PhD, MSW
Assistant Professor & Diplomate of Clinical Social Work

Jane Ariel, PhD

Ian Armstrong, MD

Joycelyn Atchison, MD

Alison Austin, MA, CRC

Ashley Austin, PhD
Associate Professor

C. Morgan Ayres
Member, World Professional Association of Transgender Health

Meg-John Barker, PhD

Lisa Baron, MD

Lorna Barton, MSW

Elizabeth Bates, MD

Lauren B. Beach, PhD, JD
Director of Research, Program for LGBTI Health, Vanderbilt University Medical Center

Aimee Beardslee, MS, LMHC
Licensed Mental Health Counselor

Christopher Beaudoin, MD

Jordan Becerril, MD

Jodi Beetlestone, PsyD

Jo-Anne Beggs, LCSW-R, RSW

Mark Behar, PA-C

Uri Belkind, MD, MS

Karla A. Bell, PT, DPT, OCS, GCS

Rosa Benato, MS

Dianne Berg, PhD
Assistant Professor

Ruth Berggren, MD
Professor of Medicine/Infectious Diseases

Ellen Berman, MD
Clinical Professor of Psychiatry, Perelman School of Medicine, University Of Pennsylvania

Anne Bernstein, PhD
Family Psychologist and Professor, The Wright Institute

Chiara Bertone, PhD
Associate Professor, University of Eastern Piedmont

Rebecca Bickel, LCSW

Megan Bird, MD
Medical Director of Gender and Sexual Health, Legacy Health

Lori Bisbey, PhD, MA
Consultant Registered Psychologist

Jacalyn Bishop, MD, FAAP

Jennifer Anne Blair, MA, LPCC

Irene Blanco, MD
Associate Professor of Medicine

Shannon Blaney, MD, MPH

Erick Blaudeau, MD

Daniel Blumrosen, MA, MFT

Susan Bonadonna, MD

Jordon Bosse, MS, RN
Nurse Educator & Researcher

Walter Pierre Bouman, MD, MA, MSCI, FRCPsych, UKCPreg

Jessica Branch, MA, LPC

Richard A. Brandon-Friedman, MSW, LCSW, LCAC
Associate Faculty and Social Work Fellow

Ari Brandsdorfer, MD

David Brennan, PhD
Associate Professor, University of Toronto

Jutta Brettschneider, MS, OTR/L

Cedric M. Bright, MD, FACP

Liam Briones, MD, MBA

Li Brookens, LCSW

Kyria Brown

Marcia Brubeck, JD, MSW
Psychotherapy & Advocacy

Delaney Bryan, SPT

Stephanie Budge, PhD
Assistant Professor, University of Wisconsin-Madison

Jenn Burleton
Founder & Executive Director, TransActive Gender Center

Jennifer A. Burnett, MS, MD, FAAFP

Loretta Bush, RN, MS, PPNP-BC

Susanne Cabrera, MD
Director, Gender Health Clinic, Children's Hospital of Wisconsin

Billy A. Caceres, MSN

Toni Calasanti, PhD
Professor

Brittney Caldera, RN, MSN, MBA

Jessica Calderon-Mora, PhD

Edward Callahan, PhD
Associate Vice Chancellor Emeritus and Professor Emeritus, University of California, Davis School of Medicine

P. Myles Cameron, LMSW

Elizabeth Camlin, LGSW

Lary Campbell, BSN, RN-BC

Edward Cannon, PhD
Associate Professor

Antonia Caretto, PhD
Licensed Clinical Psychologist

Ward Carpenter, MD
Physician

Julie Case, BSN

Catherine Cassel, MSW, LCSW

Caitlin Cassidy, MA

Scott Chaiet, MD, MBA

Belinda Chaplin, RN, BNursing(Hons1), PhD, AFHEA

Brittany Charlton, PhD
Instructor

Elise Chenier, PhD
Professor

Karen Chopra, LPC
Licensed Professional Counselor

Jules Chyten-Brennan, DO

Ethan Cicero, BSN
Nurse Researcher and Scholar

Jessie R. Cohen, MSW, LCSW, QMHP

Jason Coleman, PhD

Megan Coleman, MSN
Megan Coleman, Director of Community Research

Kara Connelly, MD
Assistant Professor

James Conniff, MD, MPH
Faculty Physician

Maureen Connolly, MD
Pediatrician

Sandra Conti, LCPC

Christopher Cook, MD, PhD
Professor

Jennifer Cook, PhD, LPC, NCC
Assistant Professor, Licensed Professional Counselor

Deborah Cooper, MA, MFT

Deanna Cor, PhD

Lea Córdova, MA, MS
LGBT Health Consultant

Heather Corliss, PhD, MPH
Professor of Public Health, San Diego State University

Brenda Cossman, LL.M, LL.B
Professor

M. Franci Crepeau-Hobson, PhD
Associate Professor & Licensed Psychologist

Jessica Cristallo, MD

Andrew Cronyn, MD

Diana Currie, MD
Clinical Faculty, Providence St Peter Family Medicine and UW Ob/Gyn

Marguerite Cusack, JD, LICSW, LCSW

Griet De Cuypere, MD, PhD

Dawn Darling, LICSW

E. Maxwell Davis, PhD
Director, Integrated Behavioral Health Program, California Social Work Education Center

Sara Derosa, MSW, LCSW

Sean DeYoung, MSW, LCSW
Chief Executive Officer, Pittsburgh AIDS Task Force

Alejandro Diaz, MD
Assistant Professor of Pediatrics

James Dinh, MSW

Brian Dodge, PhD, MS
Associate Professor

Cort Dorn-Medeiros, PhD
Assistant Professor

Parin Dossa, PhD
Professor

Nadia Dowshen, MD
Co-Director, Gender and Sexuality Development Clinic, Children's Hospital of Philadelphia,
Assistant Professor of Pediatrics, Perelman School of Medicine, University of Pennsylvania

Shannon Dubach, PsyD, MBA

L. Zachary DuBois, PhD
Assistant Professor

Mel Duffy, PhD

Marian Duggan, PhD, MA

Joanna Dunlap, PhD, MBA

Laura Durso, PhD
Vice President, LGBT Research and Communications Project, Center for American Progress

Sara Belle Earle, RN, BSN

Deborah Edberg, MD
Family Physician

Eve Edem, MSW, LCSW

Elizabeth Egan, MHS, PA-C

Alice Eggleston, MPH, PA
Clinical Reaearch Manager

Jesse Ehrenfeld, MD, MPH
Director, Program for LGBTI Health, Vanderbilt University Medical Center

Diane Ehrensaft, PhD
Associate Professor of Pediatrics, University of California San Francisco

W. Suzanne Eidson-Ton, MD, MS
Clinical Professor, Department of Family and Community Medicine, University of California Davis

Michele Eliason, PhD
Professor

Jill Elliott, PA-C

Stephanie Ellis, MPH

Anando Emryss, PGDipl
Specialist Psychotherapist

David English, MD
Faculty Physician

Patrick Ennis, MD
Family Physician

Laura Erickson-Schroth, MD

Robert Esterl, MD
Associate Dean for Student Affairs & Distinguished Teaching Professor Department of Surgery, UT Health San Antonio School of Medicine

Diane Estrada, PhD

Randi Ettner, PhD

Harmony Evans, MS

Tiffany Ewton, MHA, MPH

Joy Brooke Fairfield, PhD
Assistant Professor

Geraldine Faria, PhD

Jamie Feldman, MD, PhD

Sacha Ferguson, MSN, DNP, FNP-BC

Eduarda Ferreira, PhD

Wendy Fields, BSN, MSN, RN, FNP-C

Kristy Fiore, MS, LPC
Licensed Professional Counselor

Colleen Fisher, PhD, MSW
Associate Professor

Leticia Y. Flores, PhD

Lauren Fogel, PsyD

Allyson Foley, MSW

Catherine Forbes, PhD

Michelle Forcier, MD, MPH
Director, Gender and Sexual Health Clinics

Catherine Forest, MD, MPH
Clinical Assistant Professor of Medicine

Maureen Francis, MD

Michelle Franck, LCSW
Clinical Psychotherapist

Jefferson Frank, PhD
Professor

Laurel Freeman, LMSW

Joseph Freund, MD

Cecilia Froberg, MS, MFT

Lindsey Fuller, MD

Luke Gahan

Jerry Gale, PhD

Dylan Galos
PhD Candidate, Division of Epidemiology and Community Health, University of Minnesota

Megan Gandy-Guedes, PhD, MSW

Liliana Garcia, MD
Endocrinologist & Assistant Professor, University of Missouri

Patricia Garcia-Fernandez, PhD

Aaron Gardner, MPH, MA
Social Epidemiologist

Robert Garofalo, MD, MPH
Editor-in-Chief, Transgender Health
Professor of Pediatrics, Northwestern University

Sharon Gates, MA

Jorge Gato, PhD

Peter Gehrig, MD

Troyann Gentile, PhD
Assistant Professor

Maria Gervits, MD

Krystal Ghisyawan, PhD

Katherine Gibson, FNP
Family Nurse Practitioner

Satinder Gill, PsyD
Director of Clinical Services, University of California Davis

Nancy Giunta, PhD
Associate Professor

Eric Goepfert, MD
Assistant Professor of Psychiatry

Jacquelyn Gold, MD

Amy Goldfarb, MD

Jennifer Carolyn Gomes, MD

Cesar Gonzalez, PhD
Board Certified Clinical Psychologist

Jaimie Goralnick, MD
Child, Adolescent and Adult Psychiatrist

Allegra Gordon, PhD, MPH
Research Fellow, Boston Children's Hospital & Harvard Medical School

Hannah Gould, MPH, LCSW-C

Licensed Independent Clinical Social Worker

Julie Graham, MS, MFT
Director, Transgender Health Services

Finn V. Gratton, LMFT, LPCC

Dianne Gregory
Health Information Analyst

Lisa Griffin, PhD
Licensed Clinical Psychologist

Traci Griggs, BSN
Medical Adherence Nurse Care Manager

Paul Gross, MD

Charles Grove, PhD
Behavioral Health Consultant, Mazzoni Center Family & Community Medicine

Sara Grove, MA

Eduardo Leon Guerrero, MD
Transgender Social Worker

Jess Guerriero, MSW

Shilpa Gulati, MD, MS

Fatima Gutierrez, MD, FAAO

Ronald Gutierrez, MSW, LCSW

Evelyn Hall, MD

Michael Haller, MD, MSCI
Professor and Chief, Pediatric Endocrinology

Laura Halley, MSW

Dean Hamer, PhD
Scientist Emeritus, National Institutes of Health

Douglas Hamill, MD, MDiv

Tavi Hancock, MA, MSW

Dawn Harbatkin, MD
Medical Director

W. David Hardy, MD
Senior Director of Evidence-Based Practices

James Harrison, PhD

George Harrison, MD

Lindsay Hartley, RN, MSN, WHNP-BC

Jennifer Hastings, MD

Jean Hatton, MA

Nikki Hayfield, PhD

Lori Haymore, MA

Johnson Haynes, MD

Shea Hazarian
Academic Programs Analyst, UC Davis School of Medicine

Carol Hendler, MSW

Sarah Henkle, MD

Sarah Henn, MD, MPH
Senior Director of Health Care Operations/Medical Services

Marie Hennelly, MD

Mark Henrickson, MSW, PhD, RSW

Samuel Hensley, MSW

Amy Hequembourg, PhD
Senior Research Scientist

Shane Hill, PhD
Clinical Psychologist

Stephanie Ho, MD

Heidi Hoefinger, PhD
Professor of Science, Berkeley College

Abby Hollander, MD

Jennifer Holzman, MA

Kiri Horsey, LPC
Child and Family Therapist

Jimmy Hu, MD, Physician
Physician

Mark Hughes, PhD
Professor

Vicie Hurst, PhD
Psychologist

Courtney Hutchins, MPH

Sadie Hutson, PhD

Alex Iantaffi, PhD, MS
Family Therapist and Independent Scholar

Farah Ibrahim, PhD

Katie Imborek, MD
Assistant Professor of Family Medicine

Leona Irvine

Jay Irwin, PhD, MA
Associate Professor of Sociology, University of Nebraska at Omaha

Rita Jablonski-Jaudon, PhD, CRNP, ANP-BC, FAAN
Nurse Practitioner and Associate Professor

Ron Jackson Suresha

Jeanna Jacobsen, PhD, MSW

Amit Jain, MD, MPH

Nancy James, PsyD
Licensed Clinical Psychologist

Kristen Jarvis, RN
Registered Nurse

John Javien, MD, MPH

Anita Jaynes, MS, APRN

Joseph R. Jefferson, MA, CPRP, LMFT

Pablo Joo, MD
Assistant Dean for Medical Education

Tuula Juvonen, PhD
Academy Research Fellow

Rachel Kahn, MA, LMHC

Harrison Kalodimos, MD

Dan Karasic, MD
Health Sciences Clinical Professor of Psychiatry, UCSF

Owen Karcher, MA
Art Therapist

Alexa Kaskowitz, MD, MPH
Pediatric and Adolescent Gynecologist, The Permanente Medical Group

Sabra L. Katz-Wise, PhD
Assistant Professor

Miriam Kaufman, BSN, MD, FRCPC
Head, Division of Adolescent Medicine, SickKids and U of T

Brian Kavanagh, PhD

Marion Kavanaugh-Lynch, MD, MPH, MS
Director, California Breast Cancer Research Program

Leslie Kent, LCSW-C
Clinical Social Worker

Colton Keo-Meier, PhD
Clinical Psychologist

Haley Kerman, MSN, RN, PHN

Joyce Kermeen, LMFT

Sameer Khan, MD
Psychiatrist

Samina Khatun, PhD
Trainee Counselling Psychologist

Patrick Kilcarr, PhD

Director, Center for Personal Development

Paul Kilfoil, CAS

M.K. Kinney, MSW

Cali Kirkham

Augustus Klein, MSW

Cary Klemmer, MSW

Asher Kline, MS

Gail Knudson, MD, MPE, FRCPC

Alexander Kondakov, PhD
Assistant Professor

Eliana Korin, MA, Dipl. Psic
Director of Behavioral Science, Montefiore Medical Center

Anu Kotay, PhD

Krishna Kothary, MSN, FNP-C

Amy Krasner, MSW, LICSW

Irwin Krieger, LCSW
Clinical Social Worker

Ross Kristal, MD

Alexis Kuerbis, PhD, MSW
Assistant Professor and Licensed Clinical Social Worker

Sandhya Kumar, MD

Laura Kuper, PhD

Psychologist, GENder Education and Care Interdisciplinary Support Program at Children's Medical Center Dallas

Lindsay Kurahara, MA

Ki Kurtz, DO

Roger Lake, MS, LMFT

Shaked Laks, MD

Judith Landau, MD

Benjamin Laniakea, MD
Clinical Instructor

Marissa Lapedis, MD

Joseph De Lappe, MA

Benjamin Larisey, LCSW

Brenna Lash, MPH

Jasper J. Lawson, PhD

Adrienne Lawson-Thompson, EdD, MA
Director of Institutional Culture, Climate & Community Engagement

Carolyn Leach, CWHNP/ANP

Cynthia LeBlanc, MS, LMFT

Susan LeLacheur, MPH, DrPH, PA-C

Barbara Lewis, PA-C

Christopher Lewis, MD
Pediatric Endocrinology Fellow

David Ley, PhD

Linda Li, MD

Marguerita Lightfoot, PhD

Lisa Lindley, DrPH

Roxana Llerena-Quinn, PhD

Gemma Lock, PhD

Ana Maria Lopez, MD, MPH

Julie Loza, MD

C. Emily Lu, MD
Family Medicine Physician

Micah Lubensky, PhD, MS

Cora Ludwig, MD

Andrew Lulla, MD

Mitchell Lunn, MD
Assistant Professor of Medicine & Co-Director, The PRIDE Study, University of California, San Francisco

Elaine M. Maccio, PhD, MSW, LCSW

Jennifer Macdonald, MD, PhD
Resident Physician

Naomi Malouf, PhD, BSN
Licensed Professional Counselor

Lucrezia Mangione, MA

Liz Margolies, LCSW
Executive Director, National LGBT Cancer Network

Elisabeth Marsh, LICSW

Laura Marshall, MA

Bess Marshall, MD
Professor of Pediatrics Washington University in St. Louis

Eva Martin, MD
Georgia Department of Health

Maren Martin, LCSW

Glenna Martin, MD, MPH

Christina Martin, LPC

Mariya Masyukova, MD, MS

Ruchi Mathur, MD
Assistant Professor

Cheryl Matias, PhD
Assistant Professor

Allison Mattheis, PhD

Mary Mattis, MSW
Clinical Director, SoCo Counseling

Evan McEwing, RN, BSN, CCRP, RQAP-GCP
Nurse Specialist

Lauren McGovern, MSW, MS, LICSW

Grainne McMahon, PhD

Katie McNamara, MA, LCSW

Jacob McWilliams, PhD
Women and Gender Coordinator, University of Colorado Denver

Denise Medico, PhD
Professor of Clinical Sexology, Université du Québec à Montréal

Kody Meginnes, MA, LMFT

Neha Meht, MD, DO

William Mellman, MSW
Research Scientist

Dane Menkin, CRNP
Clinical Operations Manager

A.J. Metthe, MSW, LCSW

Elizabeth Meyer, PhD
Associate Professor

Birgit Meyer, MD
Child and Adolescent Psychiatrist

Sarah Milburn, MD

Christine Milrod, PhD, LMFT, AASECT-CST

Yasmin Miranda, MS, LMHC

Michelle Mitchell, MS

Jeanne Mitchler-Fiks, MSW, LCSW

Sara Mize, PhD

Joanna Mizielinska, PhD

Jay Mongiardo, MD, MBA

Surya Monro, PhD
Professor

Mary Moore, MSW, LCSW-C

Lee Moore, ARNP

Mayra Morales, MBA

Amy Morgan, MS, LMFT

Charles Moser, MD, PhD

Michelle Murray, MA

Arien Muzacz, PhD, LPC
Licensed Professional Counselor

Mioki Myszkowski, MD

Sunshine Nakae, PhD
Assistant Dean for Admissions, Recruitment and Student Life

Lalit Narayan, MBBS, MA

Sumathi Narayana, MD

Scott Nass, MD
Family Physician

Elijah C. Nealy, PhD, MSW

Mary Nedela, MS
Limited License Marriage and Family Therapist

Justin Neisler, MD
Founder, Equality Clinic of Augusta

John Nelson, PhD, MSN
Program Director, Rutgers School of Nursing

Matthew Newell, BSN, RN

Laine Newman, MFA, MA
PhD Candidate (ABD)

Henry Ng, MD, MPH
Associate Professor, CWRU School of Medicine

Vincent Nguyen, MD, MBA

Todd B. Nippoldt, MD

Gillian Nuding, MSW, LCSW

Coleman Nye, PhD
Assistant Professor of Gender, Sexuality, and Women's Studies, Simon Fraser University

Maeve O'Brien, PhD

Dan O'Connell, MD, MPH
Assistant Professor of Family Medicine, Montefiore Medical Center

Juno Obedin-Maliver, MD, MPH
Assistant Professor, Obstetrics Gynecology & Reproductive Sciences, University of California San Francisco

Katie Larson Ode, MD
Clinical Assistant Professor

Oladimeji Oki, MD

Steven Onken, PhD
Associate Professor

Michelle Orengo-McFarlane, MD

Phyllis Oropallo, MA
Licensed Gender Specialist

Ismael Díaz Oropeza, PsyD

John P. Ouderkirk, MD

Heather Ouellette, MD, MA

Jena Ourso, LMSW

Rachel Paneth-Pollak, MD, MPH

Maura Pantone, MA

Daniel Parker, PhD
Clinical Psychologist

Viraj Patel, MD, MPH
Assistant Professor of Medicine

Leigh Patterson, MD, MA

Ruth Pearce, PhD

Drake Pearson
Patient Navigator

Joan Pedersen, MA, ThM, LCSW-C

Jessica Peipock, MSW

M. Eli Pendleton, MD

Amy Penkin, LCSW

Raquel Peralta, MD

Christina Peterson, MSW, LICSW

Hieu Pham, MD, MPH

Psyche Philips, NP-C

Michal Pitoňák, PhD

R. Lucas Platero, PhD

Alex Pollard, MA

Tonia Poteat, PhD, MS, MPH, PA
Assistant Professor, Johns Hopkins Bloomberg School of Public Health

David Primo, MD, MS

Kay Przywojski, LPC
Licensed Professional Counselor

Jake Pyne, MSW
PhD Candidate & Researcher, McMaster University

Samantha Quesada, BSN

Molly Rabinowitz, MPH

Katherine Rachlin, PhD
Member, Board of Directors, World Professional Association for Transgender Health

Sara L. Raftery, LMSW

Lewis Raynor, PhD, MS, MPH
Investigator, Oregon Community Health Information Network

Alex Redcay, PhD
Executive Director & Assistant Professor

Jill Rees, PhD

Katelyn Regan, MEd, MSW, LSW

Clinical Social Worker

Daniel Reirden, MD
Associate Professor of Pediatrics and Internal Medicine, University of Colorado School of Medicine

Sari Reisner, ScD

Danielle Restrepo, MA

Gibran Rodriguez de los Reyes, MA

Cynthia Reyes

Scott Rhodes, PhD, MPH
Professor

Christina Richards, MSc, DCPsych, CPsychol, MBACP (Accred.), AFBPsS

Jai Richards, MA, R Psych (Provisional), CCC

Damien Riggs, PhD, MA
Associate Professor

William Robertson, MA

Sean Robinson, PhD, MBA
Associate Professor, Morgan State University

Remigio Roque, MD

Nicole Rosendale, MD

Carla Rosinski, MA, LMHC

Erica Rotondo, DO
Board Certified Family Medicine Physician

Mollie A. Ruben, PhD

Kristen Russell, MSW, LCSW

Neal Rzepkowski, MD

Aoife Sadlier, MA

Edgar Rodriguez Sanchez, MA
PhD Candidate, Counselling & Psychotherapy

Irma Santiago, MD

Kyriakie Sarafoglou, MD
Pediatric Endocrinologist & Inborn Error of Metabolism Specialist

Michelle Sariev, NP

Courtney Saw, MD

Loren Schechter, MD

Joanna Scheib, PhD

Ayden Scheim
PhD Candidate, Epidemiology and Biostatistics, Western University

Bee Scherer, PhD
Full Professor of Gender Studies & Director of the INCISE Research Centre, Canterbury Christ Church University

Anna Schettle, LICSW

Jason Schneider, MD
Associate Professor, Emory University School of Medicine

Wilma Schroeder, BSN, RN, BN, MMFT

Jeremy Schwartz, MSW, LCSW

Rachael Scicluna, PhD

Andres Sciolla, MD
Associate Professor

Maggie Scribner

Amrita Seehra, MD

Ellen Selkie, MD, MPH

Joanna Semlyen, PhD

Shervin Shadianloo, MD
Child and Adolescent Psychiatrist

Rachel Shah, MD

Sheila M. Shannon, PhD

Manisha Sharma, MD

Monica Shaw, MD, MA
Professor of Medicine

Allison Sherwood, FNP-BC

Samantha Shinberg, LGSW

Lee Shropshire

Daniel Shumer, MD, MPH

Vincent Silenzio, MD, MPH
Associate Professor of Psychiatry, Public Health Sciences, and Family Medicine, University of Rochester

Janet Silverstein, MD

Gabrijela Simetinger, MD, PhD

Rachel Simon, MSW, LSW, MEd
Psychotherapist

Lisa Simons, MD
Medical Director, Gender Development Program, Ann & Robert H. Lurie Children's Hospital of Chicago

Paul Simpson, PhD

Alexandora Siporin, DO

Matthew Skinta, PhD, ABPP
Director, Sexual & Gender Identities Clinic, Palo Alto University

Jacquelyn Smith, PhD
Pediatric Psychologist

James Smith, Dip. Psych

Jan Smith, LCSW
Clinical Social Worker

Rumeli Snyder, MSW, LCSW

Lauren Sonderegger, MD
Resident Physician

Katie Spencer, PhD
Licensed Psychologist & Gender Specialist

Rachael St. Claire, PhD
Licensed Psychologist

Sara Staley, PhD
Research Associate, University of Colorado Boulder

Heather Stambaugh, MA, LMHC NCC CAP

Agata Stasińska, MA

Researcher

Carolyn Stead, PhD
Psychologist

Carl Stein, MHS, PA-C
Physician Assistant

Stacie Steinbock, MHA
Director, Health Sciences Campus LGBT Center, University of Louisville

Jennifer Stella, MD

Hillary Stern, LCSW

Jaime Stevens, MD, MPH

Samantha Stimmel, MD

Cheryl Stobie, PhD

Kelly Storck, LCSW
Private Practice Therapist

Joan Stratton, MSW, LICSW
Charles Strauss, MSW, LICSW

Carl Streed Jr, MD
Chair, American Medical Association Advisory Committee on LGBTQ Issues

Antonio Tena Suck, DrPH

Francoise Susset, PsyD

Alenka Svab, PhD
Professor, University of Ljubljana

Robin Sweeney, MA, LMFT

Judit Takacs, PhD

Efrain Talamantes, MD, MBA, MSHPM

Lisa Talati, DO

Catherine Tallant, MA

Margaret Tandoh, MD

Angela Tang, PhD

Vin Tangpricha, MD, PhD
Associate Professor of Medicine

Cynthia Tavilla, MA

Megan Telfair, EdM

Elizabeth TenBrook, MS

Teresa Terry

Zoey Thill, MD

Fanshen Thompson, LCSW

Andrew Peter Thompson, PhD

Laura A. Thor, DMin, LCSW

Bjoerg Thorsteinsdottir, MD

Valerie Tobin, MS, PMHNP

Jean Toner, PhD
Instructor, Arizona State University

Greg Townsend, MD

Ann Travers, PhD

David Trimble, PhD
Clinical Assistant Professor of Psychiatry, Boston University School of Medicine

Carin Tunåker, PhD

Jos Twist, MS

Markie Twist, PhD
Associate Professor

Chelsea Unruh, MD

Haktan Ural, PhD

Susan Utter, MA, LMFT

Lida Vala, MA, LMFT

Ana Valentin, MSW
Clinical Social Worker and Psychotherapist

Michelle Vaughan, PhD
Associate Professor

Jaimie Veale, PhD

Sandra Veronick, LCSW

Diane Verrochi, MSN

Ana Lilia Villafuerte, PhD

Dana Vince, LPC-MHSP

Dawn Wade, MA, MFT, ATR

A. Waggoner, RN, BSN

Ruth Walker, MD, PhD

Oakland Walters

Caroline Walters, PhD

Lin-Fan Wang, MD, MPH

Chen Wang, MD
Family Medicine Resident

Adam Ward, MS
PhD student, Infectious Disease Epidemiology, The George Washington University

Nicki Ward, PhD, MA

Susanne Watson, PhD
Clinical Psychologist

Antonia Way, MD

Carolyn Wellford, RN

Erica Werfel, MSW, LCSW/LCSW-C/LICSW

Norbert A. Wetzel, ThD, MFT
Licensed Psychologist

Michelle Wexelblat, LICSW

G. Zachariah White, MFA, PsyD, LP
Licensed Psychologist

Sara Wiener, LMSW
Director of Mental Health Services

Jesse Wilkinson, MA
Researcher & Clinician

Sara Willott, LCSW
Psychotherapist

Erin Wilson, DrPH

Liesl Wolf, BSN, PHN, RN

Carolyn Wolf-Gould, MD

Margaret Wolff, DPH, MSW
Research Project Director & Adjunct Assistant Professor

Michael R. Woodford, PhD
Associate Professor

Joshua Yap, MD

Tracey Yeadon-Lee, PhD

Abraham Young, MD

Barry Zevin, MD
Medical Director, Transgender Health Services

Suzanne Zinck, MD

Hannah Zipple, MSW

Anna Zoli, PhD

Institutions are listed for identification purposes only.

Selected References

1. Hatzenbuehler ML. Advancing Research on Structural Stigma and Sexual Orientation Disparities in Mental Health Among Youth. J Clin Child Adolesc Psychol. 2016:1-13.
2. Hayon R. Gender and Sexual Health: Care of Transgender Patients. FP Essent. 2016;449:27-36.
3. Carmel TC, Erickson-Schroth L. Mental Health and the Transgender Population. J Psychosoc Nurs Ment Health Serv. 2016;54(12):44-48.
4. Hatzenbuehler ML, Pachankis JE. Stigma and Minority Stress as Social Determinants of Health Among Lesbian, Gay, Bisexual, and Transgender Youth: Research Evidence and Clinical Implications. Pediatr Clin North Am. 2016;63(6):985-997.
5. Blosnich JR, Marsiglio MC, Gao S, et al. Mental Health of Transgender Veterans in US States With and Without Discrimination and Hate Crime Legal Protection. Am J Public Health. 2016;106(3):534-540.
6. Gridley SJ, Crouch JM, Evans Y, et al. Youth and Caregiver Perspectives on Barriers to Gender-Affirming Health Care for Transgender Youth. J Adolesc Health. 2016;59(3):254-261.
7. Everett BG, Hatzenbuehler ML, Hughes TL. The impact of civil union legislation on minority stress, depression, and hazardous drinking in a diverse sample of sexual-minority women: A quasi-natural experiment. Soc Sci Med. 2016;169:180-190.
8. Hatzenbuehler ML, Phelan JC, Link BG. Stigma as a Fundamental Cause of Population Health Inequalities. American Journal of Public Health. 2013;103(5):813-821.
9. Hatzenbuehler ML, Bellatorre A, Lee Y, Finch BK, Muennig P, Fiscella K. Structural stigma and all-cause mortality in sexual minority populations. Soc Sci Med. 2014;103:33-41.
10. Danoff A. Transgender Care Matters. Endocr Pract. 2016;22(7):899-901.
11. Murad MH, Elamin MB, Garcia MZ, et al. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. Clin Endocrinol (Oxf). 2010;72(2):214-231.
12. The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Washington, D.C.: The Institute of Medicine; 2011.
13. Committee On Adolescence. Office-based care for lesbian, gay, bisexual, transgender, and questioning youth. Pediatrics. 2013;132(1):198-203.
14. Levine DA, Committee On Adolescence. Office-based care for lesbian, gay, bisexual, transgender, and questioning youth. Pediatrics. 2013;132(1):e297-313.
15. Lick DJ, Durso LE, Johnson KL. Minority Stress and Physical Health Among Sexual Minorities. Perspect Psychol Sci. 2013;8(5):521-548.
16. Meyer IH. Prejudice, social stress, and mental health in lesbian, gay, and bisexual populations: conceptual issues and research evidence. Psychol Bull. 2003;129(5):674-697.

17. Standards of Care for the Health of Transsexual, Transgender, and Gender Non-Conforming People. World Professional Association for Transgender Health; 2011.
18. Advancing Effective Communication, Cultural Competence, and patient- and family-centered care for the lesbian, gay, bisexual, and transgender community: A field guide. Oakbrook Terrance, IL: The Joint Commission; 2011.
19. Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, et al. Endocrine Treatment of Transsexual Persons: An Endocrine Society Clinical Practice Guideline. J Clin Endocr Metab. 2009;94(9):3132-3154.
20. Policies on Lesbian, Gay, Bisexual, Transgender & Queer (LGBTQ) Issues. American Medical Association; https://www.ama-assn.org/delivering-care/policies-lesbian-gay-bisexual-transgender-queer-lgbtq-issues. Accessed January 9, 2017.
21. Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. American Psychological Association; 2015.
22. Guidelines for Psychological Practice with Lesbian, Gay & Bisexual Clients. American Psychological Association; 2011.
23. Reisner SL, Poteat T, Keatley J, et al. Global health burden and needs of transgender populations: a review. Lancet. 2016;388(10042):412-436.
24. Makadon HJ, Mayer KH, Potter J, Goldhammer H, American College of Physicians (2003-). The Fenway guide to lesbian, gay, bisexual, and transgender health. Second edition. ed. Philadelphia: American College of Physicians; 2015.
25. Guidelines for Care of Lesbian, Gay, Bisexual and Transgender Patients. Gay and Lesbian Medical Association; 2006.

Exhibit C

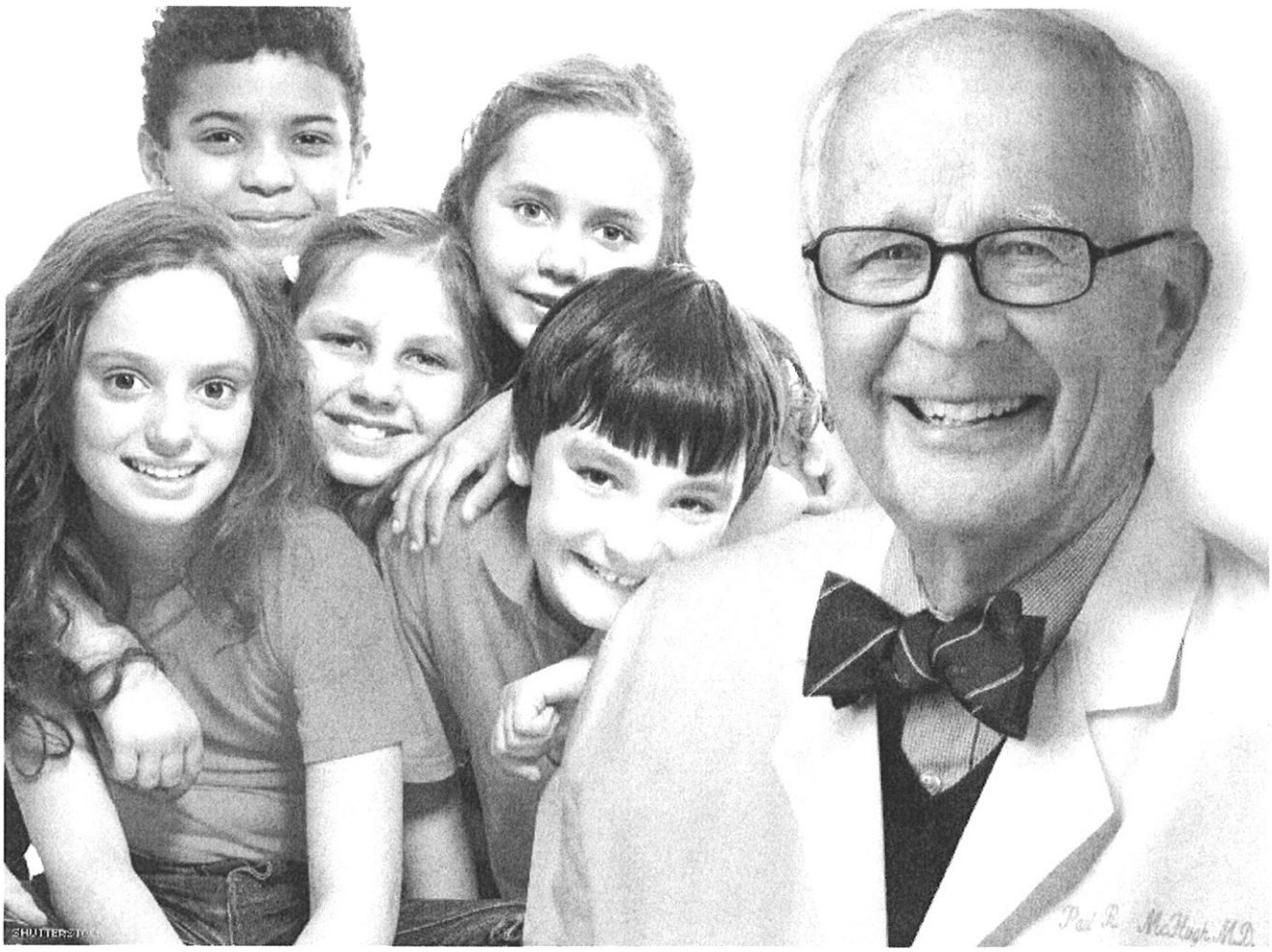
New 'Scientific' Study on Sexuality, Gender Is Neither New nor Scientific

advocate.com/commentary/2016/8/29/new-scientific-study-sexuality-gender-neither-new-nor-scientific

August 29, 2016

Commentary

New 'Scientific' Study on Sexuality, Gender Is Neither New nor Scientific



Dr. Paul McHugh

The right wing is pushing a study that isn't based in sound science, says famed geneticist Dean Hamer.

By Dean Hamer

August 29 2016 2:21 PM EDT

The thing I've always loved about science is that, in the end, the truth really does win out, and most scientists are eager to know what it is. But there are always exceptions. When it comes to emotionally and politically charged topics like human sexuality and gender, even highly regarded

professionals may find themselves tempted to bend the facts to support their own viewpoint rather than reality.

Such appears to be the case for Drs. Lawrence Mayer and Paul McHugh, coauthors of a recent report on sexuality and gender that has attracted substantial media attention. It was published by the Ethics and Public Policy Center, a conservative think tank "dedicated to applying the Judeo-Christian moral tradition to critical areas of public policy," in its non-peer reviewed journal *The New Atlantis*.

The article claims to be "a careful summary and an up-to-date explanation of research — from the biological, psychological, and social sciences — related to sexual orientation and gender identity." It claims to show sexual orienation is chosen and not fixed, and that gay people are not "born gay." In truth, it is a selective and outdated collection of references and arguments aimed at confusing rather than clarifying our understanding of sexual orientation and gender identity.

Mayer and McHugh begin by baldly stating that sexual orientation is an "ambiguous" concept compared to other psychological traits, and that there are "currently no agreed-upon definitions for purposes of empirical research."

This is pure balderdash. The scientists who actually work in this area widely accept the American Psychological Asdociation's definition of sexual orientation as "an enduring pattern of emotional, romantic and/or sexual attractions to men, women or both sexes," and we have reliable, empirically validated ways to study it. Sexual orientation may be complex — every human characteristic is — but it is certainly far less complicated and ambiguous than many of the facets of personality that psychologists spend their time attempting to measure and study; e.g., "warmth," "self-esteem," and "imagination."

The authors' review of the role of genes in sexual orientation, the area of my own research, is revealing of their methodology. Of the six studies using proper probability sampling methods that have been published in the peer-reviewed literature in the past 16 years, they include only one — and it just so happens to be the one with the lowest estimate of genetic influence of the entire set. They then discuss, at great length, an obscure study of 7th-to 12th-graders, published in a sociology journal, that doesn't even measure sexual orientation, instead relying on a single question about "romantic attraction." It's an odd choice of articles to review given Mayer and McHugh's emphasis on proper trait measurement; perhaps they were driven by the fact that it failed to find any heritability, thus supporting their claim that nobody is "born gay." A very different conclusion was reached by a careful meta-analysis of *all* the available twin data, recently published in a large review that Mayer and McHugh fail to even mention.

This type of data cherry-picking makes the section of the report on gender identity equally unreliable. For example, the authors come out strongly against affirming the identities of transgender children, arguing that their "dysphoria," as they insist on pathologizing gender fluidity, might be transient. But they neglect two very important recent studies showing that trans children who are affirmed by their parents are as happy and healthy as their peers, and that allowing them to express their true gender decreases depression and anxiety.

The section of the report on mental health correlates rings especially false. It begins by acknowledging several studies demonstrating that the prejudice, discrimination, and stigma experienced by LGBT people are significant contributors to their increased rates of depression, substance abuse, and suicidality. But instead of focusing on how such social stressors might be reduced, the authors jump to the conclusion, with no supporting evidence or calculations

whatsoever, that these factors are insufficient to fully explain the observed mental health discrepancies. The not-too-subtle implication is that LGBT people are intrinsically defective, and that no amount of legal or societal acceptance will ever fix them.

Equally dubious are the authors' repeated calls for "more research." Mayer has never published a single article on human sexuality or gender (his name doesn't even appear in the paper's bibliography), and McHugh actually has a long history of blocking such efforts, beginning with his closure of the pioneering gender identity clinic at Johns Hopkins in 1979. McHugh claimed that his decision was based in science, but his real motivation became clear through his repeated reference to gender-confirmation surgery as a "mutilation" and his decision to explain his actions not in a scientific journal but in a conservative Catholic publication.

Rest assured that this report will have zero impact in the scientific world, which gives vanity journals like *The New Atlantis* about the same credence as the *National Enquirer.* It does, however, lend a certain air of legitimacy to the anti-LGBT arguments of various right-wing groups in the U.S. (which have received the publication with glee), the religious fundamentalists who are working to export homophobia to the developing world, and of course to pseudo-scientific organizations such as NARTH that promote "conversion therapy."

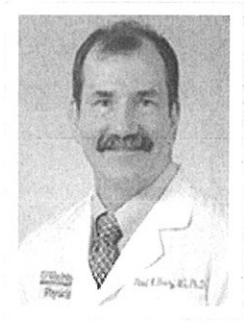
Over the past two decades, I've been gratified by the gradual increase in knowledge and acceptance of the deeply rooted, intrinsic origins of sexual orientation and gender identity, and equally pleased by the growing realization that freedom of sexuality and gender are basic human rights independent of any scientific explanation. It doesn't upset me all that much when politicians and priests dispute the facts; after all, the Catholic Church only admitted that Galileo was right in 1992 (the same year I started my research at the National Institutes of Health), and it still doesn't accept Darwin.

But when the data we have struggled so long and hard to collect is twisted and misinterpreted by people who call themselves scientists, and who receive the benefits and protection of a mainstream institution such as John Hopkins Medical School, it disgusts me.

DEAN HAMER, Ph.D., is a scientist emeritus at the National Institutes of Health.

Exhibit D

Paul W. Hruz, M.D., Ph.D. Hruz_P@wustl.edu (mailto:Hruz_P@wustl.edu)



Division Chief, Endocrinology and Diabetes
Associate Professor of Pediatrics, Endocrinology and Diabetes
Associate Professor of Pediatrics, Cell Biology & Physiology

View my lab (http://research.peds.wustl.edu/labs/hruz_paul_w)

Cell Biology & Physiology (http://www.cellbiology.wustl.edu/)
Endocrinology and Diabetes (http://peds.wustl.edu/endodiabetes/)

phone: (314) 454-6051

Research Interests

Dr. Hruz's research interests include intermediary carbohydrate metabolism, glucose transporter structure and function and mechanism of insulin action. Currently, the mechanism(s) by which HIV protease inhibitors cause serious adverse metabolic effects including peripheral lipoatrophy, visceral adiposity, hypertriglyceridemia, and insulin resistance are being investigated. The laboratory has discovered that HIV protease inhibitors selectively and reversibly inhibit the GLUT4 facilitative glucose transporter. Ongoing studies are being directed toward elucidating the selectivity of these drugs in blocking the activity of each of the known facilitative glucose transport proteins. The tertiary structure of the facilitative glucose transporters is also being investigated using state-of-the-art biophysical approaches.

Education

- BS, Marquette University, 1987
- PhD, Medical College of Wisconsin, 1993
- MD, Medical College of Wisconsin, 1994

Training

- Pediatric Residency, University of Washington, 1994 - 1997
- Pediatric Endocrinology Fellowship, Washington University, 1997 - 2000
- Certification in Healthcare Ethics, National Catholic Bioethics Center, 2017

Licensure and Board Certification

- Board Certified in General Pediatrics , 1997
- MO, Stae License , 2000
- Board Certified in Pediatric Endocrinology & Metabolism , 2001

Honors

- National Institute of Chemists Research and Recognition Award, 1987
- Phi Beta Kappa, 1987
- Phi Lambda Upsilon (Honorary Chemical Society), 1987
- American Heart Association Predoctoral Fellowship Award, 1988
- Alpha Omega Alpha, 1994
- Armond J. Quick Award for Excellence in Biochemistry, 1994
- NIDDK/Diabetes Branch Most Outstanding Resident, 1994
- Pfizer Postdoctoral Fellowship Award, 1998
- Scholar, Child Health Research Center of Excellence in Developmental Biology at Washington University, 2002
- Julio V Santiago, M.D. Scholar in Pediatrics, 2013
- Redemptor Hominis Award for Outstanding Contributions to the Study of Bioethics , 2017
- Eli Lilly Outstanding Contribution to Drug Discovery: Emerging Biology Award, 2018

Selected Publications

view all (52)

Publication Co-Authors


(odom_a)


(rudnick_david_a)


(DeBosch_B)


(jay_p)


(turmelle_y)

Washington University has a long tradition of collaboration amongst colleagues.The faculty above have co-authored publications with Paul W. Hruz, M.D., Ph.D.

1. Hresko RC, Kraft TE, Quigley A, Carpenter EP, Hruz PW. Mammalian Glucose Transporter Activity is Dependent upon Anionic and Conical Phospholipids. *J Biol Chem*. 2016.
doi: 10.1074/jbc.M116.730168 (https://doi.org/10.1074/jbc.M116.730168)
(https://doi.org/10.1074/jbc.M116.730168)
PMID: 27302065 (https://www.ncbi.nlm.nih.gov/pubmed/?term=27302065)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=27302065)
2. DeBosch BJ, Heitmeier MR, Mayer AL, Higgins CB, Crowley JR, Kraft TE, Chi M, Newberry EP, Chen Z, Finck BN, Davidson NO, Yarasheski KE, Hruz PW, Moley KH. Trehalose inhibits solute carrier 2A (SLC2A) proteins to induce autophagy and prevent hepatic steatosis. *Sci Signal*. 2016;9(416):ra21.
doi: 10.1126/scisignal.aac5472 (https://doi.org/10.1126/scisignal.aac5472)
(https://doi.org/10.1126/scisignal.aac5472)
PMID: 26905426 (https://www.ncbi.nlm.nih.gov/pubmed/?term=26905426)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=26905426)
3. Kraft TE, Armstrong C, Heitmeier MR, Odom AR, Hruz PW. The Glucose Transporter PfHT1 Is an Antimalarial Target of the HIV Protease Inhibitor Lopinavir. *Antimicrob Agents Chemother*. 2015;59(10):6203-9.
doi: 10.1128/AAC.00899-15 (https://doi.org/10.1128/AAC.00899-15)
(https://doi.org/10.1128/AAC.00899-15)
PMCID: PMC4576095 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4576095/?report=abstract) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4576095/?report=abstract)
PMID: 26248369 (https://www.ncbi.nlm.nih.gov/pubmed/?term=26248369)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=26248369)
4. Kraft TE, Hresko RC, Hruz PW. Expression, purification, and functional characterization of the insulin-responsive facilitative glucose transporter GLUT4. *Protein Sci*. 2015.
doi: 10.1002/pro.2812 (https://doi.org/10.1002/pro.2812)
(https://doi.org/10.1002/pro.2812)
PMID: 26402434 (https://www.ncbi.nlm.nih.gov/pubmed/?term=26402434)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=26402434)
5. Mishra RK, Wei C, Hresko RC, Bajpai R, Heitmeier M, Matulis SM, Nooka AK, Rosen ST, Hruz PW, Schiltz GE, Shanmugam M. In Silico Modeling-based Identification of Glucose Transporter 4 (GLUT4)-selective Inhibitors for Cancer Therapy. *J Biol Chem*. 2015;290(23):14441-53.
doi: 10.1074/jbc.M114.628826 (https://doi.org/10.1074/jbc.M114.628826)
(https://doi.org/10.1074/jbc.M114.628826)
PMID: 25847249 (https://www.ncbi.nlm.nih.gov/pubmed/?term=25847249)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=25847249)

6. Hresko RC, Kraft TE, Tzekov A, Wildman SA, Hruz PW. Isoform-selective inhibition of facilitative glucose transporters: elucidation of the molecular mechanism of HIV protease inhibitor binding. *J Biol Chem*. 2014;289(23):16100-16113.
doi: 10.1074/jbc.M113.528430 (https://doi.org/10.1074/jbc.M113.528430)
(https://doi.org/10.1074/jbc.M113.528430)
PMCID: PMC4047383 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4047383/?report=abstract) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4047383/?report=abstract)
PMID: 24706759 (https://www.ncbi.nlm.nih.gov/pubmed/?term=24706759)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=24706759)
7. Vyas AK, Aerni-Flessner LB, Payne MA, Kovacs A, Jay PY, Hruz PW. Saxagliptin Improves Glucose Tolerance but not Survival in a Murine Model of Dilated Cardiomyopathy. *Cardiovasc Endocrinol*. 2012;1(4):74-82.
doi: 10.1097/XCE.0b013e32835bfb24
(https://doi.org/10.1097/XCE.0b013e32835bfb24)
(https://doi.org/10.1097/XCE.0b013e32835bfb24)
PMCID: PMC3686315 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3686315/?report=abstract) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3686315/?report=abstract)
PMID: 23795310 (https://www.ncbi.nlm.nih.gov/pubmed/?term=23795310)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=23795310)
8. Aerni-Flessner L, Abi-Jaoude M, Koenig A, Payne M, Hruz PW. GLUT4, GLUT1, and GLUT8 are the dominant GLUT transcripts expressed in the murine left ventricle. *Cardiovasc Diabetol*. 2012;11:63.
doi: 10.1186/1475-2840-11-63 (https://doi.org/10.1186/1475-2840-11-63)
(https://doi.org/10.1186/1475-2840-11-63)
PMCID: PMC3416696 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3416696/?report=abstract) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3416696/?report=abstract)
PMID: 22681646 (https://www.ncbi.nlm.nih.gov/pubmed/?term=22681646)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=22681646)
9. Remedi MS, Agapova SE, Vyas AK, Hruz PW, Nichols CG. Acute sulfonylurea therapy at disease onset can cause permanent remission of KATP-induced diabetes. *Diabetes*. 2011;60(10):2515-22.
doi: 10.2337/db11-0538 (https://doi.org/10.2337/db11-0538)
(https://doi.org/10.2337/db11-0538)
PMCID: PMC3178299 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3178299/?report=abstract) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3178299/?report=abstract)
PMID: 21813803 (https://www.ncbi.nlm.nih.gov/pubmed/?term=21813803)
(https://www.ncbi.nlm.nih.gov/pubmed/?term=21813803)

10. Hruz PW. Molecular mechanisms for insulin resistance in treated HIV-infection. *Best Pract Res Clin Endocrinol Metab*. 2011;25(3):459-68.
doi: 10.1016/j.beem.2010.10.017 (https://doi.org/10.1016/j.beem.2010.10.017) (https://doi.org/10.1016/j.beem.2010.10.017)
PMCID: PMC3115529 (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3115529/?report=abstract) (http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3115529/?report=abstract)
PMID: 21663839 (https://www.ncbi.nlm.nih.gov/pubmed/?term=21663839) (https://www.ncbi.nlm.nih.gov/pubmed/?term=21663839)

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Exhibit E

No. 16-273

In The
Supreme Court of the United States

GLOUCESTER COUNTY SCHOOL BOARD,

Petitioner,

v.

G.G., by his next friend and mother, DEIRDRE GRIMM,

Respondent.

On Writ Of Certiorari To The United States Court Of Appeals For The Fourth Circuit

BRIEF OF *AMICI CURIAE* DR. PAUL R. MCHUGH, M.D., DR. PAUL HRUZ, M.D., PH.D., AND DR. LAWRENCE S. MAYER, PH.D. IN SUPPORT OF PETITIONER

GERARD V. BRADLEY
Counsel of Record
NOTRE DAME LAW SCHOOL
3156 Eck Hall of Law
Notre Dame, IN 46556
(574) 631-8385
Gerard.V.Bradley.16@nd.edu

TORY H. LEWIS
Attorney at Law
1320 Robb Court
Little Rock, AR 72223
(615) 712-1573
thlewis84@gmail.com

Counsel for Amici Curiae

COCKLE LEGAL BRIEFS (800) 225-6964
WWW.COCKLELEGALBRIEFS.COM

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INTEREST OF *AMICI CURIAE*[1]

Amicus curiae Paul R. McHugh, M.D. is the University Distinguished Service Professor of Psychiatry at the Johns Hopkins University School of Medicine. From 1975 until 2011, Dr. McHugh was the Henry Phipps Professor of Psychiatry and the director of the Department of Psychiatry and Behavioral Science at Johns Hopkins. At the same time, he was psychiatrist-in-chief at the Johns Hopkins Hospital with overall responsibility for the proper care and treatment of patients with, among other issues, sexual disorders.

Amicus curiae Paul W. Hruz, M.D., Ph.D. is Associate Professor of Pediatrics and Chief of Pediatric Endocrinology at Washington University School of Medicine. He also holds an appointment as Associate Professor of Cell Biology and Physiology. Dr. Hruz is an active member of the Washington University Disorders of Sexual Development ("DSD") Interdisciplinary Team. Over the past twenty years, Dr. Hruz has participated in the care of hundreds of children with DSDs.

Amicus curiae Lawrence S. Mayer, M.D., Ph.D. is a professor of statistics and biostatistics at Arizona

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[1] Parties to this case have consented to the filing of this Brief. As reflected in the Court's docket on November 22, 2016, counsel for Petitioner consented to the filing of *amicus curiae* briefs in support of either party or of neither party. A letter indicating Respondent's consent is on file with the Clerk. *Amici* state that no counsel for a party authored this Brief in whole or in part. The Witherspoon Institute provided financial support for printing this Brief; otherwise, neither the parties nor anyone else contributed financial support for this Brief.

State University and a Scholar in Residence in the Department of Psychiatry at the Johns Hopkins University School of Medicine. Before July 1, 2016, he was an Adjunct Professor of Psychiatry and Public Health in the Bloomberg School of Public Health and School of Medicine at Johns Hopkins University and a member of the research faculty at Mayo Clinic. Dr. Mayer has lectured and published extensively on models of human development including adolescent and teen psychosexual development.

Drs. McHugh, Hruz, and Mayer appear as *amici* to critically evaluate, on the basis of their clinical and scientific expertise, the Fourth Circuit's mandate, which was urged upon that court by the Respondent, that school districts (and other affected entities) enforce "gender-affirming" policies and practices for students who identify as a gender that is different from their biological sex. These policies include providing these children with unimpeded access to restrooms and other private areas according to their self-identified gender.

Amici do not in this Brief address the considerable distress that some children (a little girl, say) are likely to experience if they are exposed in a bathroom, shower, or locker room to someone who identifies as being her sex (female), but who is, according to all or most appearances, a member of the opposite sex (male). *Amici* instead focus on the children these policies are intended to help – those (like Respondent) who are "transgendered" in that they have an insistent, persistent and consistent identification as the opposite sex.

Amici consider the medical and scientific evidence bearing upon the question: Does the Fourth Circuit's ruling help or harm these vulnerable and needy children?

SUMMARY OF ARGUMENT

Amici are physician scientists who do not hold themselves out as experts in any area of the law including statutory construction. They proffer no account of what was being debated at the time of the passage of Title IX and its ban upon sex discrimination. *Amici* leave the legal arguments to others.

Amici nonetheless observe that the legal issues in this lawsuit center upon the meaning of the term *sex* in Title IX, added in 1972 to the federal Civil Rights Acts. *Amici* further observe that, for the duration of their long professional careers (McHugh graduated from Harvard Medical School in 1956, Hruz has treated sexual disorders in children for twenty years, and Mayer began working as a medical doctor in 1970), the term *sex* has almost invariably referred to one's being male or female in the objective, biological sense. *Amici* note too that the term *gender* came into use to indicate something quite different from *sex* – namely, a society's expectations for how males and females should behave. *Sex* is innate, fixed, and binary; *gender* is a fluid cultural construct.

Amici do not claim to know exactly how or why Respondent and the Fourth Circuit came to so thoroughly

confuse *sex* and *gender* (or to transpose them, as if gender was innate and fixed at birth, while sex was malleable and the body configurable to one's sense of gender identity). But this confusion is surely founded, at least in part, upon a host of mostly unsupported, and some glaringly mistaken, assertions regarding what the contemporary scientific research has shown.

Respondent maintains that, although in every biological and physiological way a girl, she is *really* a boy.[2] But gender is culturally defined. Currently in the United States, it is defined as a persistent identification with a set of norms promoted by society as the behaviors, attitudes, and preferences associated with each sex. The definition is not biological. Choosing a gender – i.e., deciding to live as one sex or the other – neither is caused by nor causes any biological changes. There is no credible scientific literature that suggests that a person's choice of gender affects their biology in any way. One's sense of self and one's desire to present to others as a member of the opposite sex have no bearing whatsoever upon the objective biological reality that one is male or female.

No doubt many people, including some children, experience disquiet with their sex. They struggle with the project of identifying with their sex. Some feel a distressing and persisting incongruity between their sex and their sense of themselves as male or female.

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[2] G.G. says, "I was born in the wrong sex," App. 151a, meaning (evidently) that she was at birth a boy, albeit one saddled with a girl's body.

But no matter how disturbing this condition of *gender dysphoria* may be, nothing about it affects the objective reality that those suffering from it remain the male or female persons that they were at conception, at birth, and thereafter – any more than an anorexic's belief that she is overweight changes the fact that she is, in reality, slender.

In this Brief, *amici* leave aside all questions about how best to treat gender dysphoria in adults. *Amici* focus instead on how to treat children and adolescents like G.G. who suffer from this psychological disorder. More exactly, *amici* critically evaluate the scientific bases, if any, for the gender-affirming policies the Fourth Circuit has required.

According to the court below, school districts are required by law to treat students in accordance with their asserted gender identity instead of their biological sex. There is, however, no scientific evidence that such a gender-affirming mandate helps the children it aims to help.

In fact, and to the contrary, there is abundant scientific evidence that (1) the Fourth Circuit's mandated policy does none of the children it is meant to serve any real or lasting good; (2) it harms the vast majority of them; and (3) it leads to catastrophic outcomes for many such afflicted children.

Amici conclude, based upon decades of academic study and clinical experience in the fields of psychiatry, psychology, and the biological bases of both of those

fields, that the Fourth Circuit has mandated a scientifically unwarranted, dangerous experiment upon our nation's children, with no apparent consideration at all of its far-reaching implications.

ARGUMENT

I. A Child's *Gender Identity* Has No Bearing on His or Her *Sex*.

Sex and *gender* represent two very distinct features of our world. While *sex* is binary and objective, determined fundamentally by one's chromosomal constitution, and ultimately by clearly defined reproductive capacities, *gender* is a subjective sense of a social role generated by cultural norms. Respondent maintains that her subjective sense of herself – i.e., her *gender identity* – is and should be accepted as her sex. That is simply not the case.

The central underlying basis for *sex* is the distinction between the reproductive roles of males and females. *See* Lawrence S. Mayer and Paul R. McHugh, *Sexuality and Gender: Findings from the Biological, Psychological, and Social Sciences*, New Atlantis, Fall 2016, at 89-90. In biology, an organism is male or female if it is biologically and physiologically designed to perform one of the respective roles in reproduction. This definition does not depend upon amorphous physical characteristics or behaviors; it requires understanding the reproductive system and its processes.

Reproductive roles provide the conceptual basis for the differentiation of animals into the biological categories of male and female. There is no other widely accepted biological classification for the sexes. One's reality as male or female is more than a matter of reproductive "plumbing." Sex is a physiological reality which permeates every cell of an organism.

Sex is thus innate and immutable. The genetic information directing development of male or female gonads and other primary sexual traits, which normally are encoded on chromosome pairs "XY" and "XX," are present immediately upon conception. As early as eight weeks' gestation, endogenously produced sex hormones cause prenatal brain imprinting that ultimately influences postnatal behaviors. *See* Francisco I. Reyes *et al.*, *Studies on Human Sexual Development*, 37 J. of Clin. Endocrinology & Metabolism 74-78 (1973); Michael Lombardo, *Fetal Testosterone Influences Sexually Dimorphic Gray Matter in the Human Brain*, 32 J. of Neuroscience 674-80 (2012); Geneva Foundation for Medical Education and Research, "Human Sexual Differentiation" (2016), *available at* http://www.gfmer.ch/Books/Reproductive_health/Human_sexual_differentiation.html. It is therefore not the reproductive system alone that carries one's sexual identity. Every cell in the body is marked with a sexual identity by its chromosomal constitution XX or XY.

Thus, sex is not "assigned" at birth, as Respondent suggests; rather, it "declares itself anatomically in utero and is acknowledged at birth." Michelle A.

Cretella, *Gender Dysphoria in Children and Suppression of Debate*, 21 J. of Am. Physicians & Surgeons 50, 51 (2016). A baby's sex – male or female – is recognized and recorded at birth.

In contrast, *gender* has come to refer to "the socially constructed roles, behaviors, activities, and attributes that a given society considers appropriate for boys and men or girls and women," which "influence the ways that people act, interact, and feel about themselves." American Psychological Association, *Answers to Your Questions About Transgender People, Gender Identity and Gender Expression* (2011), *available at* http://www.apa.org/topics/lgbt/transgender.pdf. A child's *gender* reflects the extent to which he or she conforms to or deviates from socially normative behavior for boys or girls.

When it is defined in this manner, gender is fuzzy and mercurial. There is no objective definition for what it means to behave like a boy or a girl. Moreover, what is considered gender-typical behavior for boys and girls changes over time within a given culture[3] and varies between cultures. A girl who behaves like a tomboy may modify her behavior as she ages, and a boy who

[3] Just a few decades ago, in the United States it would have been atypical for women to attend law school or medical school. It is projected that women will outnumber men in law schools in 2017. Debra Cassens Weiss, "Women Could Be a Majority of Law Students in 2017; These Schools Have 100-Plus Female Majorities," ABA Journal, Mar. 16, 2016, http://www.abajournal.com/news/article/women_could_be_majority_of_law_students_in_2017_these_schools_have_100_plus.

prefers quiet play may eventually develop an interest in sports or hunting. Consequently, *gender* is a fluid concept with no truly objective meaning. Judith Butler, *Gender Trouble: Feminism and the Subversion of Identity* 6-7 (1990) (stating that "[g]ender is neither the causal result of sex nor as seemingly fixed as sex," but rather "a free-floating artifice, with the consequence that *man* and *masculine* might just as easily signify a female body as a male one, and *woman* and *feminine* a male body as easily as a female one") (emphases in original).

II. *Gender Dysphoria* Is a Psychological Disorder Distinguished by Confused and Distressed Thinking About the Reality of One's Sex.

A gender dysphoric child such as Respondent experiences a marked sense of incongruity between the gender expectations linked to her biological sex and her biological sex itself. Tomer Shechner, *Gender Identity Disorder: A Literature Review from a Developmental Perspective*, 47 Isr. J. of Psychiatry & Related Sci. 132-38 (2010). Gender dysphoric boys subjectively feel as if they are girls, and gender dysphoric girls subjectively feel as if they are boys – according to their sense (at whatever stage of childhood they happen to be) of what that feeling of being a member of the opposite sex must be like. *See* American Psychological Association, *Diagnostic & Statistical Manual of Mental Disorders* [hereinafter, "*DSM-5*"] 452 (5th ed. 2013).

Yet those subjective feelings, strong as they may be, cannot and do not constitute (or transform) objective reality. Cretella, *supra*, at 51 ("[T]his 'alternate perspective' of an 'innate gender fluidity' arising from prenatally 'feminized' or 'masculinized' brains trapped in the wrong body is an ideological belief that has no basis in rigorous science."); J. Michael Bailey and Kiira Triea, *What Many Transsexual Activists Don't Want You to Know and Why You Should Know It Anyway*, 50 Perspectives in Biology & Med. 521-34 (2007) (finding little scientific basis for the belief that male-to-female transsexuals are women trapped in men's bodies). A gender dysphoric girl is not a boy trapped in a girl's body, and a gender dysphoric boy is not a girl trapped in a boy's body.[4] Respondent is a girl, even though she feels the way she thinks a boy feels.

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[4] Studies of brain structure and function have not demonstrated any conclusive, biological basis for transgenderism. *See* Giuseppina Rametti *et al*., *White Matter Microstructure in Female to Male Transsexuals Before Cross-sex Hormonal Treatment. A Diffusion Tensor Imaging Study*, 45 J. of Psychiatric Res. 199-204 (2011) (offering no evidence to support the hypothesis that transgenderism is caused by differences in the structure of the brain); Giuseppina Rametti *et al.*, *The Microstructure of White Matter in Male to Female Transsexuals Before Cross-sex Hormonal Treatment. A DTI Study*, 45 J. of Psychiatric Res. 949-54 (2011) (same); Emiliano Santarnecchi *et al*., *Intrinsic Cerebral Connectivity Analysis in an Untreated Female-to-Male Transsexual Subject: A First Attempt Using Resting-State fMRI*, 96 Neuroendoctrinology 188-93 (2012) (in a study of brain activity, finding that a transsexual's brain profile was more closely related to his biological sex than his desired one); Hans Berglund *et al*., *Male-to-Female Transsexuals Show Sex-Atypical Hypothalamus Activation When Smelling Odorous Steroids*, 18 Cerebral Cortex 1900-08 (2008) (in a study of brain activity, finding no support for

III. There Is No Scientific or Medical Support for Treating Gender Dysphoric Children in Accordance with Their *Gender Identity* Rather than Their *Sex*.

In standard medical and psychological practice, a child who has a persistent, mistaken belief that is inconsistent with reality is not encouraged in his or her belief. *See* Cretella, *supra*, at 51 (listing other similar such conditions); Anne Lawrence, *Clinical and Theoretical Parallels Between Desire for Limb Amputation and Gender Identity Disorder*, 35 Archives of Sexual Behavior 263-78 (2006) (finding similarities between body integrity identity disorder and gender dysphoria). For instance, an anorexic child is not encouraged to lose weight. She is not treated with liposuction; instead, she is encouraged to align her belief with reality – i.e., to see herself as she really is. Indeed, this approach is not just a good guide to sound medical practice. It is common sense.

Until recently this was precisely how gender dysphoric children were treated. Dr. Kenneth Zucker, long acknowledged as one of the foremost authorities on gender dysphoria in children, spent years helping his

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the hypothesis that transgenderism is caused by some innate, biological condition of the brain). Some researchers believe that transgenderism can be attributed to other biological causes, such as hormone exposure in utero. *See, e.g.*, Nancy Segal, *Two Monozygotic Twin Pairs Discordant for Female-to-Male Transsexualism*, 35 Archives of Sexual Behav. 347-58 (2006) (examining two sets of twins and hypothesizing, without evidence, that uneven prenatal androgen exposures led one twin in each set to be transsexual). Presently, no scientific evidence supports that belief.

patients align their subjective gender identity with their objective biological sex. He used psychosocial treatments (talk therapy, organized play dates, and family counseling) to treat gender dysphoria and had much success.[5] *See* Cretella, *supra*, at 51 (describing his work); Kenneth J. Zucker *et al.*, *A Developmental, Biopsychosocial Model for the Treatment of Children with Gender Identity Disorder*, 59 J. of Homosexuality 369-97 (2012).

Dr. Zucker's eminently sound practice is anchored by recognition of the ineradicable reality that each child is immutably either male or female. It is also influenced by the universally recognized fact that gender dysphoria in children is almost always transient: the vast majority of gender dysphoric children naturally reconcile their gender identity with their biological sex. All competent authorities agree that between 80 and 95 percent of children who say that they are transgender naturally come to accept their sex and to enjoy emotional health by late adolescence. The American College of Pediatricians, for example, recently concluded that approximately 98 percent of gender-confused boys, and 88 percent of gender-confused girls,

[5] In a follow-up study by Dr. Zucker and colleagues of children treated by them over the course of thirty years at the Center for Mental Health and Addiction in Toronto, they found that gender dysphoria persisted in only three of the twenty-five girls they had treated. Kelley D. Drummond *et al.*, *A Follow-up Study of Girls with Gender Identity Disorder*, 44 Developmental Psychology 34-45 (2008).

naturally resolve.[6] The American Psychological Association's Diagnostic and Statistical Manual of Mental Disorders concurs. *DSM-5*, *supra*, at 455.

Traditional psychosocial treatments for gender dysphoria, such as those employed by Dr. Zucker, are therefore prudent and natural; they work with and not against the facts of science and the predictable rhythms of children's psycho-sexual development. They give gender dysphoric children the opportunity to reconcile their subjective gender identity with their objective biological sex without any irreversible effects or the use of harmful medical treatments.

Although some researchers report that they have identified certain factors which are associated with the persistence of gender dysphoria into adulthood,[7] there is no evidence that any clinician can identify the perhaps one-in-twenty children for whom gender dysphoria will last with anything approaching certainty. Because such a large majority of these children will surely naturally resolve their confusion, proper medical practice calls for a cautious, wait-and-see, approach for all gender dysphoric children. This sensible approach can be and often is rightly supplemented in many cases by family or individual psychotherapy to

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[6] American College of Pediatricians, *Gender Ideology Harms Children*, Aug. 17, 2016, *available at* https://www.acpeds.org/the-college-speaks/position-statements/gender-ideology-harms-children.

[7] *See, e.g.*, Thomas D. Steensma *et al*., *Factors Associated with Desistence and Persistence of Childhood Gender Dysphoria: A Quantitative Follow-up Study*, 52 J. of the Am. Acad. of Child & Adolescent Psychiatry 582-90 (2013).

identify and treat the underlying problems which present as the belief that one belongs to the opposite sex.

Policies and protocols that treat children who experience gender-atypical thoughts or behavior as if they belong to the opposite sex, on the contrary, interfere with the natural progress of psycho-sexual development. Such treatments encourage a gender dysphoric child like the Respondent to adhere to his or her false belief that he or she is the opposite sex. These treatments would help the child to maintain his or her delusion but with less distress by, among other aspects, requiring others in the child's life to go along with the charade. This is essentially what the Fourth Circuit is requiring here. Importantly, there are no long-term, longitudinal, control studies that support the use of gender-affirming policies and treatments for gender dysphoria. Cretella, *supra*, at 52.[8]

The Fourth Circuit's mandated gender-affirming therapy is therefore a novel experiment. In light of all the existing scientific evidence – some more of which we shall explore forthwith – it amounts to nothing more than quackery.

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[8] Nonetheless, gender affirmance is on the rise – particularly among children. Chris Smyth, *Better Help Urged for Children With Signs of Gender Dysphoria*, The Times (London), October 25, 2013, http://www.thetimes.co.uk/tto/health/news/article3903783.ece (stating that the United Kingdom saw a fifty percent increase in the number of children referred to gender dysphoria clinics from 2011 to 2012). There are now forty gender clinics across the United States that provide and promote gender-affirming treatments. Cretella, *supra*, at 52.

IV. Gender-Affirming Policies Generally Harm, Rather than Help, Gender Dysphoric Children.

The Fourth Circuit would require those affected by its writ and who interact with G.G. to affirm (at least implicitly, by action or inaction) that she is a boy. G.G.'s false belief would thus be perpetuated through name and pronoun changes, the "successful" impersonation of the opposite sex within and outside of the home, and "acceptance" (forced, from some) by others that she is really a male. This could be viewed by some as a necessary but basically harmless expedient, a bit of play-acting to help those like G.G. to feel better about themselves during a difficult time in their lives.

There is substantial evidence, however, that this approach is harmful – even when it is viewed on its own terms as a way to help the afflicted child get through a tough time. The American College of Pediatricians recently declared:

> There is an obvious self-fulfilling nature to encouraging young [gender dysphoric] children to impersonate the opposite sex and then institute pubertal suppression. If a boy who questions whether or not he is a boy (who is meant to grow into a man) is treated as a girl, then has his natural pubertal progression to manhood suppressed, have we not set in motion an inevitable outcome? All of his same-sex peers develop into young men, his opposite sex friends develop into young women, but he

> remains a pre-pubertal boy. He will be left psycho-socially isolated and alone.[9]

American College of Pediatricians, *supra*.

It is well-recognized, too, that repetition has some effect on the structure and function of a person's brain. This phenomenon, known as *neuroplasticity*, means that a child who is encouraged to impersonate the opposite sex may be less likely to reverse course later in life.[10] For instance, if a boy repeatedly behaves as a girl, his brain is likely to develop in such a way that eventual alignment with his biological sex is less likely to occur. Cretella, *supra*, at 53. Obviously then, some number of gender dysphoric children who would naturally come to peacefully accept their true sex are prevented from doing so by gender-affirming policies like those mandated by the Fourth Circuit.

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[9] G.G., for example, refuses to use any of the three unisex restrooms made available to all students at her school, because doing so made her feel "stigmatized and isolated." App. 151a. It is not meant as a criticism of G.G. to observe that the real source of her feelings of "isolation" may have nothing to do with using a restroom meant for *anyone* who needs or wants a bit more privacy.

[10] One study showed that the white matter microstructure of specific brain areas in female-to-male transsexuals was more similar to that of heterosexual males than to that of heterosexual females. *See* Giuseppina Rametti *et al*., *White Matter Microstructure in Female to Male Transsexuals Before Cross-sex Hormonal Treatment. A Diffusion Tensor Imaging Study*, 45 J. of Psychiatric Res. 199-204 (2011). The results of that study may be explained by neuroplasticity.

Policies that encourage gender dysphoric children to pursue transgender lifestyles do not exist in an ideological vacuum. Because they are not supported by medical or scientific evidence, one should not be surprised to discover that policies such as that required by the Fourth Circuit are nested within a larger ideology about how to "help" children who believe that they are trapped in the wrong bodies. Although these gender-affirming policies do not themselves *require* pharmaceutical or surgical interventions, corresponding medical treatments – puberty suppression, hormone therapy, and surgical interventions – are a common complement. The more that gender affirmance is promoted to children, the more that children can be expected to accept, and even to pursue, these drastic medical courses.

The gender dysphoric child surrounded by adults and peers who go along with his or her delusion is likely to perceive his natural biological development as a source of distress. Puberty suppressing hormones are then typically used, beginning at age eleven, to prevent the appearance of natural but (in this case) unwanted characteristics of any maturing member of the child's sex. Henriette A. Delemarre-van de Waal and Peggy T. Cohen-Kettenis, *Clinical Management of Gender Identity Disorder in Adolescents: A Protocol on Psychological and Pediatric Endocrinology Aspects*, 155 Eur. J. of Endocrinology S131, S132 (2006). Then, starting at age sixteen, cross-sex hormones are administered in order to induce something like the process of puberty that would normally occur for the opposite sex. *Id.* at S133.

Dr. Michelle Cretella, President of the American College of Pediatricians, has written that these medical treatments are "neither fully reversible nor harmless." Cretella, *supra*, at 53. Puberty suppression hormones prevent the development of secondary sex characteristics, arrest bone growth, decrease bone accretion, prevent full organization and maturation of the brain, and inhibit fertility. *Id.* Cross-gender hormones increase a child's risk for coronary disease and sterility. *Id.* at 50, 53. Oral estrogen, which is administered to gender dysphoric boys, may cause thrombosis, cardiovascular disease, weight gain, hypertriglyceridemia, elevated blood pressure, decreased glucose tolerance, gallbladder disease, prolactinoma, and breast cancer. *Id.* at 53 (citing Eva Moore *et al*., *Endocrine Treatment of Transsexual People: A Review of Treatment Regimens, Outcomes, and Adverse Effects*, 88 J. of Clin. Endocrinology & Metabolism 3467-73 (2003)). Similarly, testosterone administered to gender dysphoric girls may negatively affect their cholesterol; increase their homocysteine levels (a risk factor for heart disease); cause hepatotoxicity and polycythemia (an excess of red blood cells); increase their risk of sleep apnea; cause insulin resistance; and have unknown effects on breast, endometrial and ovarian tissues. *Id.* (citing Moore, *supra*, at 3467-73). Finally, girls may legally obtain a mastectomy at sixteen, which carries with it its own unique set of future problems, especially because it is irreversible. *Id.* (citing Lauren Schmidt, *Psychological Outcomes and Reproductive Issues Among Gender Dysphoric Individuals*, 44 Endocrinology Metabolism Clinics of N. Am. 773-85 (2015). The Hayes

Directory reviewed all the relevant literature on these treatments in 2014 and gave them its lowest possible rating: the research findings were "too sparse" and "too limited" to suggest conclusions. Hayes, Inc., "Hormone Therapy for the Treatment of Gender Dysphoria," *Hayes Medical Technology Directory* (2014).

Children are not legally capable of assessing the severity of these risks or weighing the perceived benefits of gender affirmance (if any) against their many harms. Neurologically, the adolescent brain is immature and lacks an adult capacity for risk assessment prior to the early to mid-20s. Cretella, *supra*, at 53. Yet, gender-affirming policies urge gender dysphoric children to forgo their fertility and jeopardize their physical health in order to avoid the distress of natural physical development.

Parents or guardians would of course have to consent to these interventions on behalf of their minor children. Even assuming that these adults have the true best interests of their children at heart, how many of them are going to be well-informed of the truth about gender dysphoria, especially where their children have already been treated (at school, and anywhere else that the court's mandate runs) as members of the sex to which these interventions promise greater access?

Finally, gender-affirming policies aggressively promote the false notion that a child such as G.G. is trapped in the wrong body; indeed, that is precisely these policies' presupposition, even their *raison d'etre*.

Naturally, then, many gender dysphoric children will seek (once they reach the age of maturity) the closest thing to their desired body which modern medicine can offer them. Simply put: policies such as those at issue in this lawsuit will cause some young adults who would have realigned with their true sex to instead attempt to change it through surgery.

Sadly, there is no good evidence that this dramatic surgery produces lasting benefits.[11] Upon reviewing all the evidence for the beneficial effects of attempted sex reassignment surgery, the Hayes Directory stated that "only weak conclusions" were possible, due to "serious limitations" in the research to date. Hayes, Inc., "Sex Reassignment Surgery for the Treatment of Gender Dysphoria," *Hayes Medical Technology Directory* (2014); *see also* Cecilia Dhejne *et al.*, *Long-Term Follow-up of Transsexual Persons Undergoing Sex Reassignment Surgery: Cohort Study in Sweden*, PLoS ONE, Feb. 22, 2011 (suggesting that sex reassignment surgery may not rectify the comparatively poor health outcomes associated with transgender populations); Annette Kuhn *et al.*, *Quality of Life 15 Years After Sex Reassignment Surgery for Transsexualism*, 92 Fertility & Sterility 1685-89 (2009) (finding considerably lower general life satisfaction in post-surgical transsexuals as compared with females who had at least one pelvic

[11] One study (Annelou L.C. de Vries *et al.*, "Young Adult Psychological Outcomes After Puberty Suppression and Gender Reassignment," 134 *Pediatrics* 696-704 (2014)) reported some short-term benefits. But the authors made no effort to assess long-term effects, and their study was, in any event, not properly controlled.

surgery in the past); Jon K. Meyer and Donna J. Reter, *Sex Reassignment: Follow-up*, 36 Archives of Gen. Psychiatry 1010-15 (1979) (in an assessment comparing the well-being of post-operative transsexuals to transsexuals who did not have surgery, concluding that "sex reassignment surgery confers no objective advantage in terms of social rehabilitation").

There is considerable evidence, on the other hand, that "sex-change" surgery poses very serious health risks. *See* David Batty, *Mistaken Identity*, The Guardian, July 30, 2014, http://www.theguardian.com/society/2004/jul/31/health.socialcare (in an assessment of more than 100 follow-up studies on post-operative transsexuals, concluding that none of the studies proved that sex reassignment is beneficial for patients or thoroughly investigated "[t]he potential complications of hormones and genital surgery, which include deep vein thrombosis and incontinence"). One "risk" is for sure: anyone who goes through with "sex-change" surgery will never be able to engage in a reproductive sexual act.

CONCLUSION

The Fourth Circuit has mandated an experimental "one-size-fits-all" policy of gender affirmance. Underlying that directive is the assumption that treating gender dysphoric children in accordance with their self-proclaimed gender identity rather than their

biological sex is beneficial to them. But there is no scientific evidence to support that rosy presupposition; on the contrary, the evidence shows that affirming any child's mistaken belief that he or she is a prisoner of the wrong body is ultimately harmful to that child.

We agree with the American College of Pediatricians' conclusion that conditioning children into believing that a lifetime of impersonating someone of the opposite sex, achievable only through chemical and surgical interventions, is a form of child abuse.

Respectfully submitted,

GERARD V. BRADLEY
Counsel of Record
NOTRE DAME LAW SCHOOL
3156 Eck Hall of Law
Notre Dame, IN 46556
(574) 631-8385
Gerard.V.Bradley.16@nd.edu

TORY H. LEWIS
Attorney at Law
1320 Robb Court
Little Rock, AR 72223
(615) 712-1573
thlewis84@gmail.com

January 10, 2017

Exhibit F

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Law Center

HATEWATCH

Meet the Anti-LGBT Hate Group that Filed an Amicus Brief with the Alabama Supreme Court

November 13, 2015 by Hatewatch Staff

The American College of Pediatricians (ACPeds) is an anti-LGBT hate group founded in 2002. It bills itself as "a national organization of pediatricians and other healthcare professionals dedicated to the health and well-being of children."

Like other organizations, ACPeds involves itself in judicial matters, and files amicus briefs with various courts in support of or in opposition to various cases.

What its website will not tell you is that this fringe organization, under the veneer of its professional-sounding name and claims, works to defame and discredit LGBT people, often by distorting legitimate research. It consists of around 200 members and started because a small group of anti-LGBT physicians and other healthcare professionals broke away from the 60,000 member American Academy of Pediatrics (AAP), composed of leaders in the professional field, to form its own group after the AAP issued a new policy statement in 2002 in support of adoption and foster parenting by same-sex couples.

ACPeds has a history of propagating damaging falsehoods about LGBT people, including linking homosexuality to pedophilia, and claiming that LGBT people are more promiscuous than heterosexuals, and that LGBT people are a danger to children.

^ *Anti-marriage equality protester at the Supreme Court*

In 2010, for example, ACPeds mailed a letter to over 14,000 school district superintendents pushing so-called "ex-gay" therapy and making other false claims about LGBT people in its "Facts About Youth" campaign, which brought a scathing response from a researcher whose work the group had distorted. That wasn't the first time ACPeds had been called out for distorting legitimate research, but clearly, if the brief they filed is any indication, the lesson didn't take.

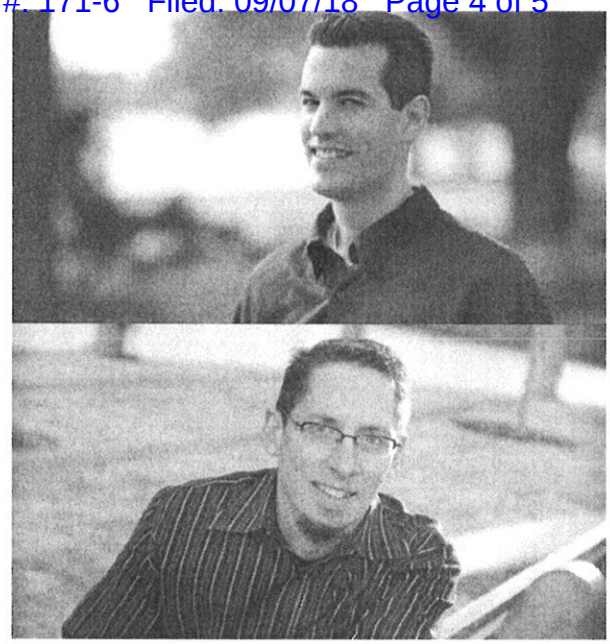
ACPeds filed the brief with the Alabama Supreme Court on Nov. 6 in response to that court's pending decision regarding the U.S. Supreme Court (SCOTUS) ruling in *Obergefell v. Hodges* last June, which legalized same-sex marriage in the United States. In defiance of Alabama federal district court judge Callie Granade, the Alabama Policy Institute and Alabama Citizens Action Program petitioned the Alabama Supreme Court to uphold Alabama's state law, which declares that marriage is between one man and one woman. While the Alabama Supreme Court requested that the parties in the case have their briefs filed by July 6, 2015, amicus briefs seem to still be tricking in and the court has yet to rule.

The ACPeds brief urges the court to defy the U.S. Supreme Court and confirm that marriage is only between one man and one woman. The brief states that ACPeds is "concerned by the delay of the Alabama Supreme Court and the immediate threat of *Obergefell* to the stability of families, the safety of children and our constitutional republic."

Unsurprisingly in the brief, ACPeds cites professors Loren D. Marks and Mark Regnerus, both of whom have attempted to claim through discredited research that children "do worse" in same-sex parent households than in heterosexual-parent households. Regnerus's infamous study, which received almost a million dollars from right-wing anti-LGBT think tanks, was released in 2012 and was immediately trumpeted by anti-LGBT groups around the country and has been used repeatedly in various amicus briefs in opposition to same-sex marriage.

Regnerus has become a darling on the anti-LGBT circuit, though in legitimate social science circles, his credibility continues to wane. Last

year, Regnerus testified in a federal court case in Michigan regarding the legality of same-sex marriage. Federal judge Paul Friedman dismissed Regnerus's testimony as "unbelievable" and "not worthy of serious consideration" and wrote that his study was "hastily concocted at the behest of a third-party funder." In addition, Regnerus's own academic department has distanced itself from him.



Loren Marks (top) is a professor of family life at BYU and Mark Regnerus is a professor of sociology at the University of Texas, Austin

In spite of that, ACPeds relies heavily on Regnerus as well as on other researchers affiliated with the National Association for the Research and Therapy of Homosexuality (NARTH; now the NARTH Institute), which supports the discredited "ex-gay" therapy movement. So-called "ex-gay" or "reparative" therapy seeks to change gay people to heterosexual.

The ACPeds brief also cites outdated sources from the 1970s, 1980s, and 1990s to bolster claims that same-sex relationships don't last very long, and that same-sex relationships are "more violent" than heterosexual. "This Court," the brief implores, "should take care that innocent and helpless Alabama children are not sacrificed on the altar of adult passions, judicial will, or politically correct opinion."

In a supreme case of irony, the brief further claims that legitimate research by professional organizations like the American Psychological Association are the result of a "biased political agenda." The brief goes on to cite, for example, a 2002 report by physician Ellin Perrin in support of ACPeds' views that legitimate research is "biased."

That 2002 report actually found the *opposite* of what ACPeds claims. The report states that, "the weight of evidence gathered during several decades using diverse samples and methodologies" is persuasive in demonstrating that "there is no systematic difference between gay and nongay parents in emotional health, parenting skills, and attitudes toward parenting." The report further notes that "no data have pointed to any risk to children" as a result of growing up in a family of one or more gay parents."

Perrin's report, co-authored by the Committee on Psychosocial Aspects of Child and Family Health is part of what caused ACPeds to break away from the AAP in the first place, because it helped form the basis for AAP's support of adoption and foster parenting by same-sex parents, which ACPeds vehemently opposes. Nevertheless, the group has no problem taking one line in that report out of context and using it to bolster their own flagging position.

But in the strange world of the anti-LGBT right, damaging falsehoods about LGBT people are considered true while legitimate science is seen as false. This is why fringe think tanks like ACPeds have formed in hard-right circles: a means to hold on to and perpetuate views that are being proven wrong with every passing day.

* * *

Exhibit G

American College of Pediatricians®
The Best for Children

PO Box 357190
Gainesville, FL 32635-7190
www.Best4Children.org

A Medical Response to DOE & DOJ Guidance for Schools

June 2016

My name is Dr. Michelle A. Cretella, President of the American College of Pediatricians, a national organization of pediatricians and other health professionals dedicated to promoting policies that will foster the optimal physical and emotional health of all children. I am joined by Dr. Jane Orient, Executive Director of the Association of American Physicians and Surgeons (AAPS), a non-partisan professional association of physicians in all types of specialties across the country, Dr. David Stevens, CEO of the Christian Medical and Dental Associations, and Dr. Les Ruppersberger, President of the Catholic Medical Association. Together we represent over 20 thousand physicians and health professionals who are gravely concerned about the "Guidance to School Districts: Creating a Safe and Supportive Environment for Transgender Students," issued May 13, 2016 by the United States Department of Education and the Department of Justice. The joint DOE and DOJ directive to allow access to sex-specific restrooms, locker rooms and sports teams in accordance with a student's gender identity is rooted in a political ideology that will threaten the health, privacy, safety and learning experience of all students.

Affirmation of gender dysphoria has no basis in science and is highly controversial among experts. Gender dysphoria (GD) describes the mental condition in which an individual experiences discordance between his gender identity and his biological sex.[1] Experts agree that 80-95% of pre-pubertal youth with gender dysphoria will come to accept their biological sex by late adolescence.[2] Consequently, affirmation of prepubertal children in their belief that they are the opposite sex is considered by many to be cooperating with a child's mental confusion and to be shepherding him along the path to a mental disorder. Recently, over 500 physicians and mental health professionals, many of them foremost experts in gender development and gay rights advocates, signed a petition to protest the termination of Dr. Kenneth Zucker and the closure of his world renowned gender identity clinic for children. Dr. Zucker has been recognized as the world's foremost expert on gender dysphoria and gender identity issues in children for decades.[3] Over the last 40 years Dr. Zucker and his colleagues effectively administered psychotherapy to families of pre-pubertal children with gender dysphoria. A fierce supporter of lesbian, gay, bisexual and adult transgender rights, Dr. Zucker nevertheless believed it best to aid young children with bringing their gender identity in line with biological reality. For this reason, he was fiercely maligned and his clinic vigorously protested by transgender activists which ultimately led to a sham evaluation, his termination and closure of the clinic. The petition on Dr. Zucker's behalf reads in part:

> *We, the undersigned, are professional clinicians and academics who work in the areas of human sexuality, gender identity, and related fields. We are writing to express our dismay and disapproval of recent actions of Toronto's Centre for Addiction and Mental Health (CAMH), specifically, the closure of the Child and Adolescent Gender Identity Clinic and the apparent firing of its Clinical Lead, Kenneth J. Zucker, Ph.D. We object to these actions because they appear primarily politically motivated and to have been rationalized and justified, after the fact, by public statements extremely damaging to Dr. Zucker's professional reputation. We further object to the indifference towards research and scholarship implied by the CAMH's closure of a 40-year-old clinic that had been a world-leader in the field of childhood gender identity disorder. We are also very concerned about the welfare of many Canadian children and families who were served by this Clinic, whose mental health needs have essentially been dismissed by CAMH through its actions.*[4]

A growing online community of similarly liberal physicians, mental health professionals and academics who are critical of the youth transgender movement is found here: https://youthtranscriticalprofessionals.org/. They write:

> *We are concerned about the current trend to quickly diagnose and affirm young people as transgender, often setting them down a path toward medical transition. Our concern is with medical transition for children and youth. We feel that unnecessary surgeries and/or hormonal treatments which have not been proven safe in the long-term represent significant risks for young people. Policies that encourage — either directly or indirectly — such medical treatment for young people who may not be able to evaluate the risks and benefits are highly suspect, in our opinion.*[5]

The belief that transgenderism is innate has no basis in science. Dr. J. Michael Bailey is an American psychologist and professor at Northwestern University. He is a longtime gay rights advocate and expert in gender dysphoria and transgenderism. In 2007, he wrote:

> *Currently the predominant cultural understanding of male-to-female transsexualism is that all male-to female (MtF) transsexuals are, essentially, women trapped in men's bodies. This understanding has little scientific basis, however, and is inconsistent with clinical observations. Ray Blanchard has shown that there are two distinct subtypes of MtF transsexuals. Members of one subtype, homosexual transsexuals, are best understood as a type of homosexual male. The other subtype, autogynephilic transsexuals, are motivated by the erotic desire to become women. The persistence of the predominant cultural understanding, while explicable, is damaging to science and to many transsexuals.*[6]

Despite the aforementioned scientific objections, one increasingly hears the fanciful claim that a child with gender dysphoria is born with a brain that is of the opposite sex of his body. This is biologically

impossible. Every cell of the human body contains identical copies of a person's sex chromosomes and the brains of biologically normal infants are imprinted prenatally by their own endogenous sex

hormones at 8 weeks' gestation.[7] Every infant boy is born with a brain imprinted by testosterone; every infant girl is born with a brain imprinted by estrogen. Brain studies of transgender adults that purport to show differences in brain microstructures are of notoriously poor quality and more than likely reflect the fact that long-term transgender behavior alters brain microstructures.[8] This latter phenomenon of behavior altering the chemical and physical structure of the brain is known as neuroplasticity, and is well established.[9]

Moreover, behavior geneticists have known for decades that while genes and hormones influence behavior, they do not hard-wire a person to think, feel, or behave in a particular way. The science of epigenetics has established that genes are not analogous to rigid "blueprints" for behavior. Rather, humans "develop traits through the dynamic process of gene-environment interaction. ... [genes alone] don't determine who we are."[10]

Regarding transgenderism, twin studies of adults prove definitively that prenatal genetic and hormone influence is minimal. The largest twin study of transgender adults found that only 28% of identical twins were both transgender-identified.[11] Since identical twins contain 100% of the same DNA from conception, and develop in exactly the same prenatal environment (therefore they are exposed to the same prenatal hormones), if genes and/or prenatal hormones contributed to a significant degree to transgenderism, the concordance rates would be close to 100%. Instead, 72% of identical twin pairs were discordant. In light of epigenetics, this means that at least 72% of what contributes to transgenderism as an adult in one co-twin consists of one or more non-shared post-natal experiences. This is consistent with the dramatic rates of resolution of gender dysphoria documented among children when they are not allowed to impersonate the opposite sex.

The claim that gender identity is the equivalent of sex as codified in Title IX has no basis in science. Human sexuality is an objective biological binary trait: "XY" and "XX" are genetic markers of sex – not genetic markers of a disordered body. The norm for human design is to be conceived either male or female. Human sexuality is binary by design with the obvious purpose being the reproduction and flourishing of our species. This principle is self-evident. The exceedingly rare disorders of sex development (DSDs), including but not limited to testicular feminization and congenital adrenal hyperplasia, are all medically identifiable deviations from the sexual binary norm, and are rightly recognized as disorders of human design. Individuals with DSDs do not constitute a third sex. Additionally, a developmental bio-psycho-social model for gender dysphoria has not been disproved. This means that it is entirely possible that a child's gender identity could be derailed by his subjective perceptions, relationships, and adverse experiences from infancy forward. Children who identify as "feeling like the opposite sex" or "somewhere in between" do not comprise a third sex. They remain biological boys or biological girls.

Gender ideology has no basis in science and harms all children. First, actively affirming gender-variant students harms them because it impairs their chances of aligning their gender-identity with physical

reality and propels them down the path of medical transition. The one study that has tracked pre-pubertal children with gender dysphoria who were affirmed as the opposite sex and treated with puberty-blocking hormones found that 100% went on to use cross-sex hormones by late adolescence.[12] Medical transition of pre-pubertal children in this fashion results in sterility and the life-time use of toxic hormones that are fraught with serious potential physical and mental health risks. Additionally, research among transgender adults indicates that medical transition may not alleviate the elevated suicide rates in the longterm.[13]

Second, normalizing the myth of innate gender fluidity will cause psychological trauma to youth who are not presently confused about their gender identity. As psychiatrist Keith Ablow has stated, "[Gender ideology] shak[es] the certain knowledge in boys and girls of whether they can count on not being seen naked by the opposite gender, not to mention whether they are themselves actually the gender they thought they were."[14] He goes on to characterize the promotion of this ideology as "a powerful, devious and pathological way to weaken [children] by making them question their sense of safety, security and certainty about anything and everything."[15]

Finally, to eliminate sex-specific private spaces in public schools violates all students' fundamental rights to privacy, safety and a secure learning environment. School locker rooms and restrooms exist for the utilitarian purpose of hygiene, not to affirm the self-identified gender of certain individuals. These facilities are traditionally restricted to persons of the same sex for the sound and self-evident reason that the separation protects the bodily privacy of all students as well as shields girls and women from offensive, criminal, or dangerous behavior by voyeurs, exhibitionists, and rapists. In view of adolescent development, it is inevitable that some male students will feign gender variance in order to gain access to girls' bathrooms and locker rooms.

Also consistent with child and adolescent development, these proposed policies will cause anxiety for the vast majority of female students, and potentially trigger symptoms of post-traumatic stress disorder for the tens of thousands of girls who are survivors of sexual abuse and/or sexual assault. Indeed, according to the National Sexual Violence Resource Center, 1 in 4 girls will be sexually abused before the age of eighteen.[16] We are likewise concerned for the well-being of biological females who are gender-discordant, who will be at risk for bullying and/or assault behind the closed doors of the men's room by male students who will feel duped and/or angered over having their own privacy violated. There are many individuals who are uncomfortable in public facilities for a variety of reasons, including religious beliefs, disability, deformity, or discomfort with their body, as well as gender dysphoria. A reasonable accommodation is a single-occupancy restroom available for all students who are uncomfortable with the standard arrangement of sex-specific bathrooms or locker rooms.

No child should be harassed for his or her unique characteristics. Schools should encourage an environment of respectful self-expression for all students. Parental involvement should be a school's primary method of resolution for particular cases with programs emphasizing general respectfulness serving to set the tone in the classrooms. It is both in keeping with this spirit of respectfulness and imperative for the optimal health of all students, to avoid all curricula, books and other media, and

policies, that promote and normalize the scientifically baseless gender fluid ideology. This includes maintaining restrooms and other private spaces that are assigned according to biological sex.

Sincerely,

Michelle Cretella, MD, FCP
President
American College of Pediatricians

Jane Orient, MD
Executive Director
Association of American Physicians & Surgeons

David Stevens, MD
CEO
Christian Medical & Dental Associations

Les Ruppersberger, MD
President
Catholic Medical Association

References:

1. American Psychiatric Association. (2013) Diagnostic and statistical manual of mental disorders (5th ed.) p. 451.

2. Cohen-Kettenis, PT, Delemarre-van de Waal, HA, Gooren, LJG. "The Treatement of Adolescent Transsexuals: Changing Insights." J Sex Med. 2008 Aug;5(8):1892-7 Available at http://www.ncbi.nlm.nih.gov/pubmed/18564158 Accessed 5/11/16.

3. Singal, J. "How the Fight Over Transgender Kids Got a Leading Sex Researcher Fired." (Feb. 7, 2016) New York Magazine. Available at http://nymag.com/scienceofus/2016/02/fight-over-trans-kids-got-a-researcher-fired.html Accessed 5/11/16.

4. Bancroft, J, et al. "Open Letter to the Board of Trustees of the Centre for Addiction and Mental Health." (Jan. 11, 2016) iPetition Available at http://www.ipetitions.com/petition/boardoftrustees-CAMH Accessed 5/11/16.

5. Youth Trans Critical Professionals. "About Us." Available at https://youthtranscriticalprofessionals.org/about/ Accessed 5/11/16.

6. Bailey, MJ and Triea, "What Many Transsexual Activists Don't Want You to Know and Why You Should Know it Anyway." Perspect Biol Med. 2007 Autumn;50(4):521-34. Available at http://www.ncbi.nlm.nih.gov/pubmed/17951886 Accessed 5/11/16.

7. Reyes FI, Winter JS, Faiman C. "Studies on human sexual development Fetal gonadal and adrenal sex steroids." J Clin Endocrinol Metab. 1973 Jul; 37(1):74-8; Lombardo, M. "Fetal Testosterone Influences Sexually Dimorphic Gray Matter in the Human Brain." The Journal of Neuroscience, 11 January 2012, 32(2); Campano, A. [ed]. Geneva Foundation for Medical Education and Research: human sexual differentiation (2016). Available at http://www.gfmer.ch/Books/Reproductive_health/Human_sexual_differentiation.html Accessed 5/11/16.

8. Whitehead, N. "Is Transsexuality Biologically Determined?" Triple Helix (UK), Autumn 2000, p6-8 Available at http://mygenes.co.nz/transsexuality.htm Accessed 5/11/16.

9. Gu, J. and Kanai, R. "What Contributes to individual differences in brain structure?" Front Hum Neurosci. 2014; 8: 262.

10. Shenk, D. The Genius in All of Us: Why everything you've been told about genetics, talent, and IQ is wong. (2010) New York, NY: Doubleday; p. 18.

11. Diamond, M. "Transsexuality Among Twins: identity concordance, transition, rearing, and orientation." International Journal of Transgenderism, 14(1), 24–38. (Note: the abstract of this article erroneously states that concordance rates for identical twins is 20%. Based upon raw data from Table 5, 21 out of 74 identical twin pairs were concordant for transsexuality. This yields the slightly higher concordance rate of 28% reported in this letter).

12. de Vries AL1, Steensma TD, Doreleijers TA, Cohen-Kettenis PT. "Puberty suppression in adolescents with gender identity disorder: a prospective follow-up study." J Sex Med. 2011 Aug;8(8):2276-83.

13. Dhejne C, Lichtenstein P, Boman M, Johansson AL, Långström N, Landén M. "Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden." PLoS One. 2011 Feb 22;6(2).

14. Ablow, K. "All Wrong: in California, girls can use urinals in boys' restroom." (Jan. 14, 2014) FoxNews.com Available at http://www.foxnews.com/opinion/2014/01/14/all-wrong-in-california-girls-can-use-urinals-in-boys-restroom.html Accessed 5/11/16.

15. Ablow, K. "All Wrong: in California, girls can use urinals in boys' restroom." (Jan. 14, 2014) FoxNews.com Available at http://www.foxnews.com/opinion/2014/01/14/all-wrong-in-california-girls-can-use-urinals-in-boys-restroom.html Accessed 5/11/16.

16. National Sexual Violence Resource Center. "Information & Statistics for Journalists: statistics about sexual violence." (2015). Available at http://www.nsvrc.org/sites/default/files/publications_nsvrc_factsheet_media-packet_statistics-aboutsexual-violence_0.pdf Accessed 5/11/16.

Exhibit H

proto MASSACHUSETTS GENERAL HOSPITAL // DISPATCHES FROM THE FRONTIERS OF MEDICINE

PUBLISHED ON JUNE 10, 2016

CLINICAL RESEARCH

Crossing Over

Most transgender people know their gender identity as children. So how do pediatricians help them become healthy adults?

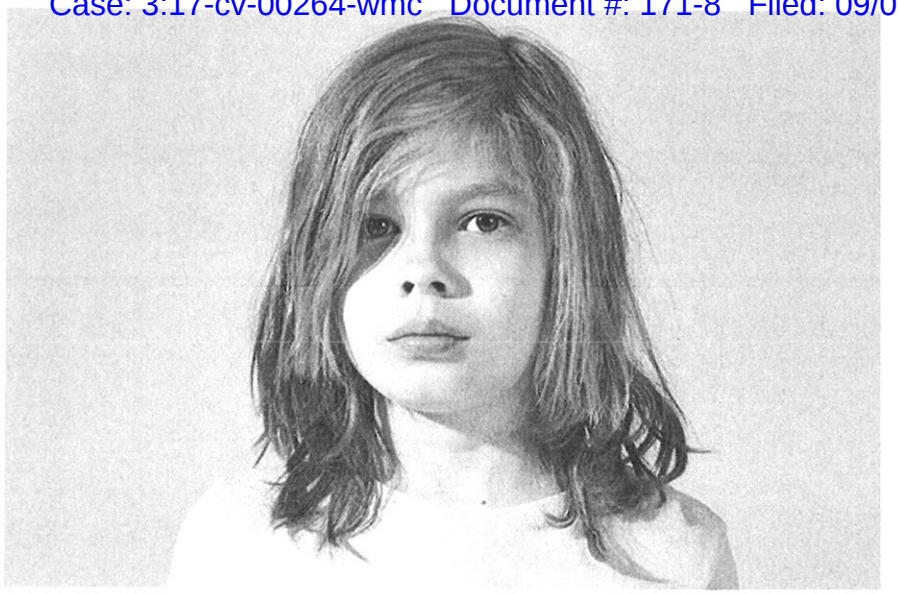
BY LINDA KESLAR //
ART BY PETER HAPAK

In many ways, Avery Jackson seems like a typical nine-year-old girl. Spunky and confident, she likes reading, gymnastics, playing with friends, and all things pink, purple or sparkly. Yet Avery was born biologically male. "At the age of four, she told us, 'You think I'm a boy, but I'm a girl on the inside,' " says her mother, Debi Jackson.

As a preschooler, Avery had preferred playing with dolls and dressing up with the girls in her class. That kind of cross-gender play is common for young children. But Avery didn't grow out of it, and when Debi tried to discourage Avery's behavior, it became obvious she wasn't confused or playing make-believe. "She wanted to wear a dress all the time at home, sleep in nightgowns, go out on weekends dressed as a girl—she called it 'me' time," says Jackson.

Within a year of telling her mother, Avery began to grow angry and depressed, and to show an aversion to her male sexual anatomy. The Jacksons took Avery to a pediatrician, to a child psychologist and eventually to a local gender therapist. The therapist helped them understand that their young child probably was transgender—that the gender she identified with was at odds with her biological sex. And while being transgender is no longer considered a psychological disorder, Avery's growing distress over the mismatch between the body she had been born with and the gender she considered hers led the specialist to diagnose her condition as gender dysphoria.

"We didn't know anything about what that was," says Jackson, but she and her husband began to read what little they could find about the condition. They decided to follow the therapist's advice—to let Avery live publicly as a girl, exploring her perceived gender identity before she reached puberty. Since then, Avery and her family have appeared across news media, advocating for transgender awareness.



The issues that the Jacksons and Avery face are at the center of a widening discussion among families, physicians and other caregivers about the proper course of treatment for children who don't identify with their biological sex. At least until recently, kids in that situation often were prescribed antidepressants or other medications, and even today, some are sent for "conversion therapy," a discredited process that, among other aims, attempts to bring gender identity and expression in line with biological sex.

In 2013, the American Psychiatric Association stopped describing gender variance as a disorder in its manuals, and several states have banned conversion therapy. "Gender variance isn't pathological; it's not something to be overcome or cured," says Diane Ehrensaft, a clinical psychologist and director of mental health at the Child and Adolescent Gender Center at University of California, San Francisco Benioff Children's Hospital.

Yet for the parents and physicians of these children who may not identify with their birth sex, there's still scant consensus on what to do or not to do. There is little reliable research about what causes gender variance, how prevalent it is, or even how to determine what gender struggles a particular child is going through. "Kids are the ones who tell us about their gender identity, and we have to listen to them," says Ehrensaft.

A major complication is that children with gender issues face a diverging path. Many outgrow their cross-gender feelings entirely, making it unnecessary and unwise to treat them pharmacologically for a condition that may not persist. But for those for whom it does persist, gender dysphoria may intensify, particularly as they begin to experience an unwanted biological puberty. Not treating those kids is also dangerous.

In the past, children at this crossroads had no choice but to see their puberty through. Today, however, a small but growing number of young children and adolescents are discovering other options, up to and including medical and even surgical gender reassignment. "There has been very rapid growth in younger patients looking to affirm their opposite sex," says Norman Spack, a pediatric endocrinologist and co-director and co-founder emeritus of the Gender Management Service (GeMS) program at Boston Children's Hospital, the first U.S. transgender youth treatment clinic, which opened in 2007.

Still, there are few experienced practitioners or standard protocols for any of this, and insurance coverage is a problem. Moreover, there's growing debate about when or whether to tamper with the bodies of otherwise healthy children. Offering gender reassignment therapies to minors can have physical consequences, including sterility. Some clinicians adamantly oppose giving hormones or other treatments to kids who identify as transgender.

"I am increasingly being contacted by mental health professionals, primary care providers, surgeons and even ob-gyns who are horrified by the conditioning of children into a life of chemical and surgical impersonation of

the opposite sex and all the suffering that entails," says Michelle Cretella, a pediatrician and president of the American College of Pediatricians in Gainesville, Fla., a socially conservative organization with 500 physician members. (The American Academy of Pediatrics, with 64,000 physician members, is on the other hand supportive of hormonal transition when appropriate for transgender youth.)

But many who counsel and treat transgender children see things differently. "Lots of people disagree with the work we're doing, but in my experience, it's lifesaving," says Stephen Rosenthal, a pediatric endocrinologist and medical director at UCSF's Child and Adolescent Gender Center.

"We don't know why anyone is the gender they are," says Johanna Olson-Kennedy, a pediatrician and medical director at the Center for Transyouth Health and Development at Children's Hospital Los Angeles. Research suggests that by the age of three most children have a sense of what it means to be male or female, and by five or six, they have identified with one gender or the other. Most often, that aligns with their biological sex and will stay that way for life.

But in rare cases—involving one in 10,000 biological males and one in 30,000 biological females, according to an estimate by the American Psychological Association—sex and gender don't align, and that can cause a range of problems. Yet while surveys suggest that two out of three transgender adults experienced gender dysphoria during childhood, making that diagnosis for children is problematic. Kids' gender identities can fluctuate, and symptoms of gender dysphoria diminish or disappear by puberty for a large percentage of children—perhaps because of hormonal changes, peer pressure or cognitive development.

Still, it is almost impossible to generalize about the psychological development of gender, in large part because there's so little reliable research. Most studies have involved small samples and many were conducted years ago, when gender variance was still regarded as a disorder by the APA.

Among the few studies considered valuable is a 2013 one that aimed to identify factors associated with the persistence of gender dysphoria into adolescence. Researchers followed 127 kids diagnosed with the condition in childhood for four years, and found that persistence of dysphoria was greater among biological females. Persisters also reported more body dissatisfaction and a higher incidence of same-sex sexual orientation. In another small but important study, published last year, researchers determined that most transgender children are certain of their gender identity on a deep level. The University of Washington study involved 32 children, ages 5 to 12, who identified as transgender; they were compared with two control groups of "cisgender" children, whose gender identities matched their birth sex.

Participants in each group answered questions about their gender identity and took the Implicit Association Test, which measures the speed with which they associate male and female genders with concepts of "me" and "not me." Transgender participants scored as strongly with their cross-gender identity as the kids in the two control groups scored with their biological gender, which the researchers took as evidence that their identities are deeply held and consistent, and not the result of confusion or fantasy.

What hasn't been found, however, are any measurable biological indicators—biomarkers—that could help confirm a child's transgenderism. A recent study published in the *Journal of Adolescent Health* ruled out circulating hormone levels. Looking at 101 transgender participants ages 12 to 24, the researchers discovered that the young people's hormone levels were in line with those of others of the same biological sex, regardless of gender identity.

Olson-Kennedy says she was struck by another finding—that while participants, on average, were eight years old when they recognized that their gender was different from their assigned sex at birth, they were 17 before they told their families. "That's a really critical period of brain development, and if that's happening while you're sitting on a core secret about yourself, and internalizing the message that your authentic self isn't okay, that's going to have consequences that we don't know much about yet," she says. And living with that secret has a negative impact on mental health, the study confirmed. More than a third of participants experienced depression; more than half said they'd considered suicide, and nearly a third reported making at least one attempt.

Because most family physicians and pediatricians consider transgender care outside of their expertise, children and their families seeking help tend to be referred to clinics or networks of specialists—where the wait for an appointment can stretch to many months. "We have patients coming from throughout New England and along the East Coast," says Michelle Forcier, a pediatrician at a clinic in Hasbro Children's Hospital in Providence, R.I. Forcier created the clinic, the only one in the state, in 2011, and today she treats 300 gender-variant patients.

Patients at such specialty clinics typically undergo extensive screening and psychotherapy to determine whether they have gender dysphoria. "We've developed a 23-page gender assessment packet that includes interview tools as well as observation and play techniques to learn about the child's gender development," says UCSF's Diane Ehrensaft. The goal is to find out which kids are most likely to continue to identify with a different gender than the one they were born with.

As kids move closer to puberty, discussions center on what patients and their families want to do. There could be "social transitions" involving a change in clothing and hairstyle or assuming a new name or gender pronoun. Yet such changes may do little to dispel the terror many adolescents feel about the prospect of unwanted changes to their bodies. And behavioral problems, including self-mutilation and suicide attempts, tend to escalate as puberty approaches.

Treatment with puberty-blocking drugs, pioneered in the Netherlands and endorsed in 2009 by the U.S. Endocrine Society, can buy time, stopping the pituitary gland from sending hormones to stimulate the ovaries and testes to produce estrogen and testosterone. For transgender children, such treatments can have

dramatic results, reducing gender dysphoria and improving social and academic performance. They may also help kids avoid future surgery; no mastectomy will be needed, for example, if a transgender male never develops breasts.

Among the possible risks of such treatment, which can affect bone density, are potential hazards to brain development, a process that continues until the mid-twenties. But in a study of several dozen adolescents published last year, Dutch researchers found no significant effects of the drugs on brain regions associated with "executive functioning" skills, which affect the ability to plan, focus attention, remember instructions and handle several tasks at once. And other evidence suggests that puberty-blocking drugs, which have been used for years to delay puberty when it comes too early, are safe and reversible. If the medications are discontinued, a normal puberty will begin.

After taking puberty blockers for several years, adolescents who choose to continue their cross-gender transition move to the next step: Instead of blocking the hormones that would bring on puberty, they begin taking those associated with the gender they identify with. Transgender females receive estrogen, the feminizing hormone that spurs breast development, the redistribution of body fat and wider hips. Transgender males get testosterone, which causes voice pitch to drop, facial and body hair to grow and shoulders to get broader. The Endocrine Society guidelines call for waiting until age 16 to start these medications, but physicians may prescribe them to children as young as 13—and clinicians say their experience in this relatively new frontier is teaching them that waiting too long may be harmful, putting transgender teens out of step with the physical development of their cisgender peers.

There are many unanswered questions about the possible health risks of cross-sex hormone therapy, in part because this generation of transgender youth is the first to start what will be lifelong treatment. Research suggests that taking estrogen puts transgender females at a higher risk for blood clots, while transgender males taking testosterone could be subject to increased hemoglobin levels and high cholesterol, among other side effects. New data from a large study of 1,000 adults has also shown that transgender females on hormone therapy have elevated risks of heart disease.

That study, published in the *European Journal of Endocrinology*, also showed that transgender female adults in the Netherlands tended to die earlier than cisgender males, with above-average rates of suicide, AIDS and drug abuse. Mortality rates for transgender males, however, were in line with those of the general female population.

With such risks looming, Michelle Cretella of the American College of Pediatricians calls "affirming gender discordance" and its treatments that help children transition to a new gender "institutionalized child abuse at the hands of professionals." Other critics also say they are concerned that children are being coerced into gender reassignment therapies. Yet Spack sees a very different dynamic at work, with parents and kids grappling with all of the implications of what is an extremely difficult decision. "No one chooses this for themselves or for their child," he says.

Research has shown that about one in 50 transgender adults regrets his or her transition, and that ratio could be even lower for young people now going through that process at an earlier age, who spend more of their life in the gender they identify with. A small Dutch study, published in 2014, followed 55 transgender people receiving treatment from youth to early adulthood. All had been diagnosed with gender dysphoria and received puberty blockers and then cross-sex hormones. Surveyed at the average age of 21, they reported they were no longer experiencing gender dysphoria, their quality of life and happiness levels were found to be at least as high as those of their cisgender peers, and none expressed any regret about delaying puberty or transitioning to the gender they identified with. Considering the high rates of depression and suicide of transgender youth who had not received any treatment, the study is a powerful argument for acting early.

More definitive answers about the long-term effects of medical treatments for transgender youth could come from a new $5.7 million five-year study funded by the National Institutes of Health. Four academic medical

centers will enroll 280 kids with gender dysphoria and look at the safety and effectiveness of treatments, including use of hormone blockers and cross-sex hormones.

Results of that study could help shape future care of transgender youth, which today continues to be based largely on expert opinion and experience rather than on conclusive scientific data. "Everything about transgenderism is pretty much conjecture," says Spack, who has been delivering transgender care since the late 1990s. "The most important thing we know is how much more we need to know."

The willingness of health insurers to pay for any kind of transgender care also remains a work in progress. In 2009, only 49 major U.S. employers offered such coverage, but by 2016 that number had increased to 511, according to the Corporate Equality Index from the Human Rights Campaign Foundation. Yet only a handful of states have expanded Medicaid benefits to include mental health treatment, hormone therapy and sexual reassignment surgery for adults. Even fewer pay for children to receive puberty-suppressing drugs, which haven't been approved by the Food and Drug Administration for use in the transgender population. Such treatment may cost as much as $30,000 annually—an insurmountable hurdle for many who would have to pay for therapy out of pocket.

Indeed, Debi Jackson and her husband are among increasing numbers of parents who consider the high cost of care essential to ensure their children's welfare. "We've been saving money for Avery for quite a while," says Jackson. If Avery's gender dysphoria persists, which they feel is likely, the Jacksons are comfortable with having Avery receive puberty blockers and cross-hormone treatments. Debi Jackson says: "We have a retirement account, a college account and a gender account, because we know our health insurance isn't going to cover Avery's care."

Dossier

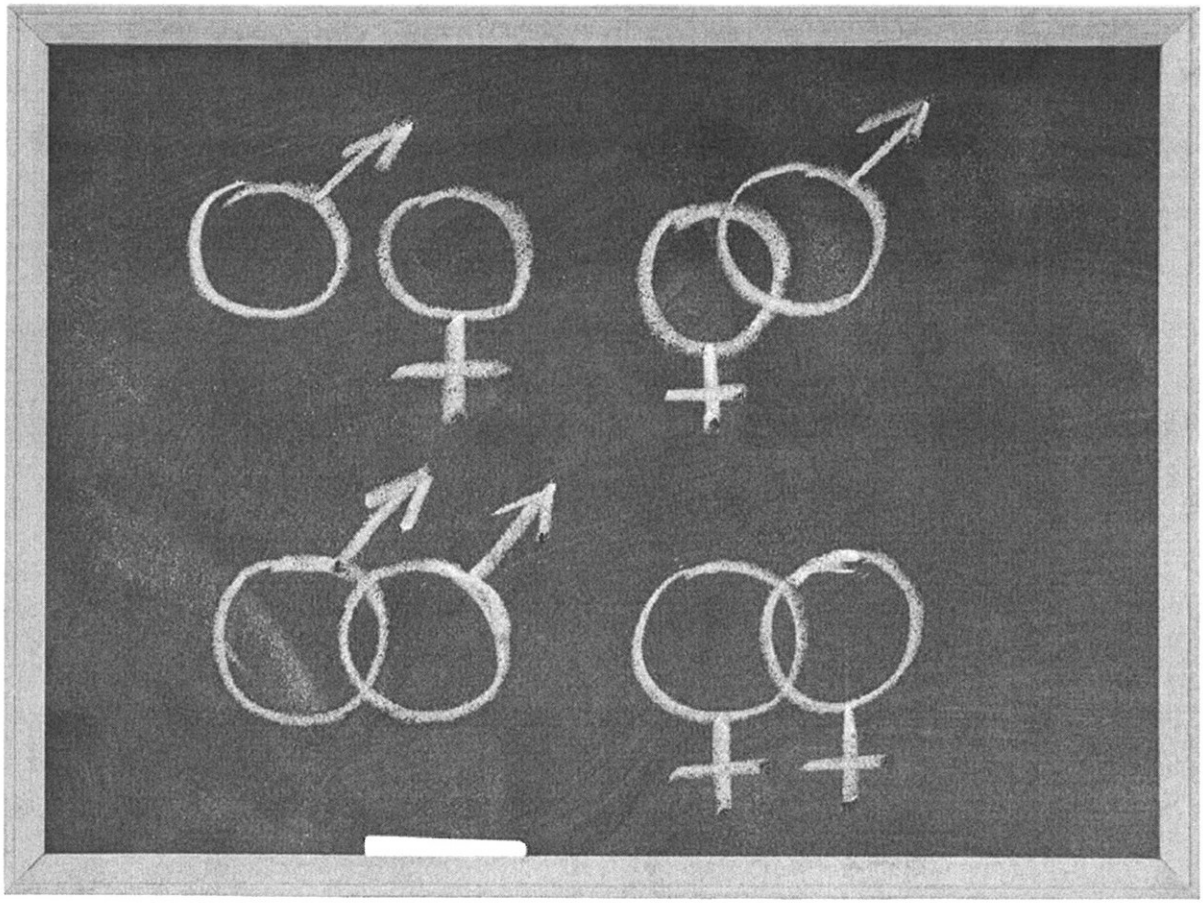
"Ethical Issues Raised by the Treatment of Gender-Variant Prepubescent Children," by Jack Drescher and Jack Pula, *Hastings Center Report*, September–October 2014. The authors outline the treatment options for gender-variant children, and address the medical and ethical challenges posed by each.

The Gender Creative Child, by Diane Ehrensaft (The Experiment, 2016). In this book, Ehrensaft, a leading authority on gender development, draws on her own clinical experience and an emerging body of research to guide young patients, parents and medical professionals through the rapidly evolving cultural, medical and legal landscape of gender and identity.

Exhibit I

University of Minnesota professor's research hijacked

Wednesday, May 26, 2010 by Nick Pinto in
News



Dr. Gary Remafedi was at a pediatrics conference in Toronto last month when he first learned that someone was using his name to justify the very thing he'd spent his life fighting.

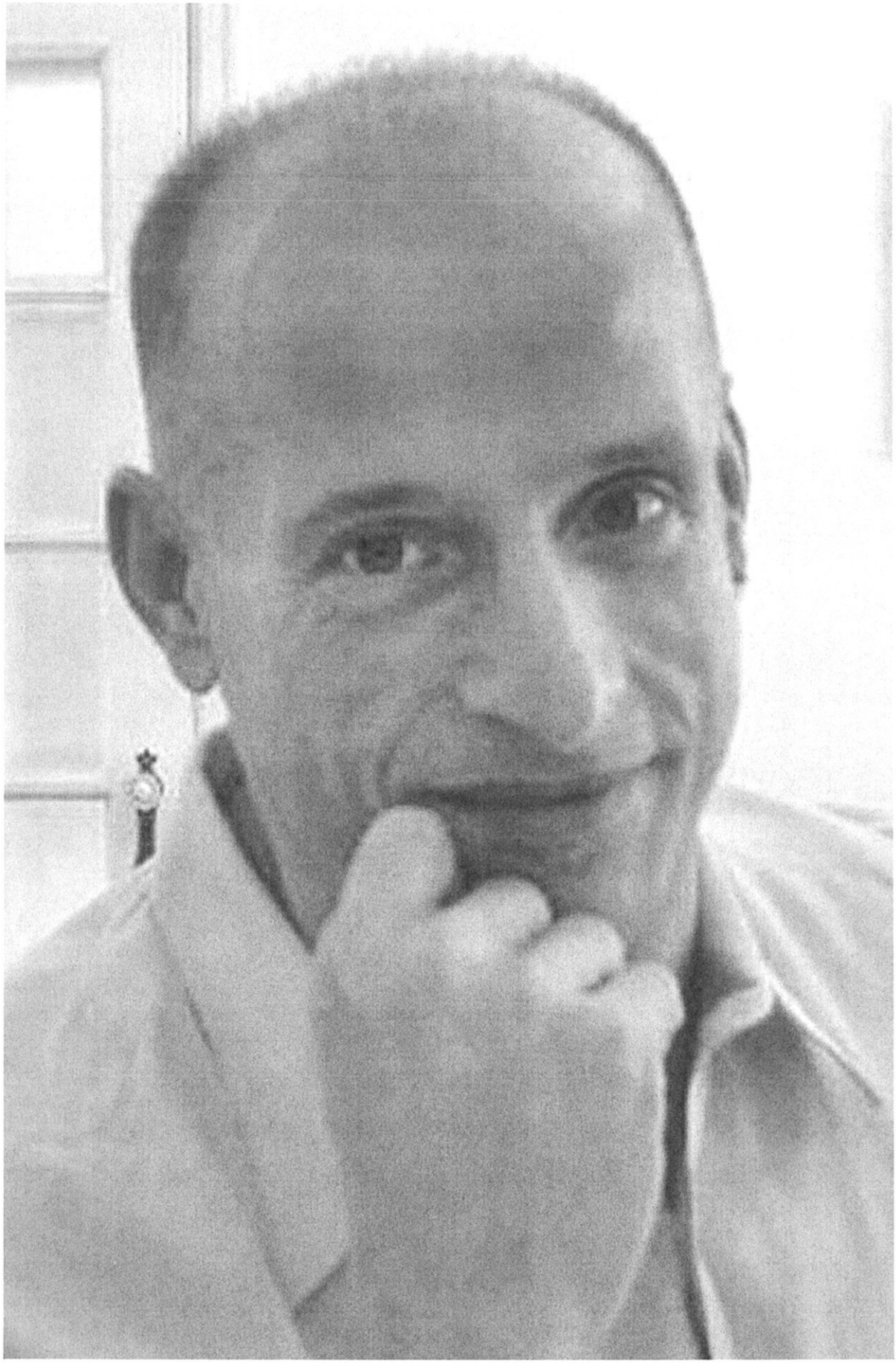
"My inbox started filling up with messages from colleagues saying, 'You might want to check this out,'" Remafedi recalls. "Some of them were saying, 'Do you really believe this?'"

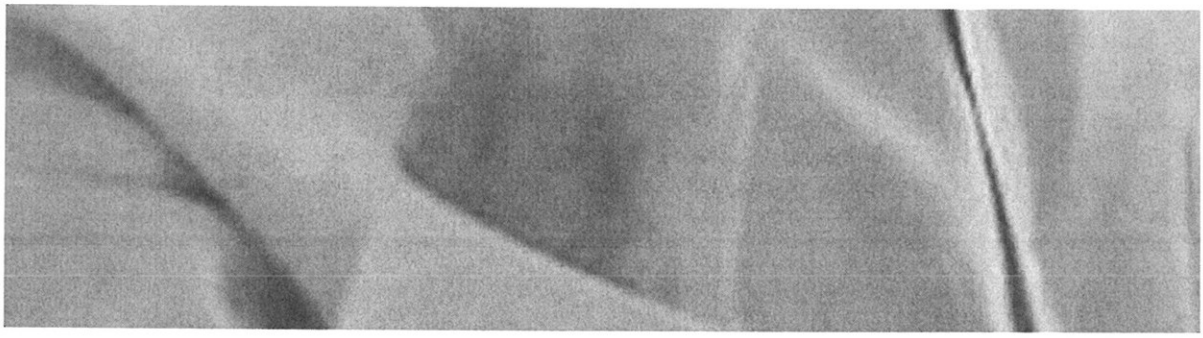
When the University of Minnesota Medical School professor followed the links he was being sent, he was dismayed. A group called the American College of Pediatricians had sent a letter to more than 14,000 superintendents across the country, claiming that the best thing schools can do for students who come out of the closet is nothing at all: no support, no affirmation, no gay-straight alliance clubs on campus.

The letter, and the Facts About Youth website it pointed school officials to, was dense with footnotes citing scientific studies. Remafedi's research was at the top of the list.

The ACP argues that schools shouldn't support gay teens because they're probably just confused. "Most adolescents who experience same-sex attraction...no longer experience such attractions at age 25," the letter says, citing a 1992 study by Remafedi.

Except that's not what Remafedi's research suggested at all. His work showed that kids who are confused about their sexuality eventually sort it out—meaning many of them accept being gay.





Dr. Gary Remafedi's research on gay teens was misrepresnted

"What was so troubling was that these were fellow doctors, fellow pediatricians," Remafedi says. "They knew better, and they have the same ethical responsibilities to their patients that I do, but they deliberately distorted my research for malicious purposes."

The ACP also claimed that the longer you can keep kids from identifying as gay, the less likely they are to kill themselves. Again, Remafedi's research was footnoted.

In this case, Remafedi says, the ACP missed the larger point: Kids who come out at a younger age are more likely to kill themselves because they are less able to deal with the stigma and isolation of being gay. If anything, the research shows the need for more support.

"It's obvious that they didn't even read my research," Remafedi says. "I mean, they spelled my name wrong every time they cited it."

Remafedi started studying sexual orientation among teens in the 1980s, at a time when almost nothing was known about the subject.

"People didn't really believe that gay teens existed," he says. "The assumption was that everyone was straight, and then some people became gay as adults."

But Remafedi wasn't convinced, and with the AIDS crisis ramping up, he thought there might be a risk to teenagers that doctors weren't considering. He finally managed to convince Minnesota officials to let him include a few questions about sexual orientation in a statewide student survey, and the results confirmed his hypothesis: Many of the kids reported some kind of same-sex attraction.

After more lobbying, Remafedi got the Department of Health to put up money for the Youth and AIDS Project, a center in Loring Park that offers HIV counseling and health services for teens.

But while scientists like Remafedi were expanding our understanding of teen sexuality, culture warriors on the right were pushing back. For decades, groups like the National Association for Research and Therapy of Homosexuality (NARTH) have argued that people are gay because of some trauma in their childhood, and that through "restorative therapy" they can be "cured" and be heterosexual.

In 2002, the American Association of Pediatrics, the 60,000-member professional organization for doctors, endorsed same-sex adoption. In protest, the most conservative members split off and formed the American College of Pediatricians. The college won't disclose how many members it has, but estimates put it around 200.

The two groups clashed again when the AAP published
Just the Facts,
a handbook for schools on teen sexual orientation. Written with the national associations of psychologists, social workers, and teachers,
Just the Facts
collected up-to-date research to debunk restorative therapy and offer schools advice on how to help gay students feel safe.

In March, the ACP fired back with its own publication for schools,
Facts About Youth.
Mimicking the rival publication, the ACP filled its handbook with more than 100 footnotes citing studies. The difference is that some of the researchers, like Remafedi, say the ACP cherry-picked, manipulated, and misstated that research.

Francis Collins, the director of the National Institute of Health, found the ACP using his work on genetics to argue that gay kids can be cured. Last month he accused the college of taking his work out of context, calling the pamphlet "misleading and incorrect."

Warren Throckmorton, a therapist who specializes in sexual orientation issues, also asked to have his research removed from the study.

"The letter and the website are just disingenuous," he says. "They say they're impartial and not motivated by political or religious concerns, but if you look at who they're affiliated with and how they're using the research, that's just obviously not true."

Indeed, the names attached to the publication read like a who's-who of the anti-gay medical message machine: Arthur Goldberg, a felon who bilked billions of dollars in a municipal-bond scheme and founded the Jewish gay-cure group JONAH; Joe Nicolosi, one of the leaders of the "ex-gay" organization NARTH; and George Rekers, the founder of the Family Research Council who fell from grace last month when he was photographed by the
Miami New Times
returning from a European vacation with a 20-year-old male prostitute.

Remafedi also wrote a letter to the American College of Pediatricians, asking them to stop citing his research. But the college isn't budging. Reached at his Florida headquarters, Dr. Tom Benton, the group's president, says he has every right to use any research he wants.

"I have the utmost respect for Dr. Remafedi," says Benton, who is a pediatrician. "He does good work. The fact is, his research supports our conclusions, even if he doesn't."

Which is why, Benton says, he won't be taking down references to Remafedi's work or making any corrections.

All of which leaves Remafedi frustrated. "I've considered litigation," he says. "It was libelous. On a personal level, when I'm dead and buried, I don't want my work to be associated with these types of organizations and ideas."

But more than that, Remafedi says, the episode makes him sad and fearful for the impact groups like the ACP will have on kids. He thinks of an elementary-school boy he treated recently for an eating disorder that was set off by a parent's fear that he was gay.

"This isn't just academic," he says. "I do my research to help expand our understanding and give us more information so that we can improve children's lives and their health. So when people try to confuse the issue, or to say things they know aren't true, my reaction to that is disgust."

Exhibit J

Decision Memo for Gender Dysphoria and Gender Reassignment Surgery (CAG-00446N)

Links in PDF documents are not guaranteed to work. To follow a web link, please use the MCD Website.

Decision Summary

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination of whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery is reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination related to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

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Decision Memo

To: Administrative File: CAG #00446N

From: Tamara Syrek Jensen, JD
Director, Coverage and Analysis Group

Joseph Chin, MD, MS
Deputy Director, Coverage and Analysis Group

James Rollins, MD, PhD
Director, Division of Items and Devices

Elizabeth Koller, MD
Lead Medical Officer

Linda Gousis, JD
Lead Analyst

Katherine Szarama, PhD
Analyst

Subject: Final Decision Memorandum on Gender Reassignment Surgery for Medicare Beneficiaries with Gender Dysphoria

Date: August 30, 2016

I. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

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II. Background

Below is a list of acronyms used throughout this document.

AHRQ - Agency for Healthcare Research and Quality
AIDS - Acquired Immune Deficiency Syndrome
ANOVA - Analysis of Variance
APA - American Psychiatric Association
APGAR - Adaptability, Partnership Growth, Affection, and Resolve test
BIQ - Body Image Questionnaire
BSRI - Bem Sex Role Inventory
CCEI - Crown Crips Experimental Index
CDC – Centers for Disease Control
CHIS - California Health Interview Survey
CI - Confidence Interval
CMS - Centers for Medicare & Medicaid Services
DAB - Departmental Appeals Board
DSM - Diagnostic and Statistical Manual of Mental Disorders
EMBASE - Exerpta Medica dataBASE
FBeK - Fragebogen zur Beurteilung des eigenen Korpers
FDA - Food and Drug Administration
FPI-R - Freiburg Personality Inventory
FSFI - Female Sexual Function Index
GAF - Global Assessment of Functioning
GID - Gender Identity Disorder
GIS - Gender Identity Trait Scale
GRS - Gender Reassignment Surgery
GSI - Global Severity Indices
HADS - Hospital Anxiety Depression Scale
HHS - U.S. Department of Health and Human Services
HIV - Human Immunodeficiency Virus
IIP - Inventory of Interpersonal Problems
IOM - Institute of Medicine
KHQ - King’s Health Questionnaire
LGB - Lesbian, Gay, and Bisexual
LGBT - Lesbian, Gay, Bisexual, and Transgender
MAC - Medicare Administrative Contractor
MMPI - Minnesota Multiphasic Personality Inventory
NCA - National Coverage Analysis
NCD - National Coverage Determination
NICE - National Institute for Health Care Excellence
NIH - National Institutes of Health
NZHTA - New Zealand Health Technology Assessment
PIT - Psychological Integration of Trans-sexuals
QOL - Quality of Life
S.D. - Standard Deviation
SADS - Social Anxiety Depression Scale
SCL-90R - Symptom Check List 90-Revised
SDPE - Scale for Depersonalization Experiences
SES - Self Esteem Scale

SF - Short Form
SMR - Standardized Mortality Ratio SOC – Standards of Care
STAI-X1 - Spielberger State and Trait Anxiety Questionnaire
STAI-X2 - Spielberger State and Trait Anxiety Questionnaire
TSCS - Tennessee Self-Concept Scale
U.S. - United States
VAS - Visual Analog Scale
WHOQOL-BREF - World Health Organization Quality of Life - Abbreviated version of the WHOQOL-100
WPATH - World Professional Association for Transgender Health

A. Diagnostic Criteria

The criteria for gender dysphoria or spectrum of related conditions as defined by the American Psychiatric Association (APA) in the Diagnostic and Statistical Manual of Mental Disorders (DSM) has changed over time (See Appendix A).

Gender dysphoria (previously known as gender identity disorder) is a classification used to describe persons who experience significant discontent with their biological sex and/or gender assigned at birth. Although there are other therapeutic options for gender dysphoria, consistent with the NCA request, this decision only focuses on gender reassignment surgery.

B. Prevalence of Transgender Individuals

For estimates of transgender individuals in the U.S., we looked at several studies.

The Massachusetts Behavior Risk Factor Surveillance Survey (via telephone) (2007 and 2009) identified 0.5% individuals as transgender (Conron et al., 2012).

Derivative data obtained from the 2004 California Lesbian Gay Bisexual and Transgender (LGBT) Tobacco Survey (via telephone) and the 2009 California Health Interview Survey (CHIS) (via telephone) suggested the LGB population constitutes 3.2% of the California population and that transgender subjects constitute approximately 2% of the California LGBT population and 0.06% of the overall California population (Bye et al., 2005; CHIS 2009; Gates, 2011).

Most recently, the Williams Institute published a report that utilized data from the Centers for Disease Control's (CDC) Behavioral Risk Factor Surveillance System (BRFSS). Overall, they found that 0.6% or 1.4 million U.S. adults identify as transgender. The report further estimated 0.7% of adults between the ages of 18-25 identify as transgender, 0.6% of adults between the ages of 25-65 identify as transgender, and 0.5% of adults age 65 or older identify as transgender (Flores et al., 2016).

In a recent review of Medicare claims data, CMS estimated that in calendar year 2013 there were at least 4,098 transgender beneficiaries (less than 1% of the Medicare population) who utilized services paid for by Medicare, of which 90% had confirmatory diagnosis, billing codes, or evidence of a hormone therapy prescription. The Medicare transgender population is racially and ethnically diverse (e.g., 74% White, 15% African American) and spans the entire country. Nearly 80% of transgender beneficiaries are under age 65, including approximately 23% ages 45-54. (CMS Office of Minority Health 2015).

For international comparison purposes, recent estimates of transgender populations in other countries are similar to those in the United States. New Zealand researchers, using passport data, reported a prevalence of 0.0275% for male-to-female adults and 0.0044% female-to-male adults (6:1 ratio) (Veale, 2008). Researchers from a centers of transgender treatment and reassignment surgery in Belgium conducted a survey of regional plastic surgeons and reported a prevalence of 0.008% male-to-female and 0.003% female-to-male (ratio 2.7:1) surgically reassigned transsexuals in Belgium (De Cuypere et al., 2007). Swedish researchers, using national mandatory reporting data on those requesting reassignment surgery, reported secular changes over time in that the number of completed reassignment surgeries per application increased markedly in the 1990s; the male-to-female/female-to-male sex ratio changed from 1:1 to 2:1; the age of male-to-female and female-to-male applicants was initially similar, but increased by eight years for male-to-female applicants; and the proportion of foreign born applicants increased (Olsson and Moller 2003).

III. History of Medicare Coverage

Date	Action
August 1, 1989	CMS published the initial NCD, titled "140.3, Transsexual Surgery" in the Federal Register. (54 Fed. Reg. 34,555, 34,572)
May 30, 2014	The HHS Departmental Appeals Board (DAB) determined that the NCD denying coverage for all transsexual surgery was not valid. As a result, MACs determined coverage on a case-by-case basis.

CMS does not currently have a NCD on gender reassignment surgery.

A. Current Request

On December 3, 2015, CMS accepted a formal complete request from a beneficiary to initiate a NCA for gender reassignment surgery.

CMS opened this National Coverage Analysis (NCA) to thoroughly review the evidence to determine whether or not gender reassignment surgery may be covered nationally under the Medicare program.

B. Benefit Category

Medicare is a defined benefit program. For an item or service to be covered by the Medicare program, it must fall within one of the statutorily defined benefit categories as outlined in the Act. For gender reassignment surgery, the following are statutes are applicable to coverage:

Under §1812 (Scope of Part A) Under §1832 (Scope of Part B)
Under §1861(s) (Definition of Medical and Other Health Services)
Under §1861(s)(1) (Physicians' Services)

This may not be an exhaustive list of all applicable Medicare benefit categories for this item or service.

IV. Timeline of Recent Activities

Timeline of Medicare Coverage Policy Actions for Gender Reassignment Surgery

Date	Action
December 3, 2015	CMS accepts an external request to open a NCD. A tracking sheet was posted on the web site and the initial 30 day public comment period commenced.
January 2, 2016	Initial comment period closed. CMS received 103 comments.
June 2, 2016	Proposed Decision Memorandum posted on the web site and the final 30 day public comment period commenced.
July 2, 2016	Final comment period closed. CMS received 45 comments.

V. FDA Status

Surgical procedures per se are not subject to the Food and Drug Administration's (FDA) approval.

Inflatable penile prosthetic devices, rigid penile implants, testicular prosthetic implants, and breast implants have been approved and/or cleared by the FDA.

VI. General Methodological Principles

In general, when making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. (§ 1862 (a)(1)(A)). The evidence may consist of external technology assessments, internal review of published and unpublished studies, recommendations from the Medicare Evidence Development & Coverage Advisory Committee (MEDCAC), evidence-based guidelines, professional society position statements, expert opinion, and public comments.

The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) specific clinical question relevant to the coverage request can be answered conclusively; and 2) the extent to which we are confident that the intervention will improve health outcomes for patients.

A detailed account of the methodological principles of study design the agency staff utilizes to assess the relevant literature on a therapeutic or diagnostic item or service for specific conditions can be found in Appendix B. In general, features of clinical studies that improve quality and decrease bias include the selection of a clinically relevant cohort, the consistent use of a single good reference standard, blinding of readers of the index test, and reference test results.

VII. Evidence

A. Introduction

Below is a summary of the evidence we considered during our review, primarily articles about clinical trials published in peer- reviewed medical journals. We also considered articles cited by the requestor, articles identified in public comments, as well as those found by a CMS literature review. Citations are detailed below.

B. Literature Search Methods

CMS staff extensively searched for primary studies for gender dysphoria. The emphasis focused less on specific surgical techniques and more on functional outcomes unless specific techniques altered those types of outcomes.

The reviewed evidence included articles obtained by searching literature databases and technology review databases from PubMed (1965 to current date), EMBASE, the Agency for Healthcare Research and Quality (AHRQ), the Blue Cross/Blue Shield Technology Evaluation Center, the Cochrane Collection, the Institute of Medicine, and the National Institute for Health and Care Excellence (NICE) as well as the source material for commentary, guidelines, and formal evidence-based documents published by professional societies. Systematic reviews were used to help locate some of the more obscure publications and abstracts.

Keywords used in the search included: Trans-sexual, transgender, gender identity disorder (syndrome), gender dysphoria and/or hormone therapy, gender surgery, genital surgery, gender reassignment (surgery), sex reassignment (surgery) and/or quality of life, satisfaction-regret, psychological function (diagnosis of mood disorders, psychopathology, personality disorders), suicide (attempts), mortality, and adverse events-reoperations. After the identification of germane publications, CMS also conducted searches on the specific psychometric instruments used by investigators.

Psychometric instruments are scientific tools used to measure individuals' mental capabilities and behavioral style. They are usually in the form of questionnaires that numerically capture responses. These tools are used to create a psychological profile that can address questions about a person’s knowledge, abilities, attitudes and personality traits. In the evaluation of patients with gender dysphoria, it is important that both validity and reliability be assured in the construction of the tool (validity refers to how well the tool actually measures what it was designed to measure, or how well it reflects the reality it claims to represent, while reliability refers to how accurately results of the tool would be replicated in a second identical piece of research). Reliability and validity are important because when evaluating patients with gender dysphoria most of the variables of interest (e.g., satisfaction, anxiety, depression) are latent in nature (not directly observed but are rather inferred) and difficult to quantify objectively.

Studies with robust study designs and larger, defined patient populations assessed with objective endpoints or validated test instruments were given greater weight than small, pilot studies. Reduced consideration was given to studies that were underpowered for the assessment of differences or changes known to be clinically important. Studies with fewer than 30 patients were reviewed and delineated, but excluded from the major analytic framework. Oral presentations, unpublished white papers, and case reports were excluded. Publications in languages other than English were excluded. The CMS initial internal search for the proposed decision memorandum was limited to articles published prior to March 21, 2016. The CMS internal search for the final decision memorandum continued through articles published prior to July 22, 2016.

Included studies were limited to those with adult subjects. Review and discussion of the management of children and adolescents with the additional considerations of induced pubertal delay are outside the scope of this NCD. In cases where the same population was studied for multiple reasons or where the patient population was expanded over time, the latest and/or most germane sections of the publications were analyzed. The excluded duplicative publications are delineated.

CMS also searched Clinicaltrials.gov to identify relevant clinical trials. CMS looked at trial status including early

termination, completed, ongoing with sponsor update, and ongoing with estimated date of completion. Publications on completed trials were sought. For this final decision, CMS also reviewed all evidence submitted via public comment.

C. Discussion of Evidence

The development of an assessment in support of Medicare coverage determinations is based on the same general question for almost all national coverage analyses (NCAs): "Is the evidence sufficient to conclude that the application of the item or service under study will improve health outcomes for Medicare patients?" For this specific NCA, CMS is interested in answering the following question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

The evidence reviewed is directed towards answering this question.

1. Internal Technology Assessment

CMS conducted an extensive literature search on gender reassignment related surgical procedures and on facets of gender dysphoria that provide context for this analysis. The latter includes medical and environmental conditions.

CMS identified numerous publications related to gender reassignment surgery. A large number of these were case reports, case series with or without descriptive statistics, or studies with population sizes too small to conduct standard parametric statistical analyses. Others addressed issues of surgical technique.

CMS identified and described 36 publications on gender reassignment surgery that included health outcomes. Because the various investigators at a site sometimes conducted serial studies on ever-enlarging cohort populations, studied sub-populations, studied different outcomes, or used different tools to study the same outcomes, not all study populations were unique. To reduce bias from over-lapping populations, only the latest or most germane publication(s) were described. Subsumed publications were delineated.

Of these 36 publications, two publications used different assessment tools on the same population, and, so for the purposes of evaluation, were classified as one study (Udeze et al., 2008; Megeri and Khoosal, 2007). A total of 33 studies were reviewed (See Figure 1). Appendices C, D, and F include more detail of each study. The publications covered a time span from 1979 to 2015. Over half of the studies were published after 2005.

Figure 1. Studies of Gender Reassignment Surgery (GRS)

ANOVA=Analysis of Variance Normative=Psychometric Tests with known normative for large populations

Figure 1 Legend: The studies in Figure 1 are categorized into three groups. The first group, depicted by the colored boxes (red, blue, and green), had explicit controls. There was a single randomized study. The remainder in the first group were observational studies. These were subdivided into longitudinal studies and cross-sectional studies. The second group, depicted by black boxes (starting with the surgery only population box) consisted of surgical series. The third group, depicted by black boxes (starting with mixed population), was composed of patients whose treatment could involve a variety of therapeutic interventions, but who were not stratified by that treatment.

When looking at the totality of studies, the 33 studies could be characterized by the following research design groups:

a. Observational, mixed population of surgical and non-surgical patients without stratification

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. Eur J Endocrinol. 2011 Apr;164(4):635 -42. Epub 2011 Jan 25.

Asscheman et al. conducted a retrospective, non-blinded, observational study of mortality using a longitudinal design to assess a mixed population treated with hormones, as well as, reassignment surgery in comparison to a population-based cohort. The study was not designed to assess the specific impact of gender reassignment surgery on clinical outcomes.

The investigators assessed mortality in patients who (a) were from a single-center, unspecified, Dutch university specialty clinic, (b) had initiated cross-sex hormone treatment prior to July 1, 1997, and (c) had been followed (with or without continued hormone treatment) by the clinic for at least one year or had expired during the first year of treatment. The National Civil Record Registry (Gemeentelijke Basis Administratie) was used to identify/confirm deaths of clinic patients. Information on the types or hormones used was extracted from clinic records, and information on the causation of death was extracted from medical records or obtained from family physicians. Mortality data for the general population were obtained through the Central Bureau of Statistics of the Netherlands (Centraal Bureau voor Statistiek). Mortality data from Acquired Immune Deficiency Syndrome (AIDS) and substance abuse were extracted from selected Statistics Netherlands reports. The gender of the general Dutch population comparator group was the natal sex of the respective gender dysphoric patient groups.

A total of 1,331 patients who met the hormone treatment requirements were identified (365 female-to-male [27.4%]; 966 male- to-female [72.6%]; ratio 1:2.6). Of these, 1,177 (88.4%) underwent reassignment surgery (343 [94.0% of female-to-male entrants]; 834 [86.3% of male-to-female entrants]; ratio difference 1:2.4 with a p-value $p<0.0001$). Later calculations did not distinguish between those with hormone therapy alone versus those with hormone therapy plus reassignment surgery. The mean age at the time of hormone initiation in female -to-male and male-to-female patients was 26.1±7.6 (range 16–56) years and 31.4±11.4 (range 16–76) years respectively, although the male-to-female subjects were relatively older ($p<0.001$). The mean duration of hormone therapy in female-to-male and male-to-female patients was 18.8±6.3 and 19.4±7.7 years respectively.

There were a total of 134 deaths in the clinic population using hormone therapy with or without surgical reassignment. Of these patients, 12 (3.3%) of the 365 female-to-male patients and 122 (12.6%) of the 966 male -to-female patients died. All-cause mortality for this mixed population was 51% higher and statistically significant (Standardized Mortality Ratio [SMR] 95% confidence interval [CI]) 1.47-1.55) for males-to-females when compared to males in the general Dutch population. The increase in all-cause mortality (12%) for females-to-males when compared to females in the general Dutch population was not statistically significant (95% CI 0.87-1.42).

Ischemic heart disease was a major disparate contributor to excess mortality in male-to-female patients but only in older patients (n=18, SMR 1.64 [95% CI 1.43-1.87]), mean age [range]: 59.7 [42-79] years. Current use of a particular type of estrogen, ethinyl estradiol, was found to contribute to death from myocardial infarction or stroke (Adjusted Hazard Ratio 3.12 [95% CI 1.28-7.63], p=0.01). There was a small, but statistically significant increase in lung cancer that was thought to possibly be related to higher rates of smoking in this cohort.

Other contributors to the mortality difference between male-to-female patients and the Dutch population at large were completed suicide (n=17, SMR 5.70 [95% CI 4.93-6.54]), AIDS (n=16, SMR 30.20 [95% CI 26.0-34.7]), and illicit drug use (n=5, SMR 13.20 [95% CI 9.70-17.6]). An additional major contributor was “unknown cause” (n=21, SMR 4.00 [95% CI 3.52-4.51]). Of the 17 male-to-female hormone treated patients who committed suicide, 13 (76.5%) had received prior psychiatric treatment and six (35.3%) had not undergone reassignment surgery because of concerns about mental health stability.

Overall mortality, and specifically breast cancer and cardiovascular disease, were not increased in the hormone-treated female-to-male patients. Asscheman et al. reported an elevated SMR for illicit drug use (n=1, SMR 25

[6.00-32.5]). This was the cause of one of the 12 deaths in the cohort.

This study subsumes earlier publications on mortality (Asscheman et al. 1989 [n=425]; Van Kesteren et al. 1997 [n=816]).

Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone- treated transsexuals report less social distress, anxiety and depression. Psychoneuroendocrinology. 2012 May;37(5):662-70. Epub 2011 Sep 19.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a cross-sectional design and non -specific psychiatric distress tools in Spain. The investigators assessed anxiety and depression in patients with gender dysphoria who attended a single-center specialty clinic with comprehensive endocrine, psychological, psychiatric, and surgical care. The clinic employed World Professional Association for Transgender Health (WPATH) guidelines. Patients were required to have met diagnostic criteria during evaluations by 2 experts. Investigators used the Hospital Anxiety and Depression Scale (HADS) and the Social Anxiety and Distress Scale (SADS) instruments. The SADS total score ranges from 0 to 28, with higher scores indicative of more anxiety. English language normative values are 9.1±8.0. HAD-anxiety and HAD-depression total score ranges from 0 to 21, with higher scores indicative of more pathology. Scores less than 8 are normal. ANOVA was used to explore effects of hormone and surgical treatment.

Of the 200 consecutively selected patients recruited, 187 (93.5% of recruited) were included in the final study population. Of the final study population, 74 (39.6%) were female-to-male patients; 113 (60.4%) were male-to-female patients (ratio 1:1.5); and 120 (64.2%) were using hormones. Of those using hormones, 36 (30.0%) were female-to-male; 84 (70.0%) were male-to-female (ratio 1:2.3). The mean age was 29.87±9.15 years (range 15-61). The current age of patients using hormones was 33.6±9.1 years (n=120) and older than the age of patients without hormone treatment (25.9±7.5) (p=0.001). The age at hormone initiation, however, was 24.6±8.1 years.

Of those who had undergone reassignment surgery, 29 (36.7%) were female-to-male; 50 (63.3%) were male-to-female (ratio 1:1.7). The number of patients not on hormones and who had undergone at least one gender-related surgical procedure (genital or non-genital) was small (n=2). The number of female-to-male patients on hormones who had undergone such surgery (mastectomy, hysterectomy, and/or phalloplasty) was 28 (77.8%). The number of male-to-female patients on hormones who had undergone such surgery (mammoplasty, facial feminization, buttock feminization, vaginoplasty, orchiectomy, and/or vocal feminization (thyroid chondroplasty) was 49 (58.3%).

Analysis of the data revealed that although the mean scores HAD-Anxiety, HAD-Depression, and SADS were statistically lower (better) in those on hormone therapy than in those not on hormone therapy, the mean scores for HAD-Depression and SADS were in the normal range for gender dysphoric patients not using hormones. The HAD-Anxiety score was 9 in transsexuals without hormone treatment and 6.4 in transsexuals with hormone

treatment. The mean scores for HAD Anxiety, HAD Depression, and SADS were in the normal range for gender dysphoric patients using hormones. ANOVA revealed that results did not differ by whether the patient had undergone a gender related surgical procedure or not.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. Qual Life Res. 2014 Mar;23(2):669-76. Epub 2013 Aug 13.

Gómez-Gil et al. conducted a prospective, non-blinded observational study using a non-specific quality of life tool. There were no formal controls for this mixed population ± non-genital reassignment surgery undergoing various stages of treatment.

The investigators assessed quality of life in the context of culture in patients with gender dysphoria who were from a single-center (Barcelona, Spain), specialty and gender identity clinic. The clinic used WPATH guidelines. Patients were required to have met diagnostic criteria during evaluations by both a psychologist and psychiatrist. Patients could have undergone non-genital surgeries, but not genital reassignment surgeries (e.g., orchiectomy, vaginoplasty, or phalloplasty). The Spanish version of the World Health Organization Quality of Life-Abbreviated version of the WHOQOL-100 (WHOQOL- BREF) was used to evaluate quality of life, which has 4 domains (environmental, physical, psychological, and social) and 2 general questions. Family dynamics were assessed with the Spanish version of the Family Adaptability, Partnership Growth, Affection, and Resolve (APGAR) test. Regression analysis was used to explore effects of surgical treatment.

All consecutive patients presenting at the clinic (277) were recruited and, 260 (93.9%) agreed to participate. Of this number, 59 of these were excluded for incomplete questionnaires, 8 were excluded for prior genital reassignment surgery, and 193 were included in the study (the mean age of this group was 31.2±9.9 years (range 16-67). Of these, 74 (38.3%) were female-to-male patients; 119 (61.7%) were male-to-female patients (ratio1:1.6). Of these, 120 (62.2%) were on hormone therapy; 29 (39.2%) of female-to-male patients had undergone at least 1 non-genital, surgical procedure (hysterectomy n=19 (25.7%); mastectomy n=29 (39.2%)); 51 (42.9%) of male-to-female patients had undergone at least one non-genital surgical procedure with mammoplasty augmentation being the most common procedure, n=47 (39.5%), followed by facial feminization, n=11 (9.2%), buttocks feminization, n=9 (7.6%), and vocal feminization (thyroid chondroplasty), n=2 (1.7%).

WHOQOL-BREF domain scores for gender dysphoric patients with and without non-genital surgery were: "Environmental" 58.81±14.89 (range 12.50-96.88), "Physical" 63.51±17.79 (range 14.29-100), "Psychological" 56.09+16.27 (range 16.67- 56.09), "Social" 60.35±21.88 (range 8.33-100), and "Global QOL and Health" 55.44+27.18 (range 0-100 with higher score representing better QOL). The mean APGAR family score was 7.23±2.86 (range 0-10 with a score of 7 or greater indicative of family functionality).

Regression analysis, which was used to assess the relative importance of various factors to WHOQOL-BREF domains and general questions, revealed that family support was an important element for all four domains and

the general health and quality of life questions. Hormone therapy was an important element for the general questions and for all of the domains except "Environmental." Having undergone non-genital reassignment surgery, age, educational levels, and partnership status, did not impact domain and general question results related to quality of life.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. J Psychosom Res. 2005 Mar;58(3):259-61.

Hepp et al. conducted a single-site (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design. There was some acquisition of retrospective data. The investigators assessed current and lifetime psychiatry co-morbidity using structured interviews for diagnosis of Axis 1 disorders (clinical syndromes) and Axis 2 disorders (developmental or personality disorders) and HADS for dimensional evaluation of anxiety and depression. Statistical description of the cohort and intra-group comparisons was performed. Continuous variables were compared using t-tests and ANOVA.

A total of 31 patients with gender dysphoria participated in the study: 11 (35.5%) female-to-male; 20 (64.5%) male-to-female (ratio 1:1.8). The overall mean age was 32.2±10.3 years. Of the participants, seven had undergone reassignment surgery, 10 pre- surgical patients had been prescribed hormone therapy, and 14 pre-surgical patients had not been prescribed hormone therapy. Forty five and one half percent of female-to-male and 20% of male-to-female patients did not carry a lifetime diagnosis of an Axis 1 condition. Sixty three and six tenths percent of female-to-male and 60% of male-to-female patients did not carry a current diagnosis of an Axis 1 condition. Lifetime diagnosis of substance abuse and mood disorder were more common in male-to-female patients (50% and 55% respectively) than female-to-male patients (36.4% and 27.3% respectively). Current diagnosis of substance abuse and mood disorder were present in male-to-female patients (15% and 20% respectively) and absent in female-to-male patients. One or more personality disorders were identified 41.9%, but whether this was a current or lifetime condition was not specified. Of the patients, five (16.1%) had a Cluster A personality disorder (paranoid-schizoid), seven (22.6%) had a Cluster B personality disorder (borderline, anti-social, histrionic, narcissistic), six (19.4%) had a Cluster C personality disorder (avoidant, dependent, obsessive-compulsive), and two (6.5%) were not otherwise classified.

HADS scores were missing for at least one person. The HADS test revealed non-pathologic results for depression (female-to-male: 6.64±5.03; male-to-female: 6.58±4.21) and borderline results for anxiety (female-to-male: 7.09±5.11; male-to-female: 7.74±6.13, where a result of 7-10 = possible disorder). There were no differences by natal gender. The investigators reported a trend for less anxiety and depression as measured by HADS in the patients who had undergone surgery.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. Arch Sex Behav. 2010 Dec;39(6):1429-37. Epub 2009 Oct 9.

Johansson et al. conducted a two center (Lund and Umeå, Sweden) non-blinded, observational study using a

semi-cross-sectional design (albeit over an extended time interval) using a self-designed tool and Axis V assessment. The study was prospective except for the acquisition of baseline Axis V data. There were no formal controls in this mixed population with and without surgery.

The investigators assessed satisfaction with the reassignment process, employment, partnership, sexual function, mental health, and global satisfaction in gender-reassigned persons from two disparate geographic regions. Surgical candidates were required to have met National Board of Health and Welfare criteria including initial and periodic psychiatric assessment, ≥1 year of real-life experience in preferred gender, and ≥1 year of subsequent hormone treatment. In addition, participants were required to have been approved for reassignment five or more years prior and/or to have completed surgical reassignment (e.g., sterilization, genital surgery) two or more years prior. The investigators employed semi-structured interviews covering a self-designed list of 55 pre-formulated questions with a three or five point ordinal scale. Clinician assessment of Global Assessment of Functioning (GAF; Axis V) was also conducted and compared to initial finding during the study. Changes or differences considered to be biologically significant were not pre- specified except for GAF, which pre-specified a difference to mean change ≥5 points. Statistical corrections for multiple comparisons were not included. There was no stratification by treatment.

Of the pool of 60 eligible patients, 42 (70.0% of eligible) (17 [40.5 %] female-to-male; 25 [59.5%] male-to-female; ratio 1:1.5) were available for follow-up. Of these, 32 (53.3% of eligible) (14 [43.8%] female-to-male; 18 [56.2%] male-to-female [ratio 1:1.3]) had completed genital gender reassignment surgery (not including one post mastectomy), five were still in the process of completing surgery, and five (one female-to-male; four male-to-female; ratio 1:4) had discontinued the surgical process prior to castration and genital surgery.

The age (ranges) of the patients at entry into the program, reassignment surgery, and follow-up were 27.8 (18-46), 31.4 (22- 49), and 38.9 (28-53) years in the female-to-male group respectively and 37.3 (21-60), 38.2 (22-57), and 46.0 (25.0-69.0) years in the male- to-female group respectively. The differences in age by cohort group were statistically significant. Of participants, 88.2% of all enrolled female-to-male versus 44.0% of all enrolled female-to-male patients had cross-gender identification in childhood (versus during or after puberty) ($p<0.01$).

Although 95.2% of all enrolled patients self-reported improvement in GAF, in contrast, clinicians determined GAF improved in 61.9% of patients. Clinicians observed improvement in 47% of female-to-male patients and 72% of male-to- female patients. A ≥5 point improvement in the GAF score was present in 18 (42.9%). Of note, three of the five patients who were in the process of reassignment and five of the five who had discontinued the process were rated by clinicians as having improved.

Of all enrolled 95.2% (with and without surgery) reported satisfaction with the reassignment process. Of these 42 patients, 33 (79%) identified themselves by their preferred gender and nine (21%) identified themselves as transgender. None of these nine (eight male-to-female) had completed reassignment surgery because of ambivalence secondary to lack of acceptance by others and dissatisfaction with their appearance. Of the patients who underwent genital surgery (n=32) and mastectomy only (n=one), 22 (66.7%) were satisfied while four (three female-to-male) were dissatisfied with the surgical treatment.

Regarding relationships after surgery, 16 (38.1%) (41.2% of female- to-male; 36.0% of male-to-female patients) were reported to have a partner. Yet more than that number commented on partner relationships: (a) 62.2 % of the 37 who answered (50.0% of female- to- male; 69.6% of male-to-female patients) reported improved partner relationships (five [11.9%] declined to answer.); (b) 70.0% of the 40 who answered (75.0% of female-to-male; 66.7% of male-to-female patients) reported an improved sex life. Investigators observed that reported post-operative satisfaction with sex life was statistically more likely in those with early rather than late cross-gender identification. In addition 55.4% self-reported improved general health; 16.1% reported impaired general health; 11.9% were currently being treated with anti-depressants or tranquilizers.

This study subsumes earlier work by Bodlund et al. (1994, 1996). The nationwide mortality studies by Dhejne et al. (2011) may include all or part of this patient population.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. Endocr Pract. 2013 Jul-Aug;19(4):644-50. (United States study)

Leinung et al. conducted a single-center (Albany, New York) a partially prospective, non-blinded, observational study using a cross-sectional design and descriptive statistics. There were no formal controls. The investigators assessed employment, substance abuse, psychiatric disease, mood disorders, Human Immunodeficiency Virus (HIV) status in patients who had met WPATH guidelines for therapy, and who had initiated cross-sex hormone treatment.

A total of 242 patients treated for gender identity disorder in the clinic from 1992 through 2009 inclusive were identified. The number of those presenting for therapy almost tripled over time. Of these patients, 50 (20.7%) were female-to-male; 192 (79.3%) male-to-female (ratio 1:3.8).

The age of female-to-male and male-to-female patients with gender dysphoria at the time of clinic presentation was 29.0 and 38.0 years respectively.

The female-to-male and male-to-female patients with gender dysphoria at the time of hormone initiation were young: 27.5 and 35.5 years old respectively ($p<0.5$). Of the male-to-female cohort, 19 (7.8%) had received hormone therapy in the absence of physician supervision; Of the patient population, 91 (37.6%) had undergone gender-reassignment surgery (32 female-to-male [64.0% of all female-to- male; 35.2% of all surgical patients]; 59 male-to-female [30.7% of all male-to-female; 64.8% of all surgical patients]; ratio 1:1.8).

Psychiatric disease was more common in those who initiated hormone therapy at an older age (>32 years) 63.9% versus 48.9% at a younger age and by natal gender (48.0% of female-to-male; 58.3% male-to-female). Mood disorders were more common in those who initiated hormone therapy at an older age (>32 years) 52.1% versus 36.0% at a younger age and this finding did not differ by natal gender (40.0% of female-to-male; 44.8% male-to- female). The presence of mood disorders increased the time to reassignment surgery in male-to-female patients.

Motmans J , Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. J Sex Med. 2012 Mar;9(3):743-50. Epub 2011 Dec 21.

Motmans et al., conducted a prospective, non-blinded, observational study using a cross-sectional design and a non-specific quality of life tool. No concurrent controls were used in this study. Quality of life in this Dutch-speaking population was assessed using the Dutch version of a SF-36 (normative data was used). Participants included subjects who were living in accordance with the preferred gender and who were from a single Belgian university specialty clinic at Ghent. The Dutch version of the SF-36 questionnaire along with its normative data were used. Variables explored included employment, pension status, ability to work, being involved in a relationship. Also explored, was surgical reassignment surgery and the types of surgical interventions. Intragroup comparisons by transgender category were conducted, and the relationships between variables were assessed by analysis of variance (ANOVA) and correlations.

The age of the entire cohort (n=140) was 39.89±10.21 years (female-to-male: 37.03±8.51; male-to-female: 42.26±10.39). Results of the analysis revealed that not all female-to-male patients underwent surgical reassignment surgery and, of those who did, not all underwent complete surgical reassignment. The numbers of female-to-male surgical interventions were: mastectomy 55, hysterectomy 55, metaoidplasty eight (with five of these later having phalloplasty), phalloplasty 40, and implantation of a prosthetic erectile device 20. The frequencies of various male-to-female surgical interventions were: vaginoplasty 48, breast augmentation 39, thyroid cartilage reduction 17, facial feminization 14, and hair transplantation three.

The final number of subjects with SF-36 scores was 103 (49 [47.6%] female-to-male; 54 [52.4%] male-to-female; ratio 1:1.1). For this measure, the scores for the vitality and mental health domains for the final female-to-male cohort (n= 49 and not limited to those having undergone some element of reassignment surgery) were statistically lower: 60.61±18.16 versus 71.9±18.31 and 71.51±16.40 versus 79.3±16.4 respectively. Scores were not different from the normative data for Dutch women: vitality: 64.3±19.7 or mental health 73.7±18.2. None of the domains of the SF-36 for the final male-to-female cohort (n=54 and not limited to those having undergone some element of reassignment surgery) were statistically different from the normative data for Dutch women.

Analysis of variance indicated that quality of life as measured by the SF-36 did not differ by whether female-to-male patients had undergone genital surgery (metaoidoplasty or phalloplasty) or not. Also, ANOVA indicated that quality of life as measured by the SF-36 did not differ by whether male-to-female patients had undergone either breast augmentation or genital surgery (vaginoplasty) or not.

Whether there is overlap with the Gherri populations studied by Heylens et al. or Weyers et al. is unknown.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. Qual Life Res. 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. (United States study)

Newfield et al. conducted a prospective, observational internet self-report survey of unknown blinding status using a cross- sectional design and a non-specific quality of life tool in a mixed population with and without hormone therapy and/or reassignment surgery. There were no formal controls.

The investigators recruited natal female participants identifying as male using email, internet bulletin boards, and flyers/postcards distributed in the San Francisco Bay Area. Reduction of duplicate entries by the same participant was limited to the use of a unique user name and password.

The investigators employed the Short-Form 36 (SF-36) Version 2 using U.S. normative data. They reported using both male and female normative data for the comparator SF-36 cohort. Data for the eight domains were expressed as normative scoring. The Bonferroni correction was used to adjust for the risk of a Type 1 error with analyses using multiple comparisons.

A total of 379 U.S. respondents classified themselves as males-or-females to males with or without therapeutic intervention. The mean age of the respondents who classified themselves as male or female-to-male was 32.6±10.8 years. Of these 89% were Caucasian, 3.6% Latino, 1.8% African American, 1.8% Asian, and 3.8% other. Of these, 254 (67.0%) reported prior or current testosterone use while 242 (63.8%) reported current testosterone use. In addition, 136 (36.7%) reported having had “top” surgery and 11 (2.9%) reported having “bottom” surgery.

Complete SF-36 data were available for 376 U.S. respondents. For the complete, non-stratified U.S. cohort the Physical Summary Score (53.45±9.42) was statistically higher (better) than the natal gender unspecified SF-36 normative score (50±10) (p=<0.001), but was within one standard deviation of the normative mean. The Mental Summary Score (39.63±12.2) was statistically lower (worse) than the natal gender unspecified SF-36 normative score (50±10) (p<0.001), but was well within two standard deviations of the normative mean. Subcomponents of this score: Mental Health (42.12±10.2), Role Emotional (42.42±11.6), Social Functioning (43.14±10.9), and Vitality (46.22±9.9) were statistically lower (worse) than the SF-36 normative sub-scores, but well within one standard deviation of the normative sub- score means. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

Additional intragroup analyses were conducted, although the data were not stratified by type of therapeutic intervention (hormonal, as well as, surgical). Outcomes of hormone therapy were considered separately and dichotomously from reassignment surgery. The Mental Summary Score was statistically higher (better) in those who had "Ever Received Testosterone" (41.22±11.9) than those with "No Testosterone Usage" (36.08±12.6) (p=0.001). The Mental Summary Scores showed a trend towards statistical difference between those who "Ever Received Top Surgery" (41.21±11.6) and those without "Top Surgery" (38.01±12.5) (p=0.067). These differences were well within one standard deviation of the normative mean. Interpretive information for these small biologic differences in a proprietary assessment tool was not provided.

b. Observational, surgical series, without concurrent controls

Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. J Consult Clin Psychol. 1985 Jun; 53(3):295-304.

Blanchard et al. conducted a single-center (Ontario, Canada), prospective, non-blinded, cross-sectional study using a self-designed questionnaire and a non- specific psychological symptom assessment with normative data. The investigators assessed social adjustment and psychopathology in patients with gender dysphoria and who were at least one year post gender reassignment surgery. Reassignment surgery was defined as either vaginoplasty or mastectomy/construction of male chest contour with or without nipple transplants, but did not preclude additional procedures. Partner preference was determined using Blanchard's Modified Androphilia-Gynephilia Index, and the nature and extent of any psychopathology was determined with the Symptom Check List 90-Revised (SCL-90R). Differences in test scores considered to be biologically significant were not pre-specified in the methods.

Of the 294 patients (111 natal females and 183 natal males, ratio: 1:1.65) initially evaluated, 263 were diagnosed with gender dysphoria. Of these 79 patients participated in the study (38 female-to-male; 32 male-to-female with male partner preference; 9 male-to-female with female partner preference). The respective mean ages for these 3 groups were 32.6, 33.2, and 47.7 years with the last group being older statistically (p=0.01).

Additional surgical procedures in female-to-male patients included: oophorectomy/hysterectomy (92.1%) and phalloplasty (7.9%). Additional surgical procedures in male-to-female patients with male partner preference included facial hair electrolysis 62.5% and breast implantation (53.1%). Additional procedures in male-to-female patients with female partner preference included facial hair electrolysis (100%) and breast implantation (33.3%). The time between reassignment surgery and questionnaire completion did not differ by group.

Psychopathology as measured by the Global Severity Index of the SCL-90R was absent in all three patient groups. Interpretation did not differ by the sex of the normative cohort.

Of participants, 65.2% of female-to-male patients cohabitated with partners of their natal gender; 46.9% of male-to-female patients with male partner preference cohabitated with partners of their natal gender; and no male-to-female patients with female partner preference cohabitated with partners of their natal gender.

Of participants, 93.7% reported that they would definitely undergo reassignment surgery again. The remaining 6.3% (one female-to-male; one male-to-female with male partner preference; three male-to-female with female partner preference) indicated that they probably would undertake the surgery again. Post hoc analysis suggested that the more ambivalent responders had more recently undergone surgery. Of responders, 98.7% indicated that they preferred life in the reassigned gender. The one ambivalent subject was a skilled and well compensated tradesperson who was unable to return to work in her male dominated occupation.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. Scand J Plast Reconstr Surg Hand Surg. 1997 Mar;31(1):39-45.

Eldh et al. conducted a non-blinded, observational study using a prospective cross-sectional design with an investigator designed questionnaire and retrospective acquisition of pre-operative data. The investigators assessed economic circumstances, family status, satisfaction with surgical results, and sexual function in patients who had undergone gender reassignment surgery.

Of the 175 patients who underwent reassignment surgery in Sweden, 90 responded. Of this number, 50 were female-to-male and 40 were male-to-female (ratio: 1:0.8). Patients reportedly were generally satisfied with the appearance of the reconstructed genitalia (no numbers provided). Of the patients who had undergone surgery prior to 1986, seven (14%) were dissatisfied with shape or size of the neo-phallus; eight (16%) declined comment. There were 14 (35%), with 12 having surgery prior to 1986 and two between 1986 and 1995 inclusive, were moderately satisfied because of insufficient vaginal volume; 8 (20%) declined comment. A neo-clitoris was not constructed until the later surgical cohort. Three of 33 reported no sensation or no sexual sensation. Eight had difficulties comprehending the question and did not respond.

A total of nine (18%) patients had doubts about their sexual orientation; 13 (26%) declined to answer the question. The study found that two female-to- male patients and two male-to-female patients regretted their reassignment surgery and continued to live as the natal gender, and two patients attempted suicide.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. Dtsch Arztebl Int. 2014 Nov 21;111(47):795-801.

Hess at al. conducted a prospective, blinded, observational study using a cross-sectional design and a self-designed anonymous questionnaire. The investigators assessed post-operative satisfaction in male-to-female patients with gender dysphoria who were followed in a urology specialty clinic (Essen, Germany). Patients had met the ICD-10 diagnostic criteria, undergone gender reassignment surgeries including penile inversion vaginoplasty, and a Likert-style questionnaire with 11 elements. Descriptive statistics were provided.

There were 254 consecutive eligible patients who had undergone surgery between 2004 and 2010 identified and sent surveys, of whom 119 (46.9%) responded anonymously. Of the participants, 13 (10.9%) reported dissatisfaction with outward appearance and 16 (13.4%) did not respond; three (2.5%) reported dissatisfaction with surgical aesthetics and 25 (21.0%) did not respond; eight (6.7%) reported dissatisfaction with functional outcomes of the surgery and 26 (21.8%) did not respond; 16 (13.4%) reported they could not achieve orgasm and 28 (23.5%) did not respond; four (3.4%) reported feeling completely male/more male than female and 28 (23.5%) did not respond; six (5.0%) reported not feeling accepted as a woman, two (1.7%) did not understand the question, and 17 (14.3%) did not respond; and 16 (13.4%) reported that life was harder and 24 (20.2%) did not respond.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. Arch Sex Behav. 2006 Dec;35(6):717-27. Epub 2006 Nov 16. (United States study)

Lawrence conducted a prospective, blinded observational study using a cross-sectional design and a partially self-designed quality of life tool using yes/no questions or Likert scales. The investigator assessed sexual function, urinary function, and other pre/post-operative complications in patients who underwent male-to-female gender reassignment surgery. Questions addressed core reassignment surgery (neo-vagina and sensate neo-clitoris) and related reassignment surgery (labiaplasty, urethral meatus revision, vaginal deepening/widening, and other procedures), use of electrolysis, and use of hormones.

Questionnaires were designed to be completed anonymously and mailed to 727 eligible patients. Of those eligible, 232 (32%) returned valid questionnaires. The age at the time reassignment surgery was 44±9 (range 18-70) years and mean duration after surgery was 3±1 (range 1-7) years.

Happiness with sexual function and the reassignment surgery was reported to be lower when permanent vaginal stenosis, clitoral necrosis, pain in the vagina or genitals, or other complications such as infection, bleeding, poor healing, other tissue loss, other tissue necrosis, urinary incontinence, and genital numbness were present. Quality of life was impaired when pain in the vagina or genitals was present.

Satisfaction with sexual function, gender reassignment surgery, and overall QOL was lower when genital sensation was impaired and when vaginal architecture and lubrication were perceived to be unsatisfactory. Intermittent regret regarding reassignment surgery was associated with vaginal hair and clitoral pain. Vaginal stenosis was associated with surgeries performed in the more distant past; whereas, more satisfaction with vaginal depth and width was present in more recent surgical treatment.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. Psychiatry Clin Neurosci. 2012 Jun; 66(4):371-2. PMID: 22624747.

Salvador et al. conducted a single center (Port Alegre, Brazil) prospective, non-blinded, observational study using a cross-sectional design (albeit over an extended time interval) and a self-designed quality of life tool. The investigators assessed regret, sexual function, partnerships, and family relationships in patients who had undergone gender reassignment surgery at least 24 months prior.

Out of the 243 enrolled in the clinic over a 10 year interval, 82 underwent sex reassignment surgery. There were 69 participants with a minimum 2-year follow up, of whom 52 patients agreed to participate in the study. The age at follow-up was 36.3±8.9 (range 15-58) years with the time to follow-up being 3.8±1.7 (2-7) years. A total of 46 participants reported pleasurable neo-vaginal sex and post-surgical improvement in the quality of their sexual experience. The quality of sexual intercourse was rated as satisfactory to excellent, average, unsatisfactory, or not applicable in the absence of sexual contact by 84.6%, 9.6%, 1.9%, and 3.8% respectively. Of the participants, 78.8% reported greater ease in initiating and maintaining relationships; 65.4% reported having a partner; 67.3% reported increased frequency of intercourse; 36.8% reported improved familial relationships. No patient reported regret over reassignment surgery. The authors did not provide information about incomplete questionnaires.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. Singapore Med J. 1993 Dec; 34(6):515 -7.

Tsoi conducted a single-center (Singapore) prospective, non-blinded, observational study using a cross-sectional design and a self-designed quality of life tool. The investigator assessed overall life satisfaction, employment, partner status, and sexual function in gender-reassigned persons who had undergone gender reassignment surgery between 1972 and 1988 inclusive and who were approximately 2 to 5 years post-surgery. Acceptance criteria for surgery included good physical health, good mental health, absence of heterosexual tendencies, willingness to undergo hormonal therapy for ≥6 months, and willingness to function in the life of the desired gender for ≥6 months. Tsoi also undertook retrospective identification of variables that could predict outcomes.

The size of the pool of available patients was not identified. Of the 81 participants, 36 (44.4%) were female-to-male and 45 (55.6%) were male-to-female (ratio 1:1.25).

The mean ages at the time of the initial visit and operation were: female-to-male 25.4±4.4 (range 14-36) and 27.4 ±4.0; (range 14-36); male-to-female 22.9±4.6 (range 14-36) and 24.7±4.3 (14-36) years respectively. Of all participants, 14.8% were under age 20 at the time of the initial visit. All were at least 20 at the time of gender

reassignment surgery. The reported age of onset was 8.6 years for female-to-male patients and 8.7 years for male-to-female patients.

All participants reported dressing without difficulty in the reassigned gender; 95% of patients reported good or satisfactory adjustment in employment and income status; 72% reported good or satisfactory adjustment in relationships with partners. Although the quality of life tool was self-designed, 81% reported good or satisfactory adjustment to their new gender, and 63% reported good or acceptable satisfaction with sexual activity. Of the female-to-male patients, 39% reported good or acceptable satisfaction with sex organ function in comparison to 91% of male-to-female patients ($p<0.001$). (The author reported that a fully functioning neo-phallus could not be constructed at the time.) The age of non-intercourse sexual activity was the only predictor of an improved outcome.

Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. J Sex Med. 2009 Mar;6(3):752 -60. Epub 2008 Nov 17.

Weyers at al. (2009) conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments including a non-specific quality of life tool and a semi-specific quality of life tool (using normative data) along with two self-designed tools.

The investigators assessed general quality of life, sexual function, and body image from the prior four weeks in Dutch-speaking male-to-female patients with gender dysphoria who attended a single-center (Ghent, Belgium), specialized, comprehensive care university clinic. Investigators used the Dutch version of the SF-36 and results were compared to normative data from Dutch women and U.S. women. The 19 items of the Dutch version of the Female Sexual Function Index (FSFI) were used to measure sexual desire, function, and satisfaction. A self-designed seven question visual analog scale (VAS) was used to measure satisfaction with gender related body traits and appearance perception by self and others. A self-designed survey measured a broad variety of questions regarding personal medical history, familial medical history, relationships, importance of sex, sexual orientation, gynecologic care, level of regret, and other health concerns. For this study, hormone levels were also obtained.

The study consisted of 50 (71.5% of the eligible recruits) participants. Analysis of the data revealed that the patient’s average age was 43.1 ±10.4 years, and all of the patients had vaginoplasty. This same population also had undergone additional feminization surgical procedures (breast augmentation 96.0%, facial feminization 36.0%, vocal cord surgery 40.0%, and cricoid cartilage reduction 30.0%). A total of two (4.0%) participants reported “sometimes” regretting reassignment surgery and 23 (46.0%) were not in a relationship. For the cohort, estradiol, testosterone, and sex hormone binding globulin levels were in the expected range for the reassigned gender. The SF-36 survey revealed that the subscale scores of the participants did not differ substantively from those of Dutch and U.S. women. VAS scores of body image were highest for self-image, appearance to others, breasts, and vulva/vagina (approximately 7 to 8 of 10). Scores were lowest for body hair, facial hair, and voice characteristics (approximately 6 to 7 of 10).

The total FSFI score was 16.95±10.04 out of a maximal 36. The FSFI scores averaged 2.8 (6 point maximum): satisfaction 3.46±1.57, desire 3.12+1.47, arousal 2.95±2.17, lubrication 2.39±2.29, orgasm 2.82±2.29, and pain 2.21±2.46. Though these numbers were reported in the study, data on test population controls were not provided.

A post hoc exploration of the data suggested the following: perceived improvement in general health status was greater in the subset that had undergone reassignment surgery within the last year; sexual orientation impacted the likelihood of being in a relationship; SF-36 scores for vitality, social functioning, and mental health were nominally better for those in relationships, but that overall SF-36 scores did not differ by relationship status; sexual orientation and being in a relationship impacted FSFI scores; and reported sexual function was higher in those with higher satisfaction with regards to their appearance.

Wierckx K, Van Caenegem E, Elaut E, Dedecker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. J Sex Med. 2011 Dec;8 (12):3379-88. Epub 2011 Jun 23.

Wierckx at al. conducted a prospective, non-blinded, observational study using a cross-sectional design and several measurement instruments (a non-specific quality of life tool with reported normative data along with three self-designed tools). The investigators assessed general quality of life, sexual relationships, and surgical complications in Dutch-speaking female-to-male patients with gender dysphoria who attended a single-center, specialized, comprehensive care, university clinic (Ghent, Belgium). Investigators used the Dutch version of the SF-36 with 36 questions, eight subscales, and two domains evaluating physical and mental health. Results were compared to normative data from Dutch women and Dutch men. Self -designed questionnaires to evaluate aspects of medical history, sexual functioning (there were separate versions for those with and without partners), and surgical results were also used. The Likert-style format was used for many of the questions.

A total of 79 female-to-male patients with gender dysphoria had undergone reassignment surgery were recruited; ultimately, 47 (59.5%) chose to participate. Three additional patients were recruited by other patients. One of the 50 participants was later excluded for undergoing reassignment surgery within the one year window. The age of patients was: 30±8.2 years (range 16 to 49) at the time of reassignment surgery and 37.1 ±8.2 years (range 22 to 54) at the time of follow-up. The time since hysterectomy, oopherectomy, and mastectomy was 8 years (range 2 to 22). The patient population had undergone additional surgical procedures: metaidoiplasty (n=9; 18.4%), phalloplasty (n=8 after metaidoiplasty, 38 directly; 93.9% total), and implantation of erectile prosthetic device (n=32; 65.3%). All had started hormonal therapy at least two years prior to surgery and continued to use androgens.

The SF-36 survey was completed by 47 (95.9%) participants. The “Vitality” and the “Mental Health” scales were lower than the Dutch male population: 62.1±20.7 versus 71.9±18.3 and 72.6±19.2 versus 79.3±16.4 respectively. These subscale scores were equivalent to the mean scores of the Dutch women.

None of the participants were dissatisfied with their hysterectomy-oophorectomy procedures; 4.1% were dissatisfied with their mastectomies because of extensive scarring; and 2.2% were dissatisfied with their phalloplasties. Of the participants, 17.9% were dissatisfied with the implantation of an erectile prosthetic device; 25 (51.0%) reported at least one post-operative complication associated with phalloplasty (e.g., infection, urethrostenosis, or fistula formation); 16 (50.0% of the 32 with an erectile prosthetic device) reported at least one post-operative complication associated with implantation of an erectile prosthetic (e.g., infection, leakage, incorrect positioning, or lack of function).

A total of 18 (36.7%) participants were not in a relationship; 12.2% reported the inability to achieve orgasm with self-stimulation less than half the time; 12.2% did not respond to the question. Of those participants with partners, 28.5% reported the inability to achieve orgasm with intercourse less than half the time and 9.7% did not respond to this question. Also, 61.3% of those with partners reported (a) no sexual activities (19.4%) or (b) activities once or twice monthly (41.9%), and there were 12.9% who declined to answer.

c. Observational, surgical patients, cross-sectional, with controls

Ainsworth TA, Spiegel JH. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. Qual Life Res. 2010 Sep;19(7):1019-24.

Ainsworth and Spiegel conducted a prospective, observational study using a cross-sectional design and a partially self-designed survey tool. The blind status is unknown. Treatment types served as the basis for controls.

The investigators, head and neck surgeons who provided facial feminization services, assessed perception of appearance and quality of life in male-to-female subjects with self-reported gender dysphoria. Patients could have received no therapeutic intervention, hormone therapy, reassignment surgery, and/or facial feminization surgery and an unrestricted length of transition. (Transition refers to the time when a transgender person begins to live as the gender with which they identify rather than the gender assigned at birth.) Criteria for the various types of interventions were not available because of the survey design of the study. Patients were recruited via website or at a 2007 health conference. Pre-specified controls to eliminate duplicate responders were not provided. The investigators employed a self-designed Likert-style facial feminization outcomes evaluation questionnaire and a "San Francisco 36" health questionnaire. No citations were provided for the latter. It appears to be the Short-form (SF) 36-version 2. Changes or differences considered to be biologically significant were not pre-specified. Power corrections for multiple comparisons were not provided.

The investigators reported that there were 247 participants. (The numbers of incomplete questionnaires was not reported.) Of the 247 participants, 25 (10.1%) received only primary sex trait reassignment surgery, 28 (11.3%) received facial surgery without primary sex trait reassignment surgery, 47 (19.0%) received both facial and primary sex trait reassignment surgery, and 147 (59.5%) received neither facial nor reassignment surgery.

The mean age for each of these cohorts was: 50 years (no standard deviation [S.D.]) only reassignment surgery, 51 years (no S.D.) only facial surgery, 49 years (no S.D.) both types of surgery, and 46 years (no S.D.) (neither surgery). Of the surgical cohorts: 100% of those who had undergone primary sex trait reassignment surgery alone used hormone therapy, 86% of those who had undergone facial feminization used hormone therapy, and 98% of those who had undergone both primary sex trait reassignment surgery and facial feminization used hormone therapy. In contrast to the surgical cohorts, 66% of the "no surgery" cohort used hormonal therapy, and a large proportion (27%) had been in transition for less than one year.

The investigators reported higher scores on the facial outcomes evaluation in those who had undergone facial feminization. Scores of the surgical cohorts for the presumptive SF-36 comprehensive mental health domain did not differ from the general U.S. female population. Scores of the "no surgery" cohort for the comprehensive mental health domain were statistically lower than those of the general U.S. female population, but within one standard deviation of the normative mean. Mean scores of all the gender dysphoric cohorts for the comprehensive physical domain were statistically higher than those of the general female U.S. population, but were well within one standard deviation of the normative mean. Analyses of inter-cohort differences for the SF-36 results were not conducted. Although the investigators commented on the potential disproportionate impact of hormone therapy on outcomes and differences in the time in "transition", they did not conduct any statistical analyses to correct for putative confounding variables.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. Psychopathology. 2008;41(2):96 -100. Epub 2007 Nov 23.

Kraemer et al. conducted a single center (Zurich, Switzerland) prospective, non-blinded, observational study using a cross-sectional design comparing pre-and post- surgical cohorts. Patients were required to meet DSM III or DSM IV criteria as applicable to the time of entry into the clinic. Post-surgical patients were from a long-term study group (Hepp et al., 2002). Pre-surgical patients were recent consecutive referrals. The assessment tool was the Fragebogen zur Beurteilung des eigenen Korpers (FBeK) which contained three domains.

There were 23 pre-operative patients: 7 (30.4%) female-to-male and 16 (69.6%) male-to-female (ratio 1:2.3). There were 22 post-operative patients: 8 (36.4 %) female-to-male and 14 (63.6%) male-to-female (ratio 1:1.8). The mean ages of the cohorts were as follows: pre-operative 33.0±11.3 years; post-operative 38.2±9.0 years. The mean duration after reassignment surgery was 51±25 months (range 5-96).

The pre-operative groups had statistically higher insecurity scores compared to normative data for the natal sex: female-to-male 9.0±3.8 versus 5.1±3.7; male-to-female 8.1±4.5 versus 4.7±3.1 as well as statistically lower self-confidence in one's attractiveness: female-to-male 3.1±2.9 versus 8.9±3.1; male-to-female 7.0±2.9 vs 9.5±2.6.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of

transsexualism. Br J Psychiatry. 1968 Apr;132: 350-3.

Mate-Kole at al. conducted a single site (London, United Kingdom) prospective non-blinded, observational study using a cross-sectional design and two psychological tests (one with some normative data). Concurrent controls were used in this study design. The investigators assessed neuroticism and sex role in natal males with gender dysphoria. Patients at various stages of management, (i.e., under evaluation, using cross-sex hormones, or post reassignment surgery [6 months to 2 years]) were matched by age of cross-dressing onset, childhood neuroticism, personal psychiatric history, and family psychiatric history. Both a psychologist and psychiatrist conducted assessments. The instruments used were the Crown Crisp Experiential Index (CCEI) for psychoneurotic symptoms and the Bem Sex Role Inventory. ANOVA was used to identify differences between the three treatment cohorts.

For each cohort, investigators recruited 50 male-to-female patients from Charing Cross Hospital. The mean ages of the three cohorts were as follows: 34 years for patients undergoing evaluation; 35 years for wait-listed patients; and 37 years for post-operative patients. For the cohorts, 22% of those under evaluation, 24% of those on hormone treatment only, and 30% of those post-surgery had prior psychiatric histories, and 24%, 24%, while 14% in each cohort, respectively, had a history of attempted suicide. More than 30% of patients in each cohort had a first degree relative with a history of psychiatric disease.

The scores for the individual CCEI domains for depression and somatic anxiety were statistically higher (worse) for patients under evaluation than those on hormone treatment alone. The scores for all of the individual CCEI domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were statistically lower in the post-operative cohort than in the other two cohorts.

The Bem Sex Role Inventory masculinity score for the combined cohorts was lower than for North American norms for either men or women. The Bem Sex Role Inventory femininity score for the combined cohorts was higher than for North American norms for either men or women. Those who were undergoing evaluation had the most divergent scores from North American norms and from the other treatment cohorts. Absolute differences were small. All scores of gender dysphoric patients averaged between 3.95 and 5.33 on a 7 point scale while the normative scores averaged between 4.59 and 5.12.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. Arch Sex Behav. 2001 Jun;30(3):301-10.

Wolfradt and Neumann conducted a controlled, prospective, non-blinded, observational study using a cross-sectional design. The investigators assessed aspects of personality in male-to-female patients who had undergone vocal cord surgery for voice feminization and in healthy non-transgender volunteers from the region. The patients had undergone gender reassignment surgery 1 to 5 years prior to voice surgery. The volunteers were matched by age and occupation.

The primary hypothesis was that depersonalization, with the sense of being detached from one's body or mental processes, would be more common in male-to- female patients with gender dysphoria. German versions of the Scale for Depersonalization Experiences (SDPE), the Body Image Questionnaire (BIQ), a Gender Identity Trait Scale (GIS), and the Self-Esteem Scale (SES) were used in addition to a question regarding global satisfaction. Three of the assessments used a 5 point scale (BIQ, GIS, and SDPE) for questions. One used a 4 point scale (SES). Another used a 7 point scale (global satisfaction). The study consisted of 30 male-to-female patients, 30 healthy female volunteers, and 30 healthy male volunteers. The mean age of study participants was 43 years (range 29- 67).

Results of the study revealed that there were no differences between the three groups for the mean scores of measures assessing depersonalization, global satisfaction, the integration of masculine traits, and body-image-rejected (subset). Also, the sense of femininity was equivalent for male-to-female patients and female controls and higher than that in male controls. The levels of self-esteem and body image-dynamic (subset) were equivalent for male-to-female patients and male controls and higher than that in female controls, and none of the numeric differences between means exceeded 0.61 units.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. Fertil Steril. 2009 Nov;92(5):1685-1689.e3. Epub 2008 Nov 6.

Kuhn et al. conducted a prospective, non-blinded, observational study using a cross-sectional design and semi-matched control cohort. The investigators assessed global satisfaction in patients who were from gynecology and endocrinology clinic (Bern, Switzerland), and who had undergone some aspect of gender reassignment surgery in the distant past, but were still receiving cross-sex hormones from the clinic. The quality of life assessment tools included a VAS and the King's Health Questionnaire (KHQ), which consists of eight domains with scores between zero and five or one and five, with lower scores indicating higher preference. The KHQ and the numerical change/difference required for clinical significance (≥5 points in a given domain, with higher scores being more pathologic) were included in the publication. Twenty healthy female controls from the medical staff who had previously undergone an abdominal or pelvic surgery were partially matched by age and body mass index (BMI), but not sex. No corroborative gynecologic or urologic evaluations were undertaken.

Of the 55 participants, three (5.4%) were female-to-male and 52 (94.5%) were male-to-female (ratio 1:17.3). Reassignment surgery had been conducted 8 to 23 years earlier (median 15 years). The median age of the patients at the time of this study was 51 years (range 39-62 years). The patients had undergone a median of nine surgical procedures in comparison to the two undergone by controls. Reassignment patients were less likely to be married (23.6% versus 65%; p=0.002); partnership status was unknown in five patients. The scores of VAS global satisfaction (maximal score eight) were lower for surgically reassigned patients (4.49±0.1 SEM) than controls (7.35±0.26 SEM) (p<0.0001).

The abstract stated that quality of life was lower in reassignment patients 15 years after surgery relative to controls. One table in the study, Table 2, delineated statistically and biologically significant differences for four of the eight KHQ domains between the patients and controls: physical limitation: 37.6±2.3 versus 20.9±1.9 (p<0.0001), personal limitation: 20.9±1.9 versus 11.6±0.4 (p<0.001), role limitation: 27.8+2.4 versus 34.6+1.7 (p=0.046), and general health: 31.7±2.2 versus 41.0±2.3 (p<0.02). There is a related paper by Kuhn

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. Acta Psychiatr Scand. 2000 Oct;102(4):276-81.

Haraldsen and Dahl conducted a single-center (Oslo, Norway) partially prospective, non-blinded, observational study using a cross-sectional design and a non-specific psychometric test. There was a control group, but it was not concurrent.

In the germane sub-study, the investigator assessed psychopathology in patients with gender dysphoria. Patients, who were independently evaluated by two senior psychiatrists, were required to meet DSM III-R or DSM IV diagnostic criteria and the Swedish criteria for reassignment surgery. The Norwegian version of the SCL-90 was used. The testing was conducted from 1987 to 1989 for those who had undergone reassignment surgery between 1963 and 1987 and from 1996 to 1998 for pre- surgical patients who had applied for reassignment surgery between 1996 and 1998. In addition, Axis I, Axis II, and Axis V (Global Functioning) was assessed.

Of 65 post–surgical and 34 pre-surgical patients, 59 post-surgical and 27 pre-surgical patients ultimately entered the study. The combined cohorts consisted of 35 (40.7%) female-to-male patients and 51 (59.3%) male-to-female patients (ratio 1:1.5). The ages were female-to-male 34±9.5 years and female-to-male 33.3±10.0 years. The other control group consisted of patients with personality disorder. Of these, 101 (27 men (33.9±7.3 years) and 74 women (31.6±8.2) were tested during a treatment program. One year later, 98% were evaluated. A total of 28 (32.5%) of the pre- and post- reassignment surgery patients had an Axis I diagnosis compared to 100 (99.0%) of those with personality disorders. Depression and anxiety were the most common diagnoses in both groups, but were approximately three to four times more common in the personality disorder cohort. Seventeen (19.8%) of the pre- and post-reassignment surgery patients had an Axis II diagnosis whereas the mean number of personality disorders in the personality disorder cohort was 1.7±1. The Global Assessment of Function was higher (better) in the gender dysphoric groups (78.0±8.9) than in the personality disorder cohort (53.0±9.0).

Global Severity Indices (GSI) were highest for those with personality disorder regardless of gender and exceeded the cut-point score of 1.0. The GSI scores for females-to-males and males-to-females were 0.67±57 and 0.56±0.45. Although they were nominally higher than the healthy normative controls (males: 0.32±0.36 and females 0.41±0.43), they were well within the non- pathologic range. The same was true for the subscales.

SCL-90 GSI scores did not differ substantively between pre- and post-surgical patients, nor did the SCI subscale scores differ substantively between pre- and post-surgical patients. Any small non-significant differences tracked with the age and sex differences.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. J Nerv Ment Dis. 1985 Jun;173(6):358-65. (United States study)

Beatrice conducted a prospective, non-blinded, observational study using a cross-sectional design and control cohorts in the U.S. The investigator assessed psychological adjustment and functioning (self-acceptance) in male-to-female patients with gender dysphoria (with and without GRS), transvestites from two university specialty clinics, and self-identified heterosexual males recruited from the same two universities. The criteria to qualify for the study included being known to the clinic for at least one year, cross-dressing for at least one year without arrest, attendance at 10 or more therapy sessions, emotionally self-supporting, and financially capable of payment for reassignment surgery, and all of these criteria were met by the pre-operative cohort as well as the post-operative cohort. The cohorts were matched to the post-operative cohort (age, educational level, income, ethnicity, and prior heterosexual object choice). The post-operative cohort was selected not on the basis of population representation, but on the basis of demographic feasibility for a small study. The instruments used were the Minnesota Multiphasic Personality Inventory (MMPI) and the Tennessee Self-Concept Scale (TSCS). Changes or differences considered to be biologically significant were not pre-specified.

Of the initial 54 recruits, ten subjects were left in each of the cohorts because of exclusions identified due to demographic factors. The mean age of each cohort were as follows: pre-operative gender dysphoric patients 32.5 (range 27-42) years, postoperative patients 35.1 (30-43) years old, transvestite 32.5 (29-37) years old, and heterosexual male 32.9 (28-38) years old. All were Caucasian. The mean age for cross-dressing in pre-operative patients (6.4 years) and post-operative patients (5.8 years) was significantly lower than for transvestites (11.8 years).

The scores for self-acceptance did not differ by diagnostic category or surgical status as measured by the TSCS instrument. As measured by the T-scored MMPI instrument (50±10), levels of paranoia and schizophrenia were higher for post-operative (GRS) patients (63.0 and 68.8) than transvestites (55.6 and 59.6) and heterosexual males (56.2 and 51.6). Levels of schizophrenia were higher for pre-operative patients (65.1) than heterosexual males (51.6). There were no differences between patients with gender dysphoria. Scores for the Masculine-Feminine domain were equivalent in those with transvestitism and gender dysphoria with or without surgery, but higher than in heterosexual males. The analysis revealed that despite the high level of socio-economic functioning in these highly selected subjects, the MMPI profiles based on the categories with the highest scores were notable for antisocial personality, emotionally unstable personality, and possible manic psychosis in the pre-operative GRS patients and for paranoid personality, paranoid schizophrenia, and schizoid personality in the post-operative GRS patients. By contrast, the same MMPI profiling in heterosexual males and transvestites was notable for the absence of psychological dysfunction.

d. Observational, surgical patients, longitudinal, with controls

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. PLoS One. 2011;6(2):e16885. Epub 2011 Feb 22.

Dhejne et al. conducted a retrospective, non-blinded, observational study of nation-wide mortality using a longitudinal and a population-based matched cohort. The investigators assessed conditions such as, but not limited to, mortality, suicide attempts, psychiatric hospitalization, and substance abuse in gender-reassigned persons and randomly selected unexposed controls matched by birth year and natal sex (1:10) as well as by birth year and the reassigned gender (1:10). Data were extracted from national databases including the Total Population Register (Statistics Sweden), the Medical Birth Register, the Cause of Death Register (Statistics Sweden), the Hospital Discharge Register (National Board of Health and Welfare), the Crime Register (National Council of Crime), and those from the Register of Education for highest educational level. The criteria required to obtain the initial certificate for reassignment surgery and change in legal status from the National Board of Health and Welfare were the 2002 WPATH criteria and included evaluation and treatment by one of six specialized teams, name change, a new national identity number indicative of gender, continued use of hormones, and sterilization/castration. Descriptive statistics with hazard ratios were provided.

Investigators identified 804 patients with gender identity disorder (or some other disorder) in Sweden during the period from 1973 to 2003 inclusive. Of these patients, 324 (40.3%) underwent gender-reassignment surgery (133 female-to-male [41.0%]; 191 male-to-female [59.0%]; ratio 1:1.4). The average follow-up time for all-cause mortality was 11.4 years (median 9.1). The average follow-up time for psychiatric hospitalization was 10.4 years (median 8.1).

The mean ages in female-to-male and male-to-female reassigned patients were: 33.3±8.7 (range 20–62) and 36.3± 10.1 (range 21–69) years, respectively. Immigrant status was two times higher in reassigned patients (n=70, 21.6%) than in either type of control (birth [natal] sex matched n=294 [9.1%] or reassigned gender matched n=264 [8.1%]). Educational attainment (10 or more years) was somewhat lower for reassigned patients (n=151 [57.8%]) than in either type of control (birth sex matched n=1,725 [61.5%] or reassigned gender matched n=1804 [64.3%]) (cohort data were incomplete). The biggest discordance in educational attainment was for female-to-male reassigned patients regardless of the control used. Prior psychiatric morbidity (which did not include hospitalization for gender dysphoria) was more than four times higher in reassigned patients (n=58, 17.9%) than in either type of control (birth sex matched n=123 [3.8%] or reassigned gender matched n=114 [3.5%]).

All-cause mortality was higher for patients who underwent gender reassignment surgery (n=27 [8.3%]) than in controls (hazard ratio 2.8 [CI 1.8-4.3]) even after adjustment for covariants (prior psychiatric morbidity and immigration status). Divergence in the survival curves began at 10 years. Survival rates at 20 year follow-up (as derived from figure 1) were: female control 97%, male controls 94%, female-to-male patients 88%, and male-to-female patients 82%. The major contributor to this mortality difference was completed suicide (n=10 [3.1%]; adjusted hazard ratio 19.1 [CI 5.8-62.9]). Mortality due to cardiovascular disease was modestly higher for reassigned patients (n=9 [2.8%]) than in controls (hazard ratio 2.5 [CI 1.2-5.3]).

Suicide attempts were more common in patients who underwent gender reassignment surgery (n= 29 [9.0%] than in controls (adjusted hazard ratio 4.9 [CI 2.9–8.5]). Male-to-female patients were at higher adjusted risk for attempted suicide than either control whereas female-to-male patients were at higher adjusted risk compared to only male controls and maintained the female pattern of higher attempted suicide risk. Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common in reassigned persons n= 64 [20.0%] than in controls (hazard ratio 2.8 [CI 2.0–3.9]) even after adjusting for prior psychiatric morbidity. Hospitalization for substance abuse was not greater than either type of control.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landen (1998) patient population and much of the Dhejne et al. (2014) population.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. Arch Sex Behav. 2014 Nov;43(8):1535-45. Epub 2014 May 29 and Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. Acta Psychiatr Scand. 1998 Apr;97(4):284 (Dhejne et al., 2014; Landén et al., 1998) Sweden-All

Dhejne et al. conducted a non-blinded, observational study that was longitudinal for the capture of patients with "regret" in a national database. This same group (Landén et al., 1998) conducted a similar study along with retrospective acquisition of clinical data to explore the differences between the cohorts with and without regret. There were no external controls; only intra- group comparisons for this surgical series.

The investigators assessed the frequency of regret for gender reassignment surgery. Data were extracted from registries at the National Board of Health and Welfare to which patients seeking reassignment surgery or reversal of reassignment surgery make a formal application and which has maintained such records since a 1972 law regulating surgical and legal sex reassignment. The investigators reviewed application files from 1960 through 2010. The specific criteria to qualify for gender surgery were not delineated. Patients typically underwent diagnostic evaluation for at least one year. Diagnostic evaluation was typically followed by the initiation of gender confirmation treatment including hormonal therapy and real-life experience. After two years of evaluation and treatment, patients could make applications to the national board. Until recently sterilization or castration were the required minimal surgical procedures (Dhejne et al., 2011). Secular changes in this program included consolidation of care to limited sites, changes in accepted diagnostic criteria, and provision of non-genital surgery, e.g., mastectomy during the real- life experience phase, and family support.

There were 767 applicants for legal and surgical reassignment (289 [37.7%] female-to-male and 478 [62.3%] male-to-female; ratio 1:1.6). The number of applicants doubled each ten year interval starting in 1981.

Of the applicants, 88.8% or 681 (252 [37.0%] female-to-male and 429 [63.0%] male-to-female; ratio 1:1.7] had undergone surgery and changed legal status by June 30, 2011. This number included eight (four [50.0%] female-to-male and four [50.0%] male to female; ratio 1:1) people who underwent surgery prior to the 1972 law. This number appears to include 41 (two [4.9%] female-to-male and 39 [95.1%] male-to-female; ratio 1:19.5) people who underwent surgery abroad at their own expense (usually in Thailand or the U.S.). This cohort (6% of 681) includes one person who was denied reassignment surgery by Sweden.

Twenty-five (3.3%) of the applications were denied with the two most common reasons being an incomplete application or not meeting the diagnostic criteria. An additional 61(8.0%) withdrew their application, were wait-listed for surgery, postponed surgery (perhaps in hopes of the later revocation of the sterilization requirement), or were granted partial treatment.

The formal application for reversal of the legal gender status, the "regret rate", was 2.2%. No one who underwent sex- reassignment surgery outside of Sweden (36 of these 41 had surgery after 1991) has requested reversal. The authors noted, however, that this preliminary number may be low because the median time interval to reversal request was eight years-only three of which had elapsed by publication submission- and because it was the largest serial cohort. This number did not include other possible expressions of regret including suicide (Dhejne et al., 2011).

Dhejne et al. in 2014 reported that the female-to-male (n=5): male-to-female (n=10) ratio among those who made formal applications for reversal was 1:2. The investigators also reported that the female-to-male applicants for reversal were younger at the time of initial surgical application (median age 22 years) than the complete female-to-male cohort at the time of surgical application (median age 27 years). By contrast the male-to-female applicants for reversal were older at the time of initial surgical application (median age 35 years) than the complete male-to-female cohort at the time of initial surgical application (median age 32 years). Other clinical data to explore the differences between the cohorts with and without regret were not presented in this update publication.

In their earlier publication, in addition to determining a regret rate (3.8%), Landén et al. extracted data from medical records and government verdicts. Pearson Chi-square testing with Yates' correction for small sample sizes was used to identify candidate variables predictive of regret. They observed that: (a) 25.0% of the cohort with regrets and 11.4% of the cohort without regrets were unemployed, (b) 16.7% of the cohort with regrets and 15.4% of the cohort without regrets were on "sick benefit", (c) 15.4% of the cohort with regrets and 13.9% of the cohort without regrets had problems with substance abuse, (d) 69.2% of the cohort with regrets and 34.6% of the cohort without regrets had undergone psychiatric treatment, (e) 15.4% of the cohort with regrets and 8.8% of the cohort without regrets had a mood disorder, and (f) 15.4% of the cohort with regrets and 1.5% of the cohort without regrets had a psychotic disorder.

The putative prognostic factors that were statistically different between the cohorts with and without regret included prior psychiatric treatment, a history of psychotic disorder, atypical features of gender identity, and poor family support. Factors that trended towards statistical difference included having an unstable personality, sexual orientation and transvestitism. Univariate regression analyses further clarified the most important variables. These variables were tested with logistic regression. Initial modeling included the variable "history of psychotic disorder". Although this variable was predictive, it was excluded from future analyses because it was already a contraindication to reassignment surgery. Additional multivariate regression analyses identified poor family support as the most predictive variable and atypical features of gender identity as the second most important variable. Presence of both variables had a more than additive effect.

The nationwide mortality studies by Dhejne et al. (2011) includes much, if not all, of the Landén (1998) patient population and most of the Dhejne (2014) population. There is a related paper by Landén et al. 1998b that included the criteria to qualify for surgical intervention at that time.

Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. J Sex Med. 2014 Jan;11(1):119-26. Epub 2013 Oct 28.

Heylens et al. conducted a prospective, non-blinded observational study using a longitudinal design in which patients served as their own controls. They used a non-specific psychiatric test with normative data along with two self-designed questionnaires. The investigators assessed psychosocial adjustment and psychopathology in patients with gender identity disorders. Patients were to be sequentially evaluated prior to institution of hormonal therapy, then 3 to 6 months after the start of cross-sex hormone treatment, and then again one to 12 months after reassignment surgery. The Dutch version of the SCL-90R with eight subscales (agoraphobia, anxiety, depression, hostility, interpersonal sensitivity, paranoid ideation/psychoticism, and sleeping problems) and a global score (psycho-neuroticism) was used serially. A seven parameter questionnaire was used serially to assess changes in social function. Another cross-sectional survey assessed emotional state. The cohorts at each time point consisted of patients who were in the treatment cohort at the time and who had submitted survey responses.

Ninety of the patients who applied for reassignment surgery between June 2005 and March 2009 were recruited. Fifty seven entered the study. Forty-six (51.1% of the recruited population) underwent reassignment surgery. Baseline questionnaire information was missing for 3 patients. Baseline SCL-90 scores were missing for 1 patient but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. Time point 2 (after hormone therapy) SCL-90 information was missing for 10, but included SCL-90 scores from some of the 11 recruits who had not yet undergone reassignment surgery. At time point 3, 42 (91.3% of those who underwent reassignment surgery) patients completed some part of the SCL-90 survey and the psychosocial questionnaires. Some questionnaires were incomplete. The investigators reported response rates of 73.7% for the psychosocial questionnaires and 82.5% for the SCL-90.

Of those who responded at follow-up after surgery, 88.1% reported having good friends; 52.4% reported the absence of a relationship; 47.6% had no sexual contacts; 42.9% lived alone; 40.5% were unemployed, retired, students, or otherwise not working; 2.4% reported alcohol abuse; and 9.3% had attempted suicide. The frequency of these parameters reportedly did not change statistically during the study interval, but there was no adjustment for the inclusion of patients who did not undergo surgery.

In a cross-sectional, self-report mood survey, of the 42 study entrants who completed the entire treatment regimen including reassignment surgery and the final assessment (refers to the initial 57) reported improved body-related experience (97.6%), happiness (92.9%), mood (95.2%), and self-confidence (78.6%) and reduced anxiety (81.0%). Of participants, 16.7% reported thoughts of suicide. Patients also reported on the intervention phase that they believed was most helpful: hormone initiation (57.9%), reassignment surgery (31.6%), and diagnostic-psychotherapy phase (10.5%).

The global “psycho-neuroticism” SCL-90R score, along with scores of 7 of the 8 subscales, at baseline were statistically more pathologic than the general population. After hormone therapy, the score for global “psycho-neuroticism” normalized and remained normal after reassignment surgery. More specifically the range for the global score is 90 to 450 with higher scores being more pathologic. The score for the general population was 118.3±32.4. The respective scores for the various gender dysphoric cohorts were 157.7±49.8 at initial presentation, 119.7±32.1 after hormone therapy, and 127.9±37.2 after surgery. The scores for the general population and the scores after either hormone treatment or surgical treatment did not differ.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. Arch Sex Behav. 1987 Dec;16 (6):511-22.

Kockott and Fahrner conducted a single center (Munich, Germany) prospective, observational study using a longitudinal design. Treatment cohorts were used as controls, and patients served as their own controls. The investigators assessed psychosocial adjustment in patients with gender identity issues. Patients were to have met DSM III criteria. Trans-sexuality, transvestitism, and homosexuality were differentiated. The criteria required for patients to receive hormone therapy and/or reassignment surgery were not delineated. After receiving hormone therapy, patients were later classified by surgical reassignment status (pre-operative and post-operative) and desire for surgery (unchanged desire, hesitant, and no longer desired).

The first investigative tool was a semi-structured in-person interview consisting of 125 questions. The second investigative tool was a scale that organized the clinical material into nine domains which were then scored on a scale. The Psychological Integration of Trans-sexuals (PIT) instrument developed according to the scale used by Hunt and Hampson (1980) for assessment of 17 post-operative patients. There were 15 interviews and two separate interviewers. There were 80 patients identified, but 58 (72.5%) patients (26 pre-operative; 32 post-operative) were ultimately included in the analysis. The duration of follow-up was longer for post-operative patients (6.5 years) than for pre-operative patients (4.6 years) (including time for one patient subsequently excluded). The mean age of the post-operative patients was 35.5±13.1 years, and the age of the patients who maintained a continued desire for surgery was 31.7±10.2 years. The age of the patients who hesitated about surgery was somewhat older, 40.3±9.4 years. The age of the patients who were no longer interested in surgery was 31.8±6.5 years. All were employed or in school at baseline. Patients with hesitation were financially better-off, had longer-standing relationships even if unhappy, and had a statistical tendency to place less value on sex than those with an unchanged wish for surgery.

Post-operative patients more frequently reported contentment with the desired gender and the success of adaption to the gender role than the pre-operative patients with a persistent desire for surgery. Post-operative patients more frequently reported sexual satisfaction than pre-operative patients with a continuing desire for surgery. Post-operative patients also more frequently reported financial sufficiency and employment than pre-operative patients with a persistent desire for surgery. Suicide attempts were stated to be statistically less frequent in the post-surgical cohort.

Psychosocial adjustment scores were in the low end of the range with “distinct difficulties” (19-27) at the initial evaluation for the post-operative patients (19.7), the pre-operative patients with a persistent wish for surgery (20.2), and the hesitant patients (19.7). At initial evaluation, psychosocial adjustment scores for patients no longer wanting surgery were at the high end of the range with “few difficulties” (10-18). At the final evaluation, Psychosocial adjustment scores were at the high end of the range “few difficulties” (10-18) for the post-operative patients (13.2) and the patients no longer wanting surgery (16.5). Psychosocial adjustment scores at the final evaluation were in the borderline range between “few difficulties” (10-18) and “distinct difficulties” (19-27) for both the pre-operative patients with a persistent desire for surgery (18.7), and the hesitant patients (19.1).

The changes in the initial score and the final follow-up score within each group were tracked and reported to be statistically significant for the post-operative group, but not for the other groups. Statistical differences between groups were not presented. Moreover, the post-operative patients had an additional test immediately prior to surgery. The first baseline score (19.7) would have characterized the patients as having “distinct difficulties” in

psychosocial adjustment while the second baseline score (16.7) would have categorized the patients as having "few difficulties" in psychosocial adjustment despite the absence of any intervention except the prospect of having imminent reassignment surgery. No statistics reporting on the change between scores of the initial test and the test immediately prior to surgery and the change between scores of the test immediately prior to surgery and the final follow-up were provided.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. Arch Gen Psychiatry. 1979 Aug;36(9):1010-5. (United States study)

Meyer and Reter conducted a single-center (Baltimore, Maryland, U.S.) prospective, non-blinded, observational study using a longitudinal design and retrospective baseline data. Interview data were scored with a self-designed tool. There were treatment control cohorts, and patients served as their own controls. The investigators assessed patients with gender dysphoria. The 1971 criteria for surgery required documented cross-sex hormone use as well as living and working in the desired gender for at least one year in patients subsequently applying for surgery. Clinical data including initial interviews were used for baseline data. In follow-up, the investigators used extensive two to four hour interviews to collect information on (a) objective criteria of adaptation, (b) familial relationships and coping with life milestones, and (c) sexual activities and fantasies. The objective criteria, which were the subject of the publication, included employment status (Hollingshead job level), cohabitation patterns, and need for psychiatric intervention. The investigators designed a scoring mechanism for these criteria and used it to determine a global adjustment score. The score value or the change score that was considered to be biologically significant was not pre-specified in the methods.

The clinic opened with 100 patients, but when the follow-up was completed, 52 patients were interviewed and 50 gave consent for publication. Of these, 15 (four female-to-male, 11 male-to-female; ratio 1:2.8) were part of the initial operative cohort, 14 (one female-to-male; 13 male-to-female; ratio 1:13) later underwent reassignment surgery at the institution or elsewhere, and 21 (five female-to-male; 16 male-to-female; ratio 1:3.2) did not undergo surgery. The mean ages of these cohorts were 30.1, 30.9, and 26.7 years respectively. The mean follow-up time was 62 months (range 19-142) for those who underwent surgery and 25 months (range 15-48) for those who did not. Socioeconomic status was lowest in those who subsequently underwent reassignment surgery.

Of patients initially receiving surgery, 33% had some type of psychiatric contact prior to the initial clinic evaluation and 8% had psychiatric contact during the follow-up. Of the patients who had not under gone surgery or who had done so later, 72% had some type of psychiatric contact prior to the initial clinic evaluation and 28% had psychiatric contact during follow-up. There was a single female-to-male patient with multiple surgical complications who sought partial reassignment surgery reversal.

The adjustment scores improved over time with borderline statistical significance for the initial operative group and with statistical significance for the never operated group. The absolute score value at follow-up was the same for both groups (1.07+1.53 and 1.10+1.97 respectively). By contrast, the adjustment scores did not improve for those who were not in the cohort initially approved for surgery, but who subsequently underwent surgery later. This was particularly true if the surgery was performed elsewhere. The absolute score value at follow-up was 0.21+1.89.

Related papers include Meyer et al. (1971), Meyer et al. (1974a-d), and Derogatis et al. (1978) along with commentary response by Fleming et al. (1980).

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. Arch Sex Behav. 1996 Oct;25(5):515-25.

Rakic et al. single-center (Belgrade, Yugoslavia) conducted a prospective, non-blinded, observational study using a cross-sectional design and an investigator- designed quality of life tool that asked longitudinal (pre- and post-treatment) questions. Patients served as their own controls. The authors state that the study was not designed to assess the predictors of poor outcomes.

The investigators assessed global satisfaction, body image, relationships, employment status, and sexual function in patients with gender dysphoria who underwent reassignment surgery between 1989 and 1993 and were at least six months post-operative. The criteria to qualify for gender surgery were delineated (1985 standards from the Harry Benjamin International Gender Dysphoria Association) and included cross-gender behavior for at least one year and sexual orientation to non-natal sex. The questionnaire consisted of 10 questions using yes/no answers or Likert-type scales. Findings were descriptive without statistical analysis. As such, changes or differences considered to be biologically significant were not pre-specified, and there were no adjustments for multiple comparisons.

Of the 38 patients who had undergone reassignment surgery, 34 were eligible for the study and 32 participated in the study (two were lost to follow-up and four were in the peri-operative period) - 10 (31.2%) female-to-male and 22 (68.8%) male-to-female (ratio 1:2.2). The duration of follow-up was 21.8 ±13.4 months (range 6 months to 4 years). The age was female-to-male 27.8±5.2 (range 23-37) and male-to-female 26.4±7.8 (range 19-47).

Using an investigator-designed quality of life tool, all patients reported satisfaction with having undergone the surgery. Of the total participants, four (12.5%) (all male-to-female) and eight (25%) (87.5% male-to-female) reported complete dissatisfaction or partial satisfaction with their appearance. Regarding relationships, 80% of female-to-male and 100% of male-to-female patients were dissatisfied with their relationships with others prior to surgery; whereas, no female-to-male patients and 18.1% of male-to-female patients were dissatisfied with relationships after surgery. Regarding sexual partners, 60% of female-to-male and 72.7% of male-to-female patients reported not having a sexual partner prior to surgery; whereas, 20% of female-to-male patients and 27.3% of male-to-female patients did not have a sexual partner after surgery. Of those with partners at each time interval, 100% of female-to-male and 50% of male-to-female patients reported not experiencing orgasm prior to surgery; whereas, 75% of female-to-male and 37.5% of male-to-female patients reported not experiencing orgasm after surgery.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. Arch Sex Behav. 2015 Jul;44(5):1321-9. Epub 2015 Feb 18.

Ruppin and Pfafflin conducted a single-center (Ulm, Germany) partially prospective, non-blinded, observational study using a longitudinal design and non-specific psychometric tests and a self-designed interview tool and questionnaire. Patients served as their own controls.

The investigators assessed psychological symptoms, interpersonal difficulties, gender role stereotypes, personality characteristics, societal function, sexual function, and satisfaction with new gender role in patients with gender dysphoria. Patients were required to have met the ICD-10 criteria for trans-sexualism, been seen by the clinic by prior to 2001, and completed an official change in gender including name change prior to 2001. Assessment tools included German versions of standardized surveys with normative data: the SCL 90R, the Inventory of Interpersonal Problems (IIP), Bem Sex Role Inventory (BSRI), and the Freiburg Personality Inventory (FPI-R), along with semi-structured interviews with self-designed questionnaires. The prospective survey results were compared to retrospective survey results. Changes or inter-group differences considered to be biologically significant were not pre-specified. Diagnostic cut points were not provided. Statistical corrections for multiple comparisons were not included.

Overall, 140 patients received recruitment letters and then 71 (50.7%) agreed to participate. Of these participants, 36 (50.7%) were female-to-male; 35 (49.3%) were male-to-female (ratio 1:0.97). The ages of the patients were: 41.2±5.78 years (female-to-male) and 52.9±10.82 years (male-to-female). The intervals for follow-up were 14.1±1.97 years and 13.7±2.17 years, respectively.

All female-to-male patients had undergone mastectomy; 91.7% had undergone oopherectomy and/or hysterectomy; 61.1% had undergone radial forearm flap phalloplasty or metaoidioplasty. Of male-to-female patients, 94.3% had undergone vaginoplasty and perhaps an additional procedure (breast augmentation, larynx surgery, or vocal cord surgery). Two male-to-female patients had not undergone any reassignment surgery, but were still included in the analyses.

A total of 68 patients ranked their well-being as 4.35±0.86 out of five (three patients did not respond to this question). Of respondents, 40% reported not being in a steady relationship. Regular sexual relationships were reported by 57.1% of 35 female- to-male respondents and 39.4% of 33 male-to-female respondents (three patients did not respond to this question). A total of 11 patients reported receiving out-patient psychotherapy; 69 did not express a desire for gender role reversal (two did not respond to this question). The response rate was less than 100% for most of the self-designed survey questions.

Changes from the initial visit to the follow-up visit were assessed for the SCL-90R in 62 of 71 patients. The effect size was statistically significant and large only for the "Interpersonal Sensitivity" scale (one of 10 parameters). The absolute magnitude of mean change was small: from 0.70±0.67 to 0.26±0.34 (scale range 0-4). The duration of follow-up did not correlate with the magnitude of change on the various scales. Differences in baseline SCL-90R scores of 62 participants were compared with the score of 63 of the 69 eligible recruits who declined to enter the study and were notable for higher "Depression" scores for the latter.

Changes from the initial visit to the follow-up visit were assessed for the IIP in 55 of 71 patients. The effect size was statistically significant and large only for the "Overly Accommodating" scale (one of eight parameters). The absolute magnitude of mean change was small: from 11.64±5.99 to 7.04±4.73 (scale range 0-32). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the FPI-R in 58 of 71 patients. The effect size was statistically significant and large only for the "Life Satisfaction" scale (one of 12 parameters). The absolute magnitude of mean change was substantive: from 4.43±2.99 to 8.31±2.63 (scale range 0-12). The duration of follow-up did not correlate with the magnitude of change on the various scales.

Changes from the initial visit to the follow-up visit were assessed for the BSRI in 16 of 36 female to male patients and 19 of 35 male to female patients. The "Social Desirability" score increased for the female-to-male respondents. At endpoint, both categories of respondents reported androgynous self-images.

This current report is an update of prior publications by Pfafflin including work with Junge which was published in a variety of formats and initially in German.

Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. Psychol Med. 2005 Jan;35(1):89-99.

Smith et al. conducted a single-center (Amsterdam, Netherlands) prospective, non-blinded, observational study using a longitudinal design and psychological function tools. Patients served as their own control prior to and after reassignment surgery. The investigators assessed gender dysphoria, body dissatisfaction, physical appearance, psychopathology, personality traits, and post-operative function in patients with gender dysphoria. Patients underwent some aspect of reassignment surgery. The test instruments included the Utrecht Gender Dysphoria Scale (12 items), the Body Image Scale adapted for a Dutch population (30 items), Appraisal of Appearance Inventory (3 observers, 14 items), the Dutch Short MMPI (83 items), the Dutch version of the Symptom Checklist (SCL)(90 items), and clinic-developed or modified questionnaires. Pre-treatment data was obtained shortly after the initial interview. Post- surgery data were acquired at least one year post reassignment surgery.

Three hundred twenty five consecutive adolescents and adults were screened for the study. One-hundred three (29 [28.2%] female-to-male patients and 74 [71.8%] male-to-female patients [ratio 1:2.6]) never started hormone therapy; 222 (76 [34.2%] female-to-male patients and 146 [65.8%] male-to-female patients [ratio 1:1.9]) initiated hormone therapy. Of the patients who started hormone therapy, 34 (5 [14.7%] female-to-male patients and 29 [85.3%] male-to-female patients [ratio 1:5.8]) discontinued hormone therapy.

Subsequently, the study analysis was limited to adults. One hundred sixty two (58 [35.8%] female-to-male and 104 [64.2%] male-to-female [ratio 1:1.8]) were eligible and provided pre-surgical test data, and 126 (77.8% of eligible adults) (49 [38.9%] female-to-male and 77 [61.1%] male-to-female [ratio 1:1.6]) provided post-surgical data. For those patients who completed reassignment, the mean age at the time of surgical request was 30.9 years (range 17.7-68.1) and 35.2 years (range 21.3-71.9) years at the time of follow-up. The intervals between hormone treatment initiation and surgery and surgery and follow-up were 20.4 months (range 12 to 73) and 21.3 months (range 12 to 47) respectively.

Of the 126 adults who provided post-surgical data, 50 (40.0%) reported having a steady sexual partner, three (2.3%) were retired, and 58 (46.0%) were unemployed. Regarding regret, six patients expressed some regret regarding surgery, but did not want to resume their natal gender role, and one male-to-female had significant regret and would not make the same decision.

Post-surgery Utrecht dysphoria scores dropped substantially and approached reportedly normal values. The patients' appearance better matched their new gender. No one was dissatisfied with his/her overall appearance at follow-up. Satisfaction with primary sexual, secondary sexual, and non-sexual body traits improved over time. Male-to-female patients, however, were more dissatisfied with the appearance of primary sex traits than female-to-male patients. Regarding mastectomy, 27 of 38 (71.1%) female-to-male respondents (not including 11 non-respondents) reported incomplete satisfaction with their mastectomy procedure. For five of these patients, the incomplete satisfaction was because of scarring. Regarding vaginoplasty, 20 of 67 (29.8%) male-to-female respondents (not including 10 non-respondents) reported incomplete satisfaction with their vaginoplasty.

Most of the MMPI scales were already in the normal range at the time of initial testing and remained in the normal range after surgery. SCL global scores for psycho- neuroticism were minimally elevated before surgery 143.0±40.7 (scoring range 90 to 450) and normalized after surgery 120.3±31.4. (An analysis using patient level data for only the completers was not conducted.)

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to- female people before and after surgery. Sexual and Relationship Therapy. 2008 May; 23(2):141-5. (Not in PubMed) and Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. Sexual and Relationship Therapy. 2007 Feb; 22(1):77-81. (Not in PubMed)

Udeze et al. conducted a single-center (Leicester, United Kingdom) prospective, non-blinded, longitudinal study assessing a randomized subset of patients who had completed a non-specific psychological function tool prior to and after male-to-female reassignment surgery. Patients served as their own controls. The investigators used the WPATH criteria for patient selection. Psychiatric evaluations were routine. All patients selected for treatment were routinely asked to complete the self-administered SCL-90R voluntarily on admission to the program and post-operatively. A post-operative evaluations (psychiatric and SCL-90R assessment) were conducted within six months to minimize previously determined loss rates. The patient pool was domestic and international. There were 546 gender dysphoric patients from all over the United Kingdom and abroad, of whom 318 (58.2%) progressed to surgery. Of these, 127 were from the local Leicester area in the United Kingdom and 38 (29.9%) progressed to surgery. The mean age for the selected male-to-female patients at the time of study was 47.33±13.26 years (range 25 to 80) and reflected an average wait time for surgery of 14 months (range 2 months to 6 years). For this investigation, 40 male-to-female subjects were prospectively selected.

The raw SCL-90 global scores for psycho-neuroticism were unchanged over time: 48.33 prior to surgery and 49.15 after surgery. If the scale was consistent with T-scoring, the results were non-pathologic. No psychiatric disorders were otherwise identified prior to or after surgery.

Investigators from the same clinical group (Megeri, Khoosal, 2007) conducted additional testing to specifically address anxiety and depression with the Beck Depression Inventory, General Health Questionnaire (with 4 subscales), HADS, and Spielberger State and Trait Anxiety Questionnaire (STAI-X1 and STA-X2). The test population and study design appear to be the same. No absolute data were presented. Only changes in scores were presented. There were no statistically significant changes.

e. Randomized, surgical patients, longitudinal, with controls

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. Br J Psychiatry. 1990 Aug;157:261-4.

Mate-Kole at al. conducted a prospective, non-blinded, controlled, randomized, longitudinal study using investigator-designed patient self-report questionnaires and non-specific psychological tests with some normative data. The investigators assessed neuroticism and sex role in natal males with gender dysphoria who had qualified for male-to-female reassignment surgery at a single-center specialty clinic (London, United Kingdom). Forty sequential patients were alternately assigned to early reassignment surgery or to standard wait times for reassignment surgery. Patients were evaluated after acceptance and 2 years later. The criteria used to qualify for gender surgery were the 1985 standards from the Harry Benjamin International Gender Dysphoria Association. These included a ≥2 year desire to change gender, a ≥1 year demonstrable ability to live and be self-supporting in the chosen gender, and psychiatric assessment for diagnosis and reassessment at six months for diagnostic confirmation and exclusion of psychosis.

Reassignment surgery was defined as orchidectomy, penectomy, and construction of a neo-vagina. The instruments used were the CCEI for psychoneurotic symptoms and the Bem Sex Role Inventory along with an incompletely described investigator- designed survey with questions about social life and sexual activity.

The mean age and range of the entire cohort was 32.5 years (21-53). Members of the early surgery cohort had a history of attempted suicide (one patient), psychiatric treatment for non-gender issues (six patients), and first degree relatives with psychiatric histories (four patients). Members of the standard surgery cohort were similar, with a history of attempted suicide (two patients), psychiatric treatment for non-gender issues (five patients), and first degree relatives with psychiatric histories (six patients). The early surgery group had surgery approximately 1.75 years prior to the follow-up evaluation. In both groups, cross-dressing began at about age 6.

At baseline, the Bem Sex Role Inventory femininity scores were slightly higher than masculinity scores for both cohorts and were similar to Bem North American female normative scores. The scores did not change in either group over time.

At baseline, the scores for the CCEI individual domains (free floating anxiety, phobic anxiety, somatic anxiety, depression, hysteria, and obsessionality) were similar for the cohorts. The total CCEI scores for the two cohorts were consistent with moderate symptoms (Birchnell et al. 1988). Over the two year interval, total CCEI scores increased for standard wait group and approached the relatively severe symptom category. During the same interval, scores dropped into the asymptomatic rage for the post-operative patients.

The investigator-designed survey assessed changes in social and sexual activity of the prior two years, but the authors only compared patients in a given cohort to themselves. Though the researchers did not conduct statistical studies to compare the differences between the two cohorts, they did report increased participation in some, but not all, types of social activities such as sports (solo or group), dancing, dining out, visiting pubs, and visiting others. Sexual interest also increased. By contrast, pre-operative patients did not increase their participation in these activities.

2. External Technology Assessments

a. CMS did not request an external technology assessment (TA) on this issue.

b. There were no AHRQ reviews on this topic.

c. There are no Blue Cross/Blue Shield Health Technology Assessments written on this topic within the last three years.

d.

There were two publications in the COCHRANE database, and both were tangentially related. Both noted that there are gaps in the clinical evidence base for gender reassignment surgery.
Twenty Years of Public Health Research: Inclusion of Lesbian, Gay, Bisexual, and Transgender Populations Boehmer U. Am J Public Health. 2002; 92: 1125–30.

"Findings supported that LGBT issues have been neglected by public health research and that research unrelated to sexually transmitted diseases is lacking."

A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. West Midlands Health Technology Assessment Collaboration. Health Technology Assessment Database. Meads, et al., 2009. No.3.

"Further research is needed but must use more sophisticated designs with comparison groups. This systematic review demonstrated that there are so many gaps in knowledge around LGBT health that a wide variety of studies are needed."

e. There were no National Institute for Health and Care Excellence (NICE) reviews/guidance documents on this topic.

There was a technology assessment commissioned by the New Zealand Ministry of Health and conducted by New Zealand Health Technology Assessment (NZHTA) (Christchurch School of Medicine and the University of Otago).

Tech Brief Series: Transgender Re-assignment Surgery Day P. NZHTA Report. February 2002;1(1). http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf

The research questions included the following:
1. Are there particular subgroups of people with transsexualism who have met eligibility criteria for gender reassignment surgery (GRS) where evidence of effectiveness of that surgery exists?

2. If there is evidence of effectiveness, what subgroups would benefit from GRS?"

The authors concluded that there was not enough evidence to answer either of the research questions.

3. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC) Meeting

CMS did not convene a MEDCAC meeting.

4. Evidence-Based Guidelines

a. American College of Obstetricians and Gynecologists (ACOG)

Though ACOG did not have any evidence-based guidelines on this topic, they did have the following document:
Health Care for Transgender Individuals: Committee Opinion
Committee on Health Care for Underserved Women; The American College of Obstetricians and Gynecologists.
Dec 2011, No. 512. Obstet Gyncol. 2011;118:1454-8.

"Questions [on patient visit records]

should be framed in ways that do not make assumptions about gender identity, sexual orientation, or behavior. It is more appropriate for clinicians to ask their patients which terms they prefer. Language should be inclusive, allowing the patient to decide when and what to disclose. The adoption and posting of a nondiscrimination policy can also signal health care providers and patients alike that all persons will be treated with dignity and respect. Assurance of confidentiality can allow for a more open discussion, and confidentiality must be ensured if a patient is being referred to a different health care provider. Training staff to increase their knowledge and sensitivity toward transgender patients will also help facilitate a positive experience for the patient."

b. American Psychiatric Association

Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. Arch Sex Behav. 2012; 41:759–96.

The American Psychiatric Association (APA) was unable to identify any Randomized Controlled Trials (RTCs) regarding mental health issues for transgender individuals.

"There are some level B studies examining satisfaction/regret following sex reassignment (longitudinal follow-up after an intervention, without a control group); however, many of these studies obtained data retrospectively and without a control group (APA level G). Overall, the evidence suggests that sex reassignment is associated with an improved sense of well-being in the majority of cases, and also indicates correlates of satisfaction and regret. No studies have directly compared various levels of mental health screening prior to hormonal and surgical treatments on outcome variables; however, existing studies suggest that comprehensive mental health screening may be successful in identifying those individuals most likely to experience regrets."

Relevant Descriptions of APA Evidence Coding System/Levels:

[B] Clinical trial. A prospective study in which an intervention is made and the results of that intervention are tracked longitudinally. Does not meet standards for a randomized clinical trial."

[G] Other. Opinion-like essays, case reports, and other reports not categorized above."

c. Endocrine Society

Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. J Clin Endocrinol Metab. 2009; 94:3132-54.

This guideline primarily addressed hormone management and surveillance for complications of that management. A small section addressed surgery and found the quality of evidence to be low.

"This evidence-based guideline was developed using the Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system to describe the strength of recommendations and the quality of evidence, which was low or very low."

d. World Professional Association for Transgender Health (WPATH)

Standards of Care for the Health of Transsexual, Transgender, and Gender-Nonconforming People (Version 7). Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K. www.wpath.org/_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf Int J Transgend. 2011;13:165–232.

The WPATH is "an international, multidisciplinary, professional association whose mission is to promote evidence-based care, education, research, advocacy, public policy, and respect in transsexual and transgender health."

WPATH reported, "The standards of care are intended to be flexible in order to meet the diverse health care needs of transsexual, transgender, and gender-nonconforming people. While flexible, they offer standards for promoting optimal health care and guiding the treatment of people experiencing gender dysphoria—broadly defined as discomfort or distress that is caused by a discrepancy between a person's gender identity and that person's sex assigned at birth (and the associated gender role and/or primary and secondary sex characteristics) (Fisk, 1974; Knudson, De Cuypere, & Bockting, 2010b)."

The WPATH standards of care (SOC) "acknowledge the role of making informed choices and the value of harm-reduction approaches."

The SOC noted, "For individuals seeking care for gender dysphoria, a variety of therapeutic options can be considered. The number and type of interventions applied and the order in which these take place may differ from person to person (e.g., Bockting, Knudson, & Goldberg, 2006; Bolin, 1994; Rachlin, 1999; Rachlin, Green, & Lombardi, 2008; Rachlin, Hansbury, & Pardo, 2010). Treatment options include the following:

- Changes in gender expression and role (which may involve living part time or full time in another gender role, consistent with one's gender identity);
- Hormone therapy to feminize or masculinize the body;
- Surgery to change primary and/or secondary sex characteristics (e.g., breasts/chest, external and/or internal genitalia, facial features, body contouring);
- Psychotherapy (individual, couple, family, or group) for purposes such as exploring gender identity, role, and expression; addressing the negative impact of gender dysphoria and stigma on mental health; alleviating internalized transphobia; enhancing social and peer support; improving body image; or promoting resilience."

e. American Psychological Association

Suggested citation until formally published in the American Psychologist: American Psychological Association. (2015): *Guidelines for Psychological Practice with Transgender and Gender Nonconforming People Adopted by the Council of Representatives, August 5 & 7, 2015. www.apa.org/practice/guidelines/transgender.pdf*

"The purpose of the Guidelines for Psychological Practice with Transgender and Gender Nonconforming People (hereafter Guidelines) is to assist psychologists in the provision of culturally competent, developmentally appropriate, and trans-affirmative psychological practice with TGNC people."

"These Guidelines refer to psychological practice (e.g., clinical work, consultation, education, research, training) rather than treatment."

5. Other Reviews

a. Institute of Medicine (IOM)

The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. (Study Sponsor: The National Institutes of Health). Issued March 31, 2011. http://www.nationalacademies.org/hmd/Reports/2011/The-Health-of-Lesbian-Gay-Bisexual-and- Transgender-People.aspx

"To advance understanding of the health needs of all LGBT individuals, researchers need more data about the demographics of these populations, improved methods for collecting and analyzing data, and an increased participation of sexual and gender minorities in research. Building a more solid evidence base for LGBT health concerns will not only benefit LGBT individuals, but also add to the repository of health information we have that pertains to all people."

"Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and

monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

b. National Institutes of Health (NIH)

National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf

In response to the IOM report, the NIH LBGT research Coordinating Committee noted that most of the health research for this set of populations is "focused in the areas of Behavioral and Social Sciences, HIV (human immunodeficiency virus)/AIDS, Mental Health, and Substance Abuse. Relatively little research has been done in several key health areas for LGBT populations including the impact of smoking on health, depression, suicide, cancer, aging, obesity, and alcoholism."

6. Pending Clinical Trials

ClinicalTrials.gov
There is one currently listed and recently active trial directed at assessment of the clinical outcomes pertaining to individuals who have had gender reassignment surgery. The study appears to be a continuation of work conducted by investigators cited in the internal technology assessment.

NCT01072825 (Ghent, Belgium sponsor) European Network for the Investigation of Gender Incongruence (ENIGI) is assessing the physical and psychological effects of the hormonal treatment of transgender subjects in two years prior to reassignment surgery and subsequent to surgery. This observational cohort study started in 2010 and is still in progress.

7. Consultation with Outside Experts

Consistent with the authority at 1862(l)(4) of the Act, CMS consulted with outside experts on the topic of treatment for gender dysphoria and gender reassignment surgery.

Given that the majority of the clinical research was conducted outside of the United States, and some studies either took place in or a suggested continuity-of-care and coordination-of-care were beneficial to health outcomes, we conducted expert interviews with centers across the U.S. that provided some form of specialty-focused or coordinated care for transgender patients. These interviews informed our knowledge about the current healthcare options for transgender people, the qualifications of the professionals involved, and the uniqueness of treatment options. We are very grateful to the organizations that made time to discuss treatment for gender dysphoria with us.

From our discussions with the all of the experts we spoke with, we noted the following practices in some centers: (1) specialized training for all staff about transgender healthcare and transgender cultural issues; (2) use of an intake assessment by either a social worker or health care provider that addressed physical health, mental health, and other life factors such as housing, relationship, and employment status; (3) offering primary care services for transgender people in addition to services related to gender-affirming therapy/treatments; (4) navigators who connected patients with name-change information or other legal needs related to gender; (5) counseling for individuals, groups, and families; (6) an informed-consent model whereby individuals were often referred to as "clients" instead of "patients," and (7) an awareness of depression among transgender people (often measured with tools such as the Adult Outcomes Questionnaire and the Patient Health Questionnaire).

8. Public Comments

We appreciate the thoughtful public comments we received on the proposed decision memorandum. In CMS' experience, public comments sometimes cite the published clinical evidence and give CMS useful information. Public comments that give information on unpublished evidence such as the results of individual practitioners or patients are less rigorous and therefore less useful for making a coverage determination. CMS uses the initial public comments to inform its proposed decision. CMS responds in detail to the public comments on a proposed decision when issuing the final decision memorandum. All comments that were submitted without personal health information may be viewed in their entirety by using the following link: https://www.cms.gov/medicare-coverage-database/details/nca-view-public-comments.aspx?NCAId=282&ExpandComments=n#Results

a. Initial Comment Period: December 3, 2015 – January 2, 2016

During the initial comment period, we received 103 comments. Of those, 78% supported coverage of gender reassignment surgery, 15% opposed, and 7% were neutral. The majority of comments supporting coverage were from individuals and advocacy groups.

b. Second Comment Period: June 2, 2016 – July 2, 2016

During the second 30-day public comment period, we received a total of 45 public comments, 7 of which were not posted on the web due to personal health information content. Overall, 82% supported coverage of gender reassignment surgery, 11% opposed, and 7% were neutral or silent in their comment whether they supported or opposed coverage. Half of the comments were submitted by individuals who expressed support for coverage of gender reassignment surgery (51%). We also received comments from physicians, providers, and other health professionals who specialize in healthcare for transgender individuals (17%). We received one comment from a municipality, the San Francisco Department of Public Health. Associations (American Medical Association, American College of Physicians, American Academy of Nursing, American Psychological Association, and LBGT PA Caucus) and advocates (Center for American Progress with many other signatories, Jamison Green & Associates) also submitted comments.

Below is a summary of the comments CMS received. In some instances, commenters identified typographical errors, context missed, and opportunities for CMS to clarify wording and classify articles for ease of reading in the memorandum. As noted earlier, when appropriate and to the extent possible, we updated the decision memorandum to reflect those corrections, improved the context, and clarified the language. In light of public comments, we re-evaluated the evidence and our summaries. We updated our summaries of the studies and clarified the language when appropriate.

1. Contractor Discretion and National Coverage Determination

Comment: Some commenters, including advocates, associations, and providers, supported CMS' decision for MAC contractor discretion/case-by-case determination for gender reassignment surgery. One stakeholder stated, "We agree with the conclusion that a NCD is not warranted at this time."

Response: We appreciate the support and understanding among stakeholders for our proposed decision to have the MACs determine coverage on a case-by-case basis. We have clarified in this final decision memorandum that

coverage is available for gender reassignment surgery when determined reasonable and necessary and not otherwise excluded by any other relevant statutory requirements by the MAC on a case-by-case basis. "The case-by-case model affords more flexibility to consider a particular individual's medical condition than is possible when the agency establishes a generally applicable rule." (78 Fed. Reg. 48165 (August 7, 2013)).

Comment: Some commenters cautioned that CMS' choice to not issue a NCD at this time must not be interpreted as a national non-coverage determination or used in any way to inappropriately restrict access to coverage for transgender Medicare beneficiaries or other transgender individuals. Multiple commenters indicated their disappointment that CMS did not propose a National Coverage Determination (NCD) and, instead, chose to continue to have local MACs make the coverage decisions on a case-by-case basis. Commenters stated this could result in variability in coverage.

Response: We appreciate the comments. We are not issuing a NCD at this time because the available evidence for gender reassignment surgery provides limited data on specific health outcomes and the characteristics of specific patient populations that might benefit from surgery. In the absence of a NCD, the MAC's use the same statutory authority as NCDs, section 1862(a)(1)(A) of the Social Security Act (the Act). Under section 1862(a)(1)(A) an item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member. While CMS did not have enough evidence to issue a NCD, we believe the MACs will be able to make appropriate coverage decisions on a case-by-case basis taking into account individual characteristics of the Medicare beneficiary.

Comment: Some commenters sought a NCD that would establish guidelines for coverage and include elements such as a prescribed set of surgeries and a shared decision making element.

Response: For the reasons stated above, we are not issuing a NCD at this time and, therefore, are not establishing specific gender reassignment surgery coverage guidelines for the Medicare program. We generally agree that shared decision-making is a fundamental approach to patient-centered health care decisions and strongly encourage providers to use these types of evidence based decision aids. We have not found a shared decision aid on GRS and encourage the development of this necessary element to conduct formal shared-decision making.

Comment: Some commenters expressed concern that there is a misunderstanding of transgender individuals as having a disorder or being abnormal. Some commenters indicated a history of bias and discrimination within society as a whole that has occurred when transgender individuals have sought health care services from the medical community. Some commenters are concerned that the decision not to make a NCD will subject individuals seeking these services to corporate bias by Medicare contractors.

Response: We acknowledge the public comments and that there has been a transformation in the treatment of individuals with gender dysphoria over time. In this NCA, we acknowledge that gender dysphoria is a recognized Diagnostic and Statistical Manual of Mental Disorders (DSM) condition. With respect to the concern about potential bias by Medicare contractors, we have no reason to expect that the judgments made on specific claims will be influenced by an overriding bias, hostility to patients with gender dysphoria, or discrimination. Moreover, the Medicare statue and our regulations provide a mechanism to appeal an adverse initial decision if a claim is denied and those rights may include the opportunity for judicial review. We believe the Medicare appeals process would provide an opportunity to correct any adverse decision that was perceived to have been influenced by bias.

Comment: Commenters mentioned the cost of gender reassignment surgery could influence MAC decision making.

Response: The decisions on whether to cover gender reassignment surgery in a particular case are made on the basis of the statutory language in section 1862 of the Social Security Act that establish exclusions from coverage and would not depend on the cost of the procedure.

2. Coverage with Evidence Development and Research

Comment: In our proposed decision memorandum, we specifically invited comments on whether a study could be developed that would support coverage with evidence development (CED). One organization commented, "We strongly caution against instituting a CED protocol." Commenters were opposed to coverage limited in clinical trials, suggesting that such coverage would restrict access to care. Several commenters provided suggested topics for clinical research studies for the transgender population. For example, one commenter suggested a study of non-surgical treatment for transgender children prior to puberty.

Response: While we appreciate the comments supporting further research, in general, for gender reassignment surgery, we agree that CED is not the appropriate coverage pathway at this time. While CED is an important mechanism to support research and has the potential to be used to help address gaps in the current evidence, we are not aware of any available, appropriate studies, ongoing or in development, on gender reassignment surgery for individuals with gender dysphoria that could be used to support a CED decision.

3. Gender Reassignment Surgery as Treatment

Comment: One group of commenters requested that CMS consider that, "The established medical consensus is that GRS is a safe, effective, and medically necessary treatment for many individuals with gender dysphoria, and for some individuals with severe dysphoria, it is the only effective treatment."

Response: We acknowledge that GRS may be a reasonable and necessary service for certain beneficiaries with gender dysphoria. The current scientific information is not complete for CMS to make a NCD that identifies the precise patient population for whom the service would be reasonable and necessary.

4. Physician Recommendations

Comment: Several commenters stated that gender reassignment surgery should be covered as long as it was determined to be necessary, or medically necessary by a beneficiary's physician.

Response: Physician recommendation is one of many potential factors that the local MAC may consider when determining whether the documentation is sufficient to pay a claim.

5. WPATH Standards of Care

Comment: Several commenters suggested that CMS should recommend the WPATH Standards of Care (WPATH) as the controlling guideline for gender reassignment surgery. They asserted it could satisfy Medicare's reasonable and necessary criteria for determining coverage on a case-by-case basis.

Response: Based on our review of the evidence and conversations with the experts and patient advocates, we are aware some providers consult the WPATH Standards of Care, while others have created their own criteria and requirements for surgery, which they think best suit the needs of their patients. As such, and given that WPATH acknowledges the guidelines should be flexible, we are not in the position to endorse exclusive use of WPATH for coverage. The MACs, Medicare Advantage plans, and Medicare providers can use clinical guidelines they determine useful to inform their determination of whether an item or service is reasonable and necessary. When making this determination, local MACs may take into account physician's recommendations, the individual's clinical characteristics, and available clinical evidence relevant to that individual.

6. Scope of the NCA Request

Comment: One commenter stated that CMS did not address the full scope of the NCA request.

Response: The formal request for a NCD is publicly available on our tracking sheet. (https://www.cms.gov/Medicare/Coverage/DeterminationProcess/downloads/id282.pdf) The letter did not explicitly seek a national coverage determination related to counseling or hormone therapies, but focused on surgical remedies. CMS is aware that beneficiaries with gender dysphoria use a variety of therapies.

Comment: Other commenters stated the scope of the proposed decision is unnecessarily broad because it discussed therapies other than surgery. They suggested this discussion could lead to the unintended consequence of restricting access to those services for transgender Medicare beneficiaries and other transgender individuals.

Response: As we noted in our proposed decision, our decision focused only on gender reassignment surgery. In the course of reviewing studies related to those surgeries, occasionally authors discussed other therapies that were mentioned in our summaries of the evidence. To the extent possible, we have modified our decision to eliminate the discussion of other therapies which were not fully evaluated in this NCA.

7. NCA Question

Comment: Some commenters expressed concern about the phrasing of the question in this NCA.

Response: The phrasing of the research question is consistent with most NCAs and we believe it is appropriate.

8. Evidence Summary and Analysis

Comment: Several commenters disagreed with our summary of the clinical evidence and analysis. A few commenters contended that the overall tone of the review was not neutral and seemed biased or flawed. One commenter noted that the Barrett publication was available on the Internet.

Response: We appreciate the comments that identified technical errors, and we made the necessary revisions to this document. However, we disagree with the contention that our evidence review was not neutral and seemed biased or flawed. We believe that the summary and analysis of the clinical evidence are objective. As with previous NCAs, our review of the evidence was rigorous and methodical. Additionally, we reviewed the Barrett publication, but it did not meet our inclusion criteria to be included in the Evidence section.

9. Evidence Review with Transgender Experts

Comment: Several commenters requested that CMS re-review the clinical evidence discussed in the proposed decision memorandum with outside experts in the field of transgender health and transition/gender reassignment -related surgeries. Several offered the expertise within their organization to assist in this effort.

Response: We appreciate these comments and the transgender health community’s willingness to participate. For this NCA we discussed gender reassignment surgery protocols with experts, primarily in coordinated care settings. Additionally, the public comment periods provide opportunities for expert stakeholder input. According to our process for all NCAs, we do not jointly review evidence with external stakeholders but have carefully reviewed the very detailed comments submitted by a number of outside experts in transgender health care.

10. Previous Non-Coverage NCD

Comment: One commenter noted that they thought research studies for gender reassignment surgery could not take place when the old NCD that prohibited coverage for gender reassignment surgery was in effect.

Response: CMS does not directly conduct clinical studies or pay for research grants. Some medical services are non-covered by Medicare; however, national non-coverage does not preclude research via a number of avenues and other funding entities such as the National Institutes of Health. In this instance, the previous NCD did not preclude interested parties from funding research for gender reassignment surgery that could have been generalizable to the Medicare population.

11. How the Medicare Population Differs from the General Population

Comment: One commenter questioned how the Medicare population differed from the general population, and why any differences would be important in our decision-making.

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

12. Medicare Evidence Development & Coverage Advisory Committee (MEDCAC)

Comment: One commenter suggested CMS should have convened a MEDCAC for this topic.

Response: We appreciate the comment. Given the limited evidence, we did not believe a MEDCAC was warranted according to our guidance document entitled "Factors CMS Considers in Referring Topics to the Medicare Evidence Development & Coverage Advisory Committee" (https://www.cms.gov/Regulations-and-Guidance/Guidance/FACA/MEDCAC.html).

13. §1557 of the Affordable Care Act (ACA)

Comment: Some commenters asserted that by not explicitly covering gender reassignment surgery at the national level, CMS was discriminating against transgender beneficiaries in conflict with Section 1557 of the Accountable Care Act (ACA).

Response: This decision does not affect the independent obligation of covered entities, including the Medicare program and MACs, to comply with Section 1557 in making individual coverage decisions. In accordance with Section 1557, MACs will apply neutral nondiscriminatory criteria when making case-by-case coverage determinations related to gender reassignment surgery.

14. Medicaid

Comment: Some commenters observed that some states cover gender reassignment surgery through Medicaid or require commercial insurers operating in the state to cover the surgery.

Response: We appreciate the information about Medicaid and state requirements; however, State decisions are separate from Medicare coverage determinations. We make evidence-based determinations based on our statutory standards and processes.

15. Commercial Insurers

Comment: In several instances, commenters told us that the healthcare industry looks to CMS coverage determinations to guide commercial policy coverage.

Response: CMS makes evidence-based national coverage determinations based on our statutory standards and processes as defined in the Social Security Act, which may not be the same standards that are used in commercial insurance policies or by other health care programs. In addition as noted above, the Medicare population is different (e.g., Medicare covers 95% of adults 65 and older) than the typical population under

commercial insurers. We do not issue coverage decisions to drive policy for other health organizations' coverage in one way or the other.

16. Healthcare for Transgender Individuals

Comment: Numerous professional associations wrote to CMS to explain their support for access to healthcare for transgender individuals.

Response: CMS recognizes that transgender beneficiaries have specific healthcare needs. Many health care treatments are available. We encourage all beneficiaries to utilize their Medicare benefits to help them achieve their best health.

17. Intended Use of the Decision Memorandum

Comment: Several commenters expressed concern that the analysis provided in the proposed and final decision memorandums may be used by individuals, entities, or payers for purposes unrelated to Medicare such as denial of coverage for transgender-related surgeries.

Response: The purpose of the decision memoranda is to memorialize CMS' analysis of the evidence, provide responses to the public comments received, and to make available the clinical evidence and other data used in making our decision consistent with our obligations under the § 1862 of the Act. The NCD process is open and transparent and our decisions are publicly available. Congress requires that we provide a clear statement of the basis for our determinations. The decision memoranda are an important part of the record of the NCD. Our focus is the Medicare population which, as noted above, is different than the general population in a number of ways. Other entities may conduct separate evidence reviews and analyses that are suited for their specific populations.

18. Cost Barriers to Care and Effects

Comment: A few commenters stated that without Medicare coverage, surgery is difficult to afford and there may be a risk of negative consequences for the individual. One commenter suggested that CMS should consider prior-authorization for these surgeries.

Response: CMS is aware that paying out-of-pocket for medical care is a strain on a beneficiary's finances. We are also aware of beneficiaries' hesitancy to undergo surgery prior to knowing whether or not Medicare will pay the claim. Gender reassignment surgeries are not the only procedures whereby payment is not determined until after the provider submits the claim to Medicare. Importantly, documentation for the claims need to be explicit about what procedures were performed and include the appropriate information in the documentation to justify using the code or codes for surgery. Of note, CMS has claims data that indicate Medicare has paid for gender reassignment surgeries in the recent past. Determining which services are designated for prior-authorization is outside of the scope of the NCA process.

19. Surgical Risks and Benefits

Comment: A number of commenters conveyed the benefits of gender reassignment surgery, while other commenters expressed concern that gender reassignment surgery was harmful.

Response: We appreciate these comments.

20. Expenditure of Federal Funds

Comment: Some commenters opposed spending Medicare program funds on gender reassignment surgery for a variety of reasons. For example, some commenters believe it is an "elective" procedure. Other commenters suggested that funds should first be spent on other priorities such as durable medical equipment (DME) or mobility items such as power chairs; increasing reimbursement to providers; or that spending should be limited to the proportion to the transgender adult population in the Medicare program.

Response: The purpose of this NCA is to determine whether or not CMS should issue a NCD to cover surgery for patients who have gender dysphoria. NCAs do not establish payment amounts or spending priorities and, therefore, these comments are outside the scope of this consideration.

VIII. CMS Analysis

National coverage determinations are determinations by the Secretary with respect to whether or not a particular item or service is covered nationally under § 1862(l)(6) of the Act. In general, in order to be covered by Medicare, an item or service must fall within one or more benefit categories contained within Part A or Part B and must not be otherwise excluded from coverage.

Moreover, in most circumstances, the item or service must be reasonable and necessary for the diagnosis or treatment of illness or injury or to improve the functioning of a malformed body member (§1862(a)(1)(A)). The Supreme Court has recognized that "[t]he Secretary's decision as to whether a particular medical service is 'reasonable and necessary' and the means by which she implements her decision, whether by promulgating a generally applicable rule or by allowing individual adjudication, are clearly discretionary decisions." Heckler v. Ringer, 466 U.S. 602, 617 (1984). See also, 78 Fed. Reg. 48,164, 48,165 (August 7, 2013)

When making national coverage determinations, we consider whether the evidence is relevant to the Medicare beneficiary population. In considering the generalizability of the results of the body of evidence to the Medicare population, we carefully consider the demographic characteristics and comorbidities of study participants as well as the provider training and experience. This section provides an analysis of the evidence, which included the published medical literature and guidelines pertaining to gender dysphoria, that we considered during our review to answer the question:

Is there sufficient evidence to conclude that gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria?

CMS carefully considered all the studies listed in this decision memorandum to determine whether they answered the question posed in this NCA. While there appears to be many publications regarding gender reassignment surgery, it became clear that many of the publications did not meet our inclusion/exclusion criteria as explained earlier in the decision memorandum.

Thirty-three papers were eligible based on our inclusion/exclusion criteria for the subsequent review (Figure 1). All studies reviewed had potential methodological flaws which we describe below.

A. Quality of the Studies Reviewed

Overall, the quality and strength of evidence were low due to mostly observational study designs with no comparison groups, subjective endpoints, potential confounding (a situation where the association between the intervention and outcome is influenced by another factor such as a co-intervention), small sample sizes, lack of validated assessment tools, and considerable lost to follow-up (Appendices C and F). The impact of a specific therapeutic intervention can be difficult to determine when there are multiple serial treatments such as psychotherapy, hormone treatment and surgery. To reduce confounding, outcome assessment just prior to and after surgery such as in a longitudinal study would be helpful. The objective endpoints included psychiatric treatment, attempted suicide, requests for surgical reversal, morbidity (direct and indirect adverse events), and mortality (Appendix F). CMS agrees with the utility of these objective endpoints. Quality of life, while important, is more difficult to measure objectively (Appendix E).

Of the 33 studies reviewed, published results were conflicting – some were positive; others were negative. Collectively, the evidence is inconclusive for the Medicare population. The majority of studies were non-longitudinal, exploratory type studies (i.e., in a preliminary state of investigation or hypothesis generating), or did not include concurrent controls or testing prior to and after surgery. Several reported positive results but the potential issues noted above reduced strength and confidence. After careful assessment, we identified six studies that could provide useful information (Figure 1). Of these, the four best designed and conducted studies that assessed quality of life before and after surgery using validated (albeit non-specific) psychometric studies did not demonstrate clinically significant changes or differences in psychometric test results after GRS. (Heylens et al., 2014; Ruppin, Pfafflin, 2015; Smith et al., 2005; Udeze et al., 2008) (Appendix C Panel A and Appendix G.)

Two studies (three articles) assessed functional endpoints (request for surgical reassignment reversal and morbidity/mortality) (Dhejne et al., 2011; Dhejne et al., 2014 along with Landén et al., 1998) (Figure 1 and Appendix C, Panel A and Appendix G). Although the data are observational, they are robust because the Swedish national database is comprehensive (including all patients for which the government had paid for surgical services) and is notable for uniform criteria to qualify for treatment and financial coverage by the government. Dhejne et al. (2014) and Landén et al. (1998) reported cumulative rates of requests for surgical reassignment reversal or change in legal status of 3.3% while Dhejne et al. (2014) reported 2.2%. The authors indicated that the later updated calculation had the potential to be an underestimate because the most recent surgical cohorts were larger in size and had shorter periods of follow-up.

Dhejne et al., (2011) tracked all patients who had undergone reassignment surgery (mean age 35.1 years) over a 30 year interval and compared them to 6,480 matched controls. The study identified increased mortality and psychiatric hospitalization compared to the matched controls. The mortality was primarily due to completed suicides (19.1-fold greater than in control Swedes), but death due to neoplasm and cardiovascular disease was increased 2 to 2.5 times as well. We note, mortality from this patient population did not become apparent until after 10 years. The risk for psychiatric hospitalization was 2.8 times greater than in controls even after adjustment for prior psychiatric disease (18%). The risk for attempted suicide was greater in male-to-female patients regardless of the gender of the control. Further, we cannot exclude therapeutic interventions as a cause of the observed excess morbidity and mortality. The study, however, was not constructed to assess the impact of gender reassignment surgery *per se.*

We believe at minimum study designs should have a pre-test/post-test longitudinal design accompanied by characterization of all patients lost to follow-up over the entire treatment series as well as those patients who did not complete questionnaires, and the use of psychometric quality-of-life tools which are well validated with linkage to "hard" (objective) patient outcomes in this particular patient population (Trentacosti 2007, PRO 2009) (Appendices C and D).

Patient Care

Clinical evidentiary questions regarding the care of patients with gender dysphoria remain. Many of the publications focused on aspects of surgical technique as opposed to long-term patient outcomes. The specific type(s) of gender/sex reassignment surgery (e.g., genital, non-genital) that could improve health outcomes in adults remain(s) uncertain because most studies included patients who had undertaken one or more of a spectrum of surgical procedures or did not define the specific types of surgical procedures under study. Furthermore, surgical techniques have changed significantly over the last 60 years and may not reflect current practice (Bjerrome Ahlin et al., 2014; Doornaert, 2011; Green, 1998; Pauly, 1968; Selvaggi et al., 2007; Selvaggi, Bellringer, 2011; Tugnet et al., 2007; Doornaert, 2011).

The WPATH care recommendations present a general framework and guidance on the care of the transgender individual. The standards of care are often cited by entities that perform gender reassignment surgery. WPATH notes, "More studies are needed that focus on the outcomes of current assessment and treatment approaches for gender dysphoria." Appendix D in the WPATH Standards of Care briefly describes their evidence base and acknowledges the historical problems with evidentiary standards, the preponderance of retrospective data, and the confounding impact of multiple interventions, specifically distinguishing the impact of hormone therapy from surgical intervention.

Additionally, CMS met with several stakeholders and conducted several interviews with centers that focus on healthcare for transgender individuals in the U.S. Primary care rather than gender reassignment surgery was often the main focus. Few of the U.S.-based reassignment surgeons we could identify work as part of an integrated practice, and few provide the most complex procedures.

Psychometric Tools

CMS reviewed psychometric endpoints because gender dysphoria (inclusive of prior nomenclature) describes an incongruence between the gender assigned at birth and the gender(s) with which the person identifies.

The psychometric tools used to assess outcomes have limitations. Most instruments that were specific for gender dysphoria were designed by the investigators themselves or by other investigators within the field using limited populations and lacked well documented test characterization. (Appendices E and F) By contrast, test instruments with validation in large populations were non-specific and lacked validation in the gender dysphoric patient populations. (Appendices E and F). In addition, the presentation of psychometric results must be accompanied by enough information about the test itself to permit adequate interpretation of test results. The relevant diagnostic cut-points for scores and changes in scores that are clinically significant should also be scientifically delineated for interpretation.

Generalizability

It is difficult to generalize these study results to the current Medicare population. Many of the studies are old given they were conducted more than 10 years ago. Most of these studies were conducted outside of the U.S. in very different medical systems for treatment and follow-up. Many of the programs were single-site centers without replication elsewhere. The study populations were young and without significant physical or psychiatric co -morbidity (Appendix D). As noted earlier, psychiatric co-morbidity may portend poor outcomes (Asscheman et al., 2011; Landén et al., 1998).

Knowledge Gaps

This patient population faces complex and unique challenges. The medical science in this area is evolving. This review has identified gaps in the evidentiary base as well as recommendations for good study designs. The Institute of Medicine, the National Institutes of Health, and others also identified many of the gaps in the data. (Boehmer, 2002; HHS-HP, 2011; IOM, 2011; Kreukels-ENIGI, 2012; Lancet, 2011; Murad et al., 2010; NIH-LGBT, 2013) The current or completed studies listed in ClinicalTrials.gov are not structured to assess these gaps. These gaps have been delineated as they represent areas in which patient care can be optimized and are opportunities for much needed research.

B. Health Disparities

Four studies included information on racial or ethnic background. The participants in the three U.S. based studies were predominantly Caucasian (Beatrice, 1985; Meyer, Reter, 1979; Newfield et al., 2006). All of the participants

in the single Asian study were Chinese (Tsoi, 1993). Additional research is needed in this area.

C. Summary

Based on an extensive assessment of the clinical evidence as described above, there is not enough high quality evidence to determine whether gender reassignment surgery improves health outcomes for Medicare beneficiaries with gender dysphoria and whether patients most likely to benefit from these types of surgical intervention can be identified prospectively.

The knowledge on gender reassignment surgery for individuals with gender dysphoria is evolving. Much of the available research has been conducted in highly vetted patients at select care programs integrating psychotherapy, endocrinology, and various surgical disciplines. Additional research of contemporary practice is needed. To assess long-term quality of life and other psychometric outcomes, it will be necessary to develop and validate standardized psychometric tools in patients with gender dysphoria. Further, patient preference is an important aspect of any treatment. As study designs are completed, it is important to include patient-centered outcomes.

Because CMS is mindful of the unique and complex needs of this patient population and because CMS seeks sound data to guide proper care of the Medicare subset of this patient population, CMS strongly encourages robust clinical studies with adequate patient protections that will fill the evidence gaps delineated in this decision memorandum. As the Institute of Medicine (IOM, 2011) importantly noted: "Best practices for research on the health status of LGBT populations include scientific rigor and respectful involvement of individuals who represent the target population. Scientific rigor includes incorporating and monitoring culturally competent study designs, such as the use of appropriate measures to identify participants and implementation processes adapted to the unique characteristics of the target population. Respectful involvement refers to the involvement of LGBT individuals and those who represent the larger LGBT community in the research process, from design through data collection to dissemination."

IX. Decision

Currently, the local Medicare Administrative Contractors (MACs) determine coverage of gender reassignment surgery on a case-by-case basis. We have a received a complete, formal request to make a national coverage determination on surgical remedies for gender identity disorder (GID), now known as gender dysphoria. The Centers for Medicare & Medicaid Services (CMS) is not issuing a National Coverage Determination (NCD) at this time on gender reassignment surgery for Medicare beneficiaries with gender dysphoria because the clinical evidence is inconclusive for the Medicare population.

In the absence of a NCD, coverage determinations for gender reassignment surgery, under section 1862(a)(1)(A) of the Social Security Act (the Act) and any other relevant statutory requirements, will continue to be made by the local MACs on a case-by-case basis. To clarify further, the result of this decision is not national non-coverage rather it is that no national policy will be put in place for the Medicare program. In the absence of a national policy, MACs will make the determination on whether or not to cover gender reassignment surgery based on whether gender reassignment surgery is reasonable and necessary for the individual beneficiary after considering the individual's specific circumstances. For Medicare beneficiaries enrolled in Medicare Advantage (MA) plans, the initial determination of whether or not surgery would be reasonable and necessary will be made by the MA plans.

Consistent with the request CMS received, the focus of this National Coverage Analysis (NCA) was gender reassignment surgery. Specific types of surgeries were not individually assessed. We did not analyze the clinical evidence for counseling or hormone therapy treatments for gender dysphoria. As requested by several public commenters, we have modified our final decision memorandum to remove language that was beyond the scope of the specific request. We are not making a national coverage determination relating to counseling, hormone therapy treatments, or any other potential treatment for gender dysphoria.

While we are not issuing a NCD, CMS encourages robust clinical studies that will fill the evidence gaps and help inform which patients are most likely to achieve improved health outcomes with gender reassignment surgery, which types of surgery are most appropriate, and what types of physician criteria and care setting(s) are needed to ensure that patients achieve improved health outcomes.

A. Appendix A

Diagnostic & Statistical Manual of Mental Disorders (DSM) Criteria for Disorders of Gender Identity since 1980

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III 1980 *Chapter: Psychosexual Disorders*	***Trans-sexualism*** *302.5x [Gender Identity Disorder of Child-hood (302.6)]*	Required A (cross-gender identification) and B (aversion to one's natal gender) criteria Dx excluded by physical intersex condition Dx excluded by another mental disorder, e.g., schizophrenia	Sense of discomfort and inappropriateness about one's anatomic sex. Wish to be rid of one's own genitals and to live as a member of the other sex. The disturbance has been continuous (not limited to periods of stress) for at least 2 years.	Further characterization by sexual orientation Distinguished from Atypical Gender Identity Disorder 302.85

DSM Version	Condition Name	Criteria	Criteria	Comments
DSM III-Revised 1987 *TS classified as an Axis II dx (personality disorders and mental retardation) in a different chapter. GID included under Disorders Usually First Evident in Infancy, Childhood, Adolescence*	***Trans-sexualism*** *(TS) (302.50) [GID of C]*	Required A and B criteria	Persistent discomfort and sense of inappropriateness about one's assigned sex. Persistent preoccupation for at least 2 years with getting rid of one's 1º and 2º sex characteristics and acquiring the sex characteristics of the other sex. Has reached puberty	Further characterization by sexual orientation Distinguished from Gender Identity Disorder of Adolescence or Adulthood, Non-trans-sexual Type •e.g., cross-dressing not for the purposes of sexual excitement Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions Gender Identity Disorder Not Otherwise Specified 302.85 •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
	GID of adulthood, non-trans-sexual type, added			
DSM IV 1994 *Chapter: Sexual & Gender Identity Disorders*	***Gender Identity Disorder*** in Adolescents and Adults (302.85) (Separate criteria & code for children, but same name)	Required A and B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., Stated desire to be another sex •e.g., Desire to live or be treated as a member of the other sex •e.g., conviction that he/she has the typical feelings and reactions of the other sex •e.g., frequent passing as the other sex Persistent discomfort with his/her sex or sense of inappropriateness in the gender role of that sex. •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1º and 2º sex characteristics &/or acquiring sexual traits of the other sex •Clinically significant distress or impairment in social, occupational, or other important areas of functioning	Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6 •e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM IV-Revised 2000 *Chapter: Sexual & Gender Identity Disorders*	***Gender Identity Disorder*** (Term trans-sexual-ism eliminated)	Required A & B criteria Dx excluded by physical intersex condition	Cross-gender identification •e.g., stated desire to be the other sex •e.g., desire to live or be treated as the other sex •e.g., conviction that he/she has the typical feelings & reactions of the other sex	Outcome may depend on time of onset Further characterization by sexual orientation Distinguished from Gender Identity Disorder Not Otherwise Specified 302.6

DSM Version	Condition Name	Criteria	Criteria	Comments
			•e.g., frequent passing as the other sex Persistent discomfort with his or her sex OR sense of inappropriateness in the gender role of that sex •e.g., belief the he/she was born the wrong sex •e.g., preoccupation with getting rid of 1º and 2º sex characteristics &/or acquiring sexual traits of the other sex Clinically significant distress or impairment in social, occupational, or other important areas of functioning	•e.g., intersex conditions •e.g., stress related cross-dressing •e.g., persistent preoccupation with castration or penectomy w/o desire to acquire the sex traits of the other sex
DSM V 2013 *Separate Chapter from Sexual Dysfunctions & Paraphilic Disorders*	***Gender Dysphoria*** *(302.85)*	Gender nonconformity itself not considered to be a mental disorder The dysphoria associated with the gender incongruence is Eliminates A & B criteria Considers gender incongruence to be a spectrum Considers intersex/ "disorders of sex development" to be a subsidiary and not exclusionary to dx of GD	•Marked discordance between natal 1º and 2º sex characteristics* and experienced/expressed gender •Conviction that he/she has the typical feelings & reactions of the other sex (or some alternative gender) •Marked desire to be the other sex (or some alternative gender) •Marked desire to desire be treated as the other sex (or some alternative gender) •Marked desire to be rid of natal 1º and 2º sex characteristics** •Marked desire to acquire 1º and 2º sex characteristics of the other sex (or some alternative gender) Clinically significant distress or impairment in social, occupational, or other important areas of functioning * or in young adolescents, the anticipated 2º sex characteristics ** or in young adolescents, prevent the development of the anticipated 2º sex characteristics ≥ 6 month marked discordance between natal gender & experienced/expressed gender as demonstrated by ≥ 6 criteria: •Strong desire to be of the other gender or an insistence that one is of another gender.	Includes diagnosis for post transition state to permit continued treatment access Includes disorders of sexual development such as congenital hyperplasia and androgen insensitivity syndromes

DSM Version	Condition Name	Criteria	Criteria	Comments
			•Strong preference for cross-gender roles in make-believe play. •Strong preference for the toys, games, or activities of the other gender. •Strong preference for playmates of the other gender. •In boys, strong preference for cross-dressing; in girls, strong preference for wearing masculine clothing •In boys, rejection of masculine toys, games, activities, avoidance of rough and tumble play; in girls, rejection of feminine toys, games, and activities.	
	Unspecified Gender Dysphoria (302.6) (F64.9)		This category applies to presentations in which sx c/w gender dysphoria that cause clinically significant distress or impairment, but do not meet the full criteria for gender dysphoria & the reason for not meeting the criteria is not provided.	
	Specified Gender Dysphoria 302.6 (F64.8)		If the reason that the presentation does not meet the full criteria is provided then this dx should be used	

C/W=consistent with Dx=diagnosis GD=gender dysphoria Sx=symptoms TS=transsexual 1º=primary 2º=secondary

B. Appendix B

1. General Methodological Principles of Study Design

When making national coverage determinations, CMS evaluates relevant clinical evidence to determine whether or not the evidence is of sufficient quality to support a finding that an item or service is reasonable and necessary. The overall objective for the critical appraisal of the evidence is to determine to what degree we are confident that: 1) the specific assessment questions can be answered conclusively; and 2) the intervention will improve health outcomes for patients.

We divide the assessment of clinical evidence into three stages: 1) the quality of the individual studies; 2) the

generalizability of findings from individual studies to the Medicare population, and 3) overarching conclusions that can be drawn from the body of the evidence on the direction and magnitude of the intervention's potential risks and benefits.

The methodological principles described below represent a broad discussion of the issues we consider when reviewing clinical evidence. However, it should be noted that each coverage determination has its unique methodological aspects.

Assessing Individual Studies

Methodologists have developed criteria to determine weaknesses and strengths of clinical research. Strength of evidence generally refers to: 1) the scientific validity underlying study findings regarding causal relationships between health care interventions and health outcomes; and 2) the reduction of bias. In general, some of the methodological attributes associated with stronger evidence include those listed below:

- Use of randomization (allocation of patients to either intervention or control group) in order to minimize bias.
- Use of contemporaneous control groups (rather than historical controls) in order to ensure comparability between the intervention and control groups.
- Prospective (rather than retrospective) studies to ensure a more thorough and systematical assessment of factors related to outcomes.
- Larger sample sizes in studies to demonstrate both statistically significant as well as clinically significant outcomes that can be extrapolated to the Medicare population. Sample size should be large enough to make chance an unlikely explanation for what was found.
- Masking (blinding) to ensure patients and investigators do not know to which group patients were assigned (intervention or control). This is important especially in subjective outcomes, such as pain or quality of life, where enthusiasm and psychological factors may lead to an improved perceived outcome by either the patient or assessor.

Regardless of whether the design of a study is a randomized controlled trial, a non-randomized controlled trial, a cohort study or a case-control study, the primary criterion for methodological strength or quality is the extent to which differences between intervention and control groups can be attributed to the intervention studied. This is known as internal validity. Various types of bias can undermine internal validity. These include:

- Different characteristics between patients participating and those theoretically eligible for study but not participating (selection bias).
- Co-interventions or provision of care apart from the intervention under evaluation (performance bias).
- Differential assessment of outcome (detection bias).
- Occurrence and reporting of patients who do not complete the study (attrition bias).

In principle, rankings of research design have been based on the ability of each study design category to minimize these biases. A randomized controlled trial minimizes systematic bias (in theory) by selecting a sample of participants from a particular population and allocating them randomly to the intervention and control groups. Thus, in general, randomized controlled studies have been typically assigned the greatest strength, followed by non-randomized clinical trials and controlled observational studies. The design, conduct and analysis of trials are important factors as well. For example, a well-designed and conducted observational study with a large sample size may provide stronger evidence than a poorly designed and conducted randomized controlled trial with a small sample size. The following is a representative list of study designs (some of which have alternative names) ranked from most to least methodologically rigorous in their potential ability to minimize systematic bias:

Randomized controlled trials
Non-randomized controlled trials
Prospective cohort studies
Retrospective case control studies
Cross-sectional studies
Surveillance studies (e.g., using registries or surveys)
Consecutive case series
Single case reports

When there are merely associations but not causal relationships between a study's variables and outcomes, it is important not to draw causal inferences. Confounding refers to independent variables that systematically vary with the causal variable. This distorts measurement of the outcome of interest because its effect size is mixed with the effects of other extraneous factors. For observational, and in some cases randomized controlled trials, the method in which confounding factors are handled (either through stratification or appropriate statistical modeling) are of particular concern. For example, in order to interpret and generalize conclusions to our population of Medicare patients, it may be necessary for studies to match or stratify their intervention and control groups by patient age or co-morbidities.

Methodological strength is, therefore, a multidimensional concept that relates to the design, implementation and analysis of a clinical study. In addition, thorough documentation of the conduct of the research, particularly study selection criteria, rate of attrition and process for data collection, is essential for CMS to adequately assess and consider the evidence.

Generalizability of Clinical Evidence to the Medicare Population

The applicability of the results of a study to other populations, settings, treatment regimens and outcomes assessed is known as external validity. Even well-designed and well-conducted trials may not supply the evidence needed if the results of a study are not applicable to the Medicare population. Evidence that provides accurate information about a population or setting not well represented in the Medicare program would be considered but would suffer from limited generalizability.

The extent to which the results of a trial are applicable to other circumstances is often a matter of judgment that depends on specific study characteristics, primarily the patient population studied (age, sex, severity of disease and presence of co-morbidities) and the care setting (primary to tertiary level of care, as well as the experience and specialization of the care provider). Additional relevant variables are treatment regimens (dosage, timing and route of administration), co-interventions or concomitant therapies, and type of outcome and length of follow-up.

The level of care and the experience of the providers in the study are other crucial elements in assessing a study's external validity. Trial participants in an academic medical center may receive more or different attention than is typically available in non-tertiary settings. For example, an investigator's lengthy and detailed explanations of the potential benefits of the intervention and/or the use of new equipment provided to the academic center by the study sponsor may raise doubts about the applicability of study findings to community practice.

Given the evidence available in the research literature, some degree of generalization about an intervention's potential benefits and harms is invariably required in making coverage determinations for the Medicare population. Conditions that assist us in making reasonable generalizations are biologic plausibility, similarities between the populations studied and Medicare patients (age, sex, ethnicity and clinical presentation) and similarities of the intervention studied to those that would be routinely available in community practice.

A study's selected outcomes are an important consideration in generalizing available clinical evidence to Medicare coverage determinations. One of the goals of our determination process is to assess health outcomes. These outcomes include resultant risks and benefits such as increased or decreased morbidity and mortality. In order to make this determination, it is often necessary to evaluate whether the strength of the evidence is adequate to draw conclusions about the direction and magnitude of each individual outcome relevant to the intervention under study. In addition, it is important that an intervention's benefits are clinically significant and durable, rather than marginal or short-lived. Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits.

If key health outcomes have not been studied or the direction of clinical effect is inconclusive, we may also evaluate the strength and adequacy of indirect evidence linking intermediate or surrogate outcomes to our outcomes of interest.

Assessing the Relative Magnitude of Risks and Benefits

Generally, an intervention is not reasonable and necessary if its risks outweigh its benefits. Health outcomes are one of several considerations in determining whether an item or service is reasonable and necessary. CMS places greater emphasis on health outcomes actually experienced by patients, such as quality of life, functional status, duration of disability, morbidity and mortality, and less emphasis on outcomes that patients do not directly experience, such as intermediate outcomes, surrogate outcomes, and laboratory or radiographic responses. The direction, magnitude, and consistency of the risks and benefits across studies are also important considerations. Based on the analysis of the strength of the evidence, CMS assesses the relative magnitude of an intervention or technology's benefits and risk of harm to Medicare beneficiaries.

Appendix C

Patient Population: Enrolled & Treated with Sex Reassignment Surgery Loss of Patients & Missing Data

Panel A (Controlled Studies)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Dhejne 2011	Longitudinal Controlled	804 w GD	324	324 (100%)	-
Dhejne 2014 Landén	Longitudinal for test variable Controlled	767 applied for SRS 25 applications denied. 61 not granted full legal status 15 formal applications for surgical reversal	681	681 (100%)	NA: Clinical data extracted retrospectively in earlier paper
Heylens	Longitudinal Controlled	90 applicants for SRS 33 excluded 11 later excluded had not yet received SRS by study close.	57 (46)	46 (80.7%) Only those w SRS evaluated	Psycho-social survey missing data for 3 at baseline & 4 after SRS. SCL90 not completed by 1 at baseline, 10 after hormone tx, & 4 after SRS missing data for another 1.1% to 11.1%.
Kockott	Longitudinal Controlled	80 applicants for SRS 21 excluded	59	32 (54.2%) went to surgery	1 preoperative patient was later excluded b/c lived completely in aspired gender w/o SRS. Questions on financial sufficiency not answered by 1 surgical pt.

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
					Questions on sexual satisfaction & gender contentment not answered by 1 & 2 patients awaiting surgery respectively.
Mate-Kole 1990	Longitudinal Controlled	40 sequential patients of accepted patients. The number in the available patient pool was not specified.	40	20 (50%) went to surgery	-
Meyer	Longitudinal Controlled	Recruitment pool: 100 50 were excluded.	50	15 (30%) had undergone surgery 14 (28%) underwent surgery later	The assessments of all were complete
Rakic	Longitudinal Controlled	92 were evaluated 54 were excluded from surgery 2 post SRS were lost to follow-up 2 post SRS were excluded for being in the peri-operative period	32	32 (100%)	Questionnaire completed by all.
Ruppin	Longitudinal Controlled	The number in the available patient pool was not specified. 140 received recruitment letters. 69 were excluded	71	69 (97.2%)	The SCL-90, BSRI, FPI-R, & IPP tests were not completed by 9, 34, 13, &16 respectively. Questions about romantic relationships, sexual relationships, friendships, & family relationships were not answered by 1, 3, 2, & 23 respectively. Questions regarding gender security & regret & were not answered by 1& 2 respectively.
Smith	Longitudinal Controlled	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. 103 were excluded from additional tx	162	162 (100%)	36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete various post-SRS tests.
Udeze Megeri	Longitudinal Controlled	International patient w GD 546 & post SRS 318. 40 M to F subjects were prospectively selected.	40	40 (100%)	-
Ainsworth	Internet/convention Survey Cross-sectional Controlled	Number of incomplete questionnaires not reported	247	72 (29.1%) 75 (30.6%) facial 147 (59.5%) had received neither facial nor reassignment surgery	-
Beatrice	Cross-sectional		40	10 (25%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	Controlled	14 excluded for demographic matching reasons			The assessments were completed by all
Haraldsen	Cross-sectional Controlled	Recruitment pool: 99	86	59 (68.6%)	-
Kraemer	Cross-sectional Controlled	The number in the available patient pool was not specified.	45	22 (48.9%)	-
Kuhn	Cross-sectional Controlled	The number in the available patient pool was not specified.	75	55 (73.3%)	-
Mate-Kole 1988	Cross-sectional Controlled	150 in 3 cohorts. Matched on select traits. The number in the available patient pool was not specified.	150	50 (66.7%)	-
Wolfradt	Cross-sectional Controlled	The number in the available patient pool was not specified.	90	30 (33.3%)	-

Panel B (Surgical Series: No Concurrent Controls)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Blanchard et al.	Cross-sectional Control: Normative test data	294 clinic patients w GD had completed study questionnaire 116 authorized for GRS. 103 completed GRS & 1 yr post-operative. 24 excluded	79	79(100%)	-
Weyers et al.	Cross-sectional Control: Normative test data	>300 M to F patients had undergone GRS 70 eligible patients recruited 20 excluded	50	50 (100%)	SF-26 not completed by 1
Wierckx et al.	Cross-sectional except for recall questions Control: Normative test data	79 F to M patients had undergone GRS & were recruited. 3 additional non-clinic patients were recruited by other patients. 32 excluded initially; 1 later.	49	49 (100%)	SF-36 test not completed by 2. Questions regarding sexual re -lationship, sex function, & surgical satisfaction were answered by as few as 27, 28, 32 respectively.
Eldh et al.	Cross-sectional except for 1 variable Control: Self for 1 variable-employ-ment	136 were identified. 46 excluded	90	90 (100%)	Questions regarding gender iden-tity, sex life, acceptance, & overall satisfaction were not answered by 13, 14, 14 & 16 respectively. Employment data missing for 11.
Hess et al.	Cross-sectional		119	119 (100%)	

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No control	254 consecutive eligible patients post GRS identified & sent surveys. 135 excluded.			Questions regarding the esthetics, functional, and social outcomes of GRS were not answered by 16 to 28 patients.
Lawrence	Cross-sectional No control	727 eligible patients were recruited. 495 were excluded	232	232 (100%)	-
Salvador et al.	Cross-sectional No control	243 had enrolled in the clinic 82 completed GRS 69 eligible patients were identified. 17 excluded.	52	52 (100%)	-
Tsoi	Cross-sectional No control	The number in the available patient pool was not specified.	81	81 (100%)	-

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
Gómez-Gil et al. 2012	Cross-sectional No direct control: Analysis of variance	200 consecutive patients were recruited. 13 declined participation or were excluded for incomplete questionnaires.	187	79 (42.2%)	See prior box.
Hepp et al.	Cross-sectional No direct control: Analysis of variance	The number in the available patient pool was not specified.	31	7 (22.6%)	HADS test not completed by 1
Motmans et al.	Cross-sectional No direct control: Analysis of variance & regression	255 with GD were identified. 77 were excluded.	148 (140)	Not clearly stated. At least 103 underwent some form of GRS.	8 later excluded for incomplete SF-36 tests. 37 w recent GRS or hormone initiation were excluded from analysis of SF-36 results103.
Newfield et al.	Internet survey Cross-sectional No direct control: Analysis of variance	Number of incomplete questionnaires not reported 446 respondents; 384 U.S respondents 62 non-U.S. respondents excluded from SF-36 test results 8 U.S. respondents excluded	376 (U.S.)	139 to 150 (37.0-39.9%) in U.S.	-
Gomez-Gil et al. 2014	Cross-sectional No direct control: Analysis w regression	The number in the available patient pool was not specified. 277 were recruited. 25 excluded	252(193)	80 (41.4%) non-genital surgery	59 were excluded for incomplete questionnaires. See prior box.
Asscherman	Longitudinal		1331	1177 (88.4%)	-

Author	Study Type	Recruitment Pool	Enrolled	% GRS	Completion
	No analysis by tx status	The number in the available patient pool was not specified.			
Johansson et al.	Cross-sectional except for 1 variable No analysis by tx status except for 1 question	60 eligible patients 18 excluded.	42	32 (76.2% of enrolled & 53.3% of eligible) (genital surgery)	-
Leinung et al.	Cross-sectional No analysis by tx status	242 total clinic patients	242	91 (37.6%)	Employment status data missing for 81 of all patients

*Data obtained via a survey on a website and distributed at a conference
B/C=because
BSRI=Bem Sex Role Inventory
F=Female
FP-R=Freiberg Personality Inventory
GD=Gender dysphoria
GID=Gender identity disorder
HADS=Hospital Anxiety & Depression Scale
IPP=Inventory of Interpersonal Problems
M=Male
NA=Not applicable
SCL-90=Symptom Checklist-90
SF-36=Short Form 36
GRS=Sex reassignment surgery
Tx=Treatment
W/o=without

Appendix D

Demographic Features of Study Populations

Panel A (Controlled Studies)

Author	Age (years; mean, S.D., range)	Gender	Race
Ainsworth	Only reassignment surgery:50 (no S.D.) Only facial surgery: 51 (no S.D.) Both types of surgery: 49 (no S.D.) Neither surgery: 46 (no S.D.)	247 M to F	-
Beatrice	Pre-SRS M to F: 32.5 (27-42), Post-SRS: 35.1 (30-43)	20 M to F plus 20 M controls	100% Caucasian

Author	Age (years; mean, S.D., range)	Gender	Race
Dehjne 2011	Post-SRS: all 35.1±9.7 (20-69), F to M 33.3+8.7 (20–62), M to F 36.3+ 10.1(21–69)	133 (41.0%) F to M, 191 (59.0%) M to F; ratio 1:1.4	-
Dhejne 2014 Landén	F to M SRS cohort: median age 27 M to F SRS cohort: median age 32 F to M applicants for reversal: median age 22 M to F applicants for reversal: median age 35	767 applicants for legal/surgical reassignment 289 (37.7%) F to M, 478 (62.3%) M to F; ratio 1:1.6 681 post SRS & legal change 252 (37.0%) F to M, 429 (63.0%) M to F; ratio 1:1.7 15 applicants for reversal 5 (33.3%) F to M, 10 (66.7%) M to F; ratio 1:2	-
Haraldsen	Pre-SRS & Post-SRS: F to M 34±9.5, F to M 33.3±10.0 Post-SRS cohort reportedly older. No direct data provided.	Pre & Post SRS 35 (40.7%) F to M, 51 (59.3%) M to F; ratio 1:1.5	-
Heylens	-	11 (19.3% of 57) F to M, 46 (80.7%); ratio 1:4.2 (80.7% underwent surgery)	-
Kockott	Pre-SRS (continued wish for surgery): 31.7±10.2 Post-SRS: 35.5±13.1	Pre-SRS (continued wish for surgery) 3 (25%) F to M, 9 (75%) M to F; ratio 1:3 Post SRS: 14 (43.8%) F to M, 18 (56.2%) M to F; ratio 1:1.3	-
Kraemer	Pre-SRS: 33.0±11.3, Post-SRS: 38.2±9.0	Pre-SRS 7 F to M (30.4%), 16 M to F (69.6%); ratio 1:2.3 Post-SRS 8 F to M (36.4%), 14 M to F (63.6%); ratio 1:1.8	-
Kuhn	All post SRS: median (range): 51 (39-62) (long-term follow-up)	3 (5.4%) F to M, 52 (94.5%) M to F; ratio 1:17.3.	-
Mate-Kole 1988	Initial evaluation: 34, Pre-SRS: 35, Post-SRS: 37	150 M to F	-
Mate-Kole 1990	Early & Usual wait SRS: 32.5 years (21-53)	40 M to F	-
Meyer	Pre-SRS: 26.7 Delayed, but completed SRS: 30.9 Post-SRS: 30.1	Pre-SRS: 5 (23.8%) F to M, 16 (76.2%) M to F; ratio 1:3.2 Delayed, but completed SRS: 1 (7.1%) F to M, 13 (92.9%) M to F; ratio 1:13 Post-SRS: 4 (26.7%) F to M, 11 (73.3%) M to F; ratio 1:2.8	86% Caucasian
Rakic	All: 26.8±6.9 (median 25.5, range 19-47), F to M: 27.8±5.2 (median 27, range 23-37), M to F: 26.4±7.8 (median 24, range 19-47).	10 (31.2%) F to M, 22 (68.8%) M to F; ratio 1:2.2	-
Ruppin	All: 47.0±10.42 (but 2 w/o SRS) (13.8±2.8 yrs post legal name change) (long-term follow-up) F to M: 41.2±5.78, M to F 52.9±10.82	36 (50.7%) F to M, 35 (49.3%) M to F; ratio 1:0.97	-
Smith	Time of surgical request for post-SRS: 30.9 (range 17.7-68.1) Time of follow-up for post-SRS: 35.2 (range 21.3-71.9)	Pre-SRS: 162: 58 (35.8%) F to M, 104 [64.2%] M to F; ratio 1:1.8 Post-SRS: 126: 49 (38.9%) F to M, 77 (61.1%) M to F; ratio 1:1.6	-
Udeze Megeri	M to F: 47.33±13.26 (range 25-80).	40 M to F	-
Wolfradt	Patients & controls: 43 (range 29-67).	30 M to F plus 30 F controls plus 30 M controls.	-

*Data obtained via a survey on a website and distributed at a conference SD=Standard deviation

Panel B (Surgical Series: No Concurrent Controls)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Blanchard et al.	F to M: 32.6, M to F w M partner preference: 33.2, F to M w F partner preference: 47.7 years	Post-GRS: 47 (45.6%) F to M, 56 (54.4%) M to F; ratio 1:1.19. In study: 38 (48.1%) F to M, 32 (40.5%) M to F w M partner preference, 9 (11.4%) M to F w F partner preference; ratio 1:0.8: 0.2	-
Weyers et al.	Post-GRS M to F: 43.1 ±10.4 (long-term follow-up)	50 M to F	-
Wierckx et al.	Time of GRS: 30±8.2 years (range 16 to 49) Time of follow-up: 37.1 ±8.2.4 years (range 22 to 54)	49 M to F	-
Eldh et al.	-	50 (55.6%) F to M, 40 (44.4%) M to F; ratio 1:0.8 There is 1 inconsistency in the text suggesting that these should be reversed.	-
Hess et al.	-	119 M to F	-
Lawrence	Time of GRS: 44±9 (range 18-70)	232 M to F	-
Salvador et al.	Time of follow-up for post-GRS: 36.28±8.94 (range 18-58) (Duration of follow-up: 3.8±1.7 [2-7])	52 M to F	-
Tsoi	Time of initial visit: All: 24.0±4.5, F to M: 25.4±4.4 (14-36), M to F: 22.9±4.6 (14-36). Time of GRS: All: 25.9±4.14, F to M: 27.4±4.0 (20-36), M to F: 24.7+4.3 (20-36).	36 (44.4%) F to M, 45 (55.6%) M to F; ratio 1:1.25	0% 100% Asian

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	Age (years; mean, S.D., range)	Gender	Caucasian
Gómez-Gil et al. 2012	W & W/O GRS: All: 29.87±9.15 (range 15-61), W/O hormone tx: 25.9±7.5, W current hormone tx: 33.6±9.1. (At hormone initiation: 24.6±8.1).	W/O hormone tx: 38 (56.7%) F to M, 29 (43.3%) M to F; ratio 1:0.8. W hormone tx: 36 (30.0%) F to M, 84 (70.0%) M to F; ratio 1:2.3. Post-GRS: 29 (36.7%) F to M, 50 (63.3%) M to F; ratio 1:1.7.	-
Hepp et al.	W & W/O GRS: 32.2±10.3	W & W/O GRS: 11 (35.5%) F to M; 20 (64.5%) M to F; ratio 1:1.8.	-
Motmans et al.	W & W/O GRS: All (n=140) : 39.9±10.2, F to M: 37.0±8.5, M to F: 42.3±10.4	W & W/O GRS: N=140 63(45.0%) F to M, 77 (55.0%) M to F; ratio 1:1.2 N=103 49 (47.6%) F to M; 54 (52.4%) M toF; ratio 1:1.1	-
Newfield et al.	W & W/O GRS: U.S.+ non-U.S. : 32.8±11.2, U.S. 32.6±10.8	W & W/O GRS: U.S.+ non-U.S.: F to M, 438, U.S.: F to M: 376	89% of 336 respondents Caucasian
Gomez-Gil, et al. 2014	W & W/O Non-genital GRS: 31.2±9.9 (range 16-67).		-

Author	Age (years, mean, S.D., range)	Gender	Caucasian
		W & W/O Non-genital GRS: 74 (38.3%) F to M, 119 (61.7%) M to F; ratio1:1.6.	
Asscherman	Time of hormone tx: F to M: 26.1±7.6 (16–56), M to F: 31.4±11.4 (16–76)	Met hormone tx requirements: 365 (27.4%) F to M, 966 (72.6%) M to F; ratio 1:2.6. Post-GRS: 343 (29.1%) F to M, 834 (70.9%) M to F; ratio 1:2.4.	-
Johanssen	Time of initial evaluation: F toM: 27.8 (18-46), M to F 37.3 (21-60). Time of GRS: F to M: 31.4 (22-49), M to F 38.2 (22-57). Time of follow-up for post-GRS: F to M: 38.9 (28-53), M to F 46.0 (25-69) (Long-term follow-up)	Approved for GRS: 21 (35%) F to M, 39 (65%) M to F; ratio 1:1.9) Post GRS: 14 (43.8%) F to M; 18 (56.2%) M to F; ratio 1:1.3)	-
Leinung et al.	Time of hormone initiation : F to M: 27.5, M to F 35.5	W & W/O GRS: 50 (20.7%) F to M, 192 M to F (79.3%); ratio 1:3.8. Post-GRS: 32 F to M (35.2%); 59 (64.8%) M to F; ratio 1:1.8.	-

Appendix E

Psychometric and Satisfaction Survey Instruments

Instrument Name and Developer	Development and Validation Information
APGAR Family Adaptability, Partner-ship Growth, Affection, and Resolve *Smilkstein*	Published in 1978 Initial data: 152 families in the U.S. A "friends" component was added in 1983. Utility has challenged by many including Gardner 2001
Beck Depression Inventory *Beck, Ward, Mendelson, Mock, & Erbaugh*	Published initially in 1961 with subsequent revisions It was initially evaluated in psychiatric patients in the U.S.A. Salkind (1969) evaluated its use in 80 general outpatients in the UK. Itis copyrighted and requires a fee for use
Bem Sex Role Inventory *Bem*	Published 1974 Initial data: 100 Stanford Undergraduates 1973 update: male 444; female 279 1978 update: 470; female 340
Body Image Questionnaire *Clement & Lowe*	Validity study published 1996 (German) Population: 405 psychosomatic patients, 141 medical students, 208 sports students
Body Image Scale *Lindgren & Pauly* *(Kuiper, Dutch adaptation 1991)*	1975 Initial data: 16 male and 16 female transsexual patients in Oregon
Crown Crisp Experiential Index (formerly Middlesex Hospital Questionnaire)	Developed circa 1966 Manual published 1970

Instrument Name and Developer	Development and Validation Information
Crown & Crisp	Initial data: 52 nursing students while in class in the UK
(2nd) European Quality of Life Survey *Anderson, Mikuliç, Vermeylen, Lyly-Yrjanainen, & Zigante,*	Published in 2007 The pilot survey was tested in the UK and Holland with 200 interviews. The survey was revised especially for non-response questions. Another version was tested in 25 persons of each of the 31 countries to be surveyed. Sampling methods were devised. 35,634 Europeans were ultimately surveyed. Additional updates
Female Sexual Function Index *Rosen, Brown, Heiman, Leiblum, Meston, Shabsigh, Ferguson, D'Agostino* *Wiegel, Meston, & Rosen*	Published in 2000 Initial data: 131 normal controls & 128 age-matched subjects with female sexual arousal disorder from 5 U.S. research centers. Updated 2005: the addition of those with hypoactive sexual desire disorder, female sexual orgasm disorder, dyspareunia/vaginismus, & multiple sexual dysfunctions (n=568), plus more controls (n=261).
Fragebogen zur Beurteilung des eigenen Korpers *Strauss*	Published 1996 (German)
Freiberg Personality Inventory *Fahrenberg, Hampel, & Selg*	7th edition published 2001, 8th edition in 2009 (Not in PubMed) German equivalent of MMPI
"gender identity disorder in childhood" *Smith, van Goozen, Kuiper, & Cohen-Kettenis*	11 items derived from the Biographical Questionnaire for Trans-sexuals (Verschoor Poortinga 1988) (Modified by authors of the Smith study)
Gender Identity Trait Scale *Altstotter-Gleich*	Published 1989 (German)
General Health Questionnaire *Goldberg & Blackwell (initial study)* *Goldberg & Williams (manual)*	Initial publication 1970 Manual published ?1978, 1988 (Not in PubMed) Initial data: 553 consecutive adult patients in a single UK primary care practice were assessed. Sample of 200 underwent standardized psychiatric interview. Developed to screen for hidden psychological morbidity. Proprietary test. Now 4 versions.
Hospital Anxiety & Depression Scale *Zigmond & Snaith*	Published in 1983 Initial data: Patients between 16 & 65 in outpatient clinics in the UK >100 patients; 2 refusals. 1st 50 compared to 2nd 50.
Inventory of Interpersonal Problems *Horowitz*	Published 1988 Initial data: 103 patients about to undergo psychotherapy; some patients post psycho-therapy (Kaiser Permanente-San Francisco) Proprietary test
King's Health Questionnaire *Kelleher, Cardozo, Khullar, & Salvatore*	1997 Initial data: 293 consecutive women referred for urinary incontinence evaluation in London Comparison to SF-36
Minnesota Multi-phasic Personality Inventory *Hathaway & McKinley*	Published in 1941 Updated in 1989 with new, larger, more diverse sample.

Instrument Name and Developer	Development and Validation Information
Butcher, Dahlstrom, Graham, & Tellegen	MMPI-2: 1,138 men & 462 women from diverse communities & several geographic regions in the U.S.A. The test is copyrighted.
Modified Androphia-Gynephilia Index	Neither the underlying version or the Blanchard modified version could be located in PubMed (Designed by the author of the Blanchard et al. study)
"post-operative functioning 13 items" *Doorn, Kuiper, Verschoor, Cohen-Kettenis*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
"post-operative functioning 21 items" *Doorn, Kuiper, Verschoor, Cohen-Kettenis*	Published 1996 (Dutch) (Not in PubMed) (Designed by 1 of the authors of the Smith study)
Scale for Depersonalization Experiences *Wolfradt*	Unpublished manuscript 1998 (University of Halle) (Designed by 1 of the authors of the Wolfradt study)
"sex trait function" *Cohen-Kettenis & van Goozen*	Published 1997 Assessed in 22 adolescents (Designed by 1 of the authors of the Smith Study)
Self-Esteem Scale *Rosenberg*	Published 1965 (Not in PubMed) Initial data: 5,024 high-school juniors & seniors from 10 randomly selected New York schools
Short-Form 36 *RAND* *Ware & Sherbourne1992* *McHorney, Ware, & Raczek 1993*	Originally derived from the Rand Medical Outcomes Study (n=2471 in version 1; 6742 in version 2 1989). The earliest test version is free. Alternative scoring has been developed. There is a commercial version with a manual.
Social Anxiety & Distress Scale *Watson & Friend*	Initial publication in1969 Requires permission for use
Social Support Scale *Van Tilburg 1988*	Published 1988 (Dutch) (Not in PubMed)
Spielberger State & Trait Anxiety Questionnaire *Spielberger, Gorsuch, Lushene, Vagg, & Jacobs*	Current format published in 1983 Proprietary test
Symptom Checklist-90 *Derogatis, Lipman, Covi* *Derogatis & Cleary*	Published in 1973 & 1977 Reportedly with normative data for psychiatric patients (in- & out-patient) & normal subjects in the U.S. Has undergone a revision Requires qualification for use
Tennessee Self-Concept Scale *Fitts & Warren*	In use prior to 1988 publication. Initial data: 131 psychiatric day care patients. Updated manual published 1996. Update population >3000 with age stratification. No other innformation available. Requires qualification for use
Utrecht Gender Dysphoria Scale *Cohen-Kettenis & van Goozen*	Published in 1997 Initial population: 22 transgender adolescents who underwent reassignment surgery. (Designed by 1 of the authors of the Smith study)

Instrument Name and Developer	Development and Validation Information
WHO-Quality of Life (abbreviated version) *Harper for WHO group*	Field trial version released 1996 Tested in multiple countries. The Seattle site consisted of 192 of the 8294 subjects tested). Population not otherwise described. The minimal clinically important difference has not been determined. Permission required

Althof et al., 1983; Greenberg, Frank, 1965; Gurtman, 1996; Lang, Vernon, 1977; Paap et al., 2012; Salkind et al., 1969; Vacchiano, Strauss, 1968.

Appendix F

Endpoint Data Types and Sources

Panel A (Controlled Studies)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substan-tive &/or Accessible Normative Data	Investigator-designed	Other	Other
Dhejne 2011	Yes	-	-	-	-	Mortality (Suicide, Cardiovascular Disease [possible adverse events from Hormone Tx], Cancer), Psych hx & hospitalization, Suicide attempts
Dhejne Landén	Yes	-	-	-	Includes demographics*	Education, Employment, Formal application for reversal of status, Psych dx & tx, Substance abuse** More elements in earlier paper
Beatrice	-	MMPI form R, TSCS	-	-	Demographic	Education, Income, Relationships
Haraldsen	-	SCL-90/90R	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Substan-tive &/or Accessible Normative Data	Investigator-designed	Other	Other
						DSM Axis 1, II, V (GAF), Substance abuse
Heylens	-	SCL-90	-	Yes-2	Demographic	Employment, Relationships, Substance abuse, Suicide attempts
Ainsworth	-	Likely SF-36v2*	-	Yes-1	Demographic	-
Ruppin	-	SCL-90R	BSRI, FPI-R, IIP	Yes-2	Demographic	Adverse events from surgery, Employment, Psych tx, Relationships, Substance abuse
Smith	-	MMPI-short, SCL-90?R	BIS, UGDS, ? Cohen-Kettenis', Doorn's x2, (Gid-c, SSS)	Yes-1 or 2	Demographic	Adverse events from surgery, Employment, Relationships
Udeze Megeri	-	SCL-90R	BDI, GHQ, HADS,STAI-X1, STAI-X2	-	-	Psych eval & ICD-10 dx
Kuhn	-	-	KHQ	Yes-1	Demographic	Relationships
Mate-Kole 1990	-	-	BSRI, CCEI	Yes-1	Demographic	Employment (relative change), Psych hx, Suicide hx
Wolfradt	-	-	BIQ, GITS, SDE, SES	Yes-1	-	-
Kraemer	-	-	FBeK	-	Demographic	-
Mate-Kole 1988	-	-	BSRI, CCEI	-	Demographic	Employment, Psych hx, Suicide hx,
Kockott	-	-	-	Yes-1	Demographic	Employment, Income, Relationships, Suicide attempts
Meyer	-	-	-	Yes-1	Demographic	Education, Employment, Income, Psych tx, Phallus removal request
Rakic	-	-	-	Yes-1	Demographic	Employment, Relationships

Panel B (Surgical Series: No Concurrent Controls)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Sub-stantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Weyers	-	SF-36	FSFI	Yes-2	Demographic	Hormone levels, Adverse events from surgery, Relationships
Blanchard	-	SCL-90R	(AG)	Yes-1	Demographic	Education, Employment, Income, Relationships, Suicide (Incidental finding)
Wierckx	-	SF-36	-	Yes-3	Demographic	Hormone levels, Adverse events from surgery, Relationships
Eldh	-	-	-	Yes-1	-	Adverse events from surgery, Employment, Relationships, Suicide attempts
Hess	-	-	-	Yes-1	-	-
Lawrence	-	-	-	Yes-4	Demographic	Adverse events from surgery
Salvador	-	-	-	Yes-1	Demographic	Relationships
Tsoi	-	-	-	Yes-1	Demographic	Education, Employment, Relationships (relative change)

Panel C (Mixed Treatment Series: No Direct Control Groups)

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Sub-stantive &/or Accessible Normative Data	Investigator-designed	Other	Other
Asscheman et al.	Yes	-	-	-	Demographic	

Author	National Data	Instrument w Substantive Normative Data	Instrument w/o Sub-stantive &/or Accessible Normative Data	Investigator-designed	Other	Other
						Mortality (HIV, Possible adverse events from Hormone Tx, Substance abuse, Suicide)
Motmans et al.	-	SF36 EQOLS (2nd)	-	-	Demographic	Education, Employment, Income, Relationships
Newfield et al.	-	SF-36v2	-	-	Demographic	Income
Gómez-Gil et al. 2014	-	WHOQOL-BREF	APGAR	Yes-1	Demographic	Education, Employment, Relationships
Gómez-Gil et al. 2012	-	-	HADS, SADS	-	Demographic	Education, Employment, Living arrangements
Hepp et al.	-	-	HADS	-	Demographic	DSM Axis 1& II Psych dx
Johansson et al.	-	-	-	Yes-1	Demographic	Axis V change (Pt & Clinician) Employment (relative change) Relationship (relative change)
Leinung et al.	-	-	-	-	Demographic	Employment, Disability, DVT, HIV status, Psych dx

*Listed as San Francisco-36 in manuscript
** From medical charts & verdicts ?=Possibly self-designed
AG=Androphilia-Gynephilia Index (investigator designed 1985) (used more for classification)
APGAR=Family Adaptability, Partnership growth, Affection, and Resolve
BDI=Beck Depression Inventory
BIQ=Body Image Questionnaire
BIS=Body Image Scale
BSRI=Bem Sex Role Inventory
CCEI=Crown Crisp Experiential Index
Cohen-Kettenis'= Sex trait function (An author helped design)
Dorn's x2= Post-operative functioning 13 items (An author helped design)
Post-operative functioning 21 items (An author helped design)
EQOLS (2nd)=2nd European Quality of Life Survey
FBeK=Fragebogen zur Beurteilung des eigenen Korpers
FPI-R=A version of the Freiberg Personality Inventory
FSFI+Female Sexual Function Index
GHQ=General Health Questionnaire
Gid-c=Gender identity disorder in childhood (used more for predictors) (An author helped design)
GITS=Gender Identity Trait Scale
HADS=Hospital Anxiety Depression Scale

IIP=Inventory of Interpersonal Problems
KHQ=King's Health Questionnaire
MMPI=Minnesota Multi-phasic Personality Inventory
SADS=Social Anxiety & Distress Scale
SCL-90 (±R)=A version of the Symptom Checklist 90
SDE=Scale for Depersonalized Experiences (An author designed)
SES=Self-Esteem Scale
SF-36 (v2)=Short Form-36(version2)
SSS=Social Support Scale (used more for predictors)
STAI-X1, STAI-X2=Spielberger State and Trait Anxiety Questionnaire
TSCS=Tennessee Self-Concept Scale
UGDS=Utrecht Gender Dysphoria Scale (An author helped design)
WHOQOL-BREF=World Health Organization-Quality of Life (abbreviated version)

Appendix G.

Longitudinal Studies Which Used Patients as Their Own Controls and Which Used Psychometric Tests with Extensive Normative Data or Longitudinal Studies Which Used National Data Sets

Author		Test	Patient and Data Loss	Results
	Psychometric Test			
Heylens et al. Belgium 2014		SCL-90R	90 applicants for SRS were recruited. •8 (8.9%) declined participation. •12 (13.3%) excluded b/c GID-NOS dx. •12 (13.3%) did not complete the treatment sequence b/c of psychiatric/physical co-morbidity, personal decision for no tx, or personal decision for only hormone tx. •1 (1.1%) committed suicide during follow-up. 57 (63.3% of recruited) entered the study. •1 (12.2% of initial recruits) had not yet received SRS by study close. **46 (51.1% of recruited) underwent serial evaluation** •The test was not completed by 1 at t=0, 10 at t=1 (after hormone tx), & 4 at t=2 (after SRS) **missing data for another 1.1% to 11.1%.**	At t=0, the mean global "psychoneuroticism" SCL-90R score, along with scores of 7 of 8 subscales, were statistically more pathologic than the general population. After hormone tx, the mean score for global "psychoneuroticism" normalized & remained normal after reassignment surgery.
Ruppin,Pfafflin, Germany 2015		SCL-90R	The number in the available patient pool was not specified.	

Author		Test	Patient and Data Loss	Results
			140 received recruitment letters. •2 (1.4% of those with recruitment letters) had died. •1 (0.7%) was institutionalized. •5 (3.6%) were ill. •8 (5.7%) did not have time. •8 (5.7%) stated that GD was no longer an issue. •8 (5.7%) provided no reason. •28 (20.0%) declined further contact. •9 (6.4%) were lost to follow-up. **71 (50.7%) agreed to participate.** **•2 (1.4%) had not undergone SRS** •The test was not completed by 9. **missing data for another 6.4%.**	At t=0, the "global severity index "SCL-90R score was 0.53±0.49. At post-SRS follow-up the score had decreased to 0.28±0.36. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 0-4. In the same way, all of the subscale scores were statistically different, but the effect size was reported as large only for "interpersonal sensitivity": 0.70±0.67 at t=0 and 0.26±0.34 post-SRS.
Smith et al. Holland 2005		MMPI SCL-90	The number in the available adult patient pool was not specified. 325 adult & adolescent applicants for SRS were recruited. •103 (31.7%) were not eligible to start hormone tx & real-life experience. •34 (10.7%) discontinued hormone tx 162 (an unknown percentage of the initial recruitment) provided pre-SRS test data. **•36 to 61 (22.2%-37.6% of those adults w pre-SRS data) did not complete post-SRS testing.**	Most of the MMPI scales were already in the normal range at the time of initial testing. At t=0, the global "psychoneuroticism" SCL-90 score, which included the drop-outs, was 143.0±40.7. At post SRS-follow-up, the score had decreased to 120.3±31.4. The scores were statistically different from one another, but are of limited biologic significance given the range of the score for this scale: 90 to 450, with higher scores consistent with more psychological instability.
Udeze, et al. 2008 Megeri, Khoosal 2007 UK		SCL-90R	The number in the available patient pool was not specified. 40 subjects were prospectively selected. •Post-operative testing was conducted within 6 months to minimize previously determined loss rates.	At t=0, the mean raw global score was 48.33. At post-SRS follow-up, the mean score was 49.15.

Author	Test	Patient and Data Loss	Results
			There were no statistically significant changes in the global score or for any of the subscales.
	National Databases		
Dehjne Sweden 2011	Swedish National Records	804 with GID in Sweden 1973 to 2003 were identified. •480 (59.7%) did not apply or were not approved for SRS 324 (40.3%) underwent SRS. •All were followed. 3240 controls of the natal sex and 3240 controls of the reassigned gender were randomly selected from national records	All cause mortality was higher (n=27[8%]) than in controls (H.R 2.8 [1.8-4.3]) even after adjustment for covariants. Divergence in survival curves was observed after 10 years. The major contributor was completed suicide (n=10 [3%]; adjusted H.R. 19.1 [5.8-62.9]). Suicide attempts were more common (n= 29 [9%]) than in controls (adjusted H.R. 4.9 [2.9–8.5]). Hospitalizations for psychiatric conditions (not related to gender dysphoria) were more common n= 64 [20%] than in controls (H.R. 2.8 [2.0–3.9]) even after adjusting for prior psychiatric morbidity.
Dhejne et al. 2014 Landén et al. 1998 Sweden	Swedish National Registry	767 applied for SRS/legal status (1960-2010) •25 (3.3%) applications denied. •61 (8.0%) not granted full legal status 681 (88.7%) underwent SRS. •All were followed.	15 formal applications for reversal to natal/original gender (2.2% of the SRS population) were identified thus far (preliminary number). (Does not reflect other manifestations of regret such as suicide.)

GID-NOS=Gender Identity Disorder-Not Otherwise Specified HR=Hazard Ratio SRS=Sex reassignment surgery Tx=Treatment Back to Top

Bibliography

ACA 2010: Patient Protection and Affordable Care Act, Pub. L. No. 111 -148, §3502, 124 Stat. 119, 124 (2010).

Ahmed SF, Morrison S, Hughes IA. Intersex and gender assignment; the third way? *Arch Dis Child*. 2004 Sep;89(9):847-50. PMID:> 15321864.

Ainsworth T, Spiegel J. Quality of life of individuals with and without facial feminization surgery or gender reassignment surgery. *Qual Life Res.* 2010 Sep;19(7):1019-24. Epub 2010 May 12. PMID: 20461468.

Altstotter-Gleich, C. (1989). *Theoriegeleitete Itemkonstruktion und -auswahl: Eine Modifikation des Einsatzes der Repertory-Grid-Technik dargestellt am Beispiel der Erfassung der Geschlechtsidentitat* [Theory oriented item construction and selection: A modification of the use of the Repertory-Grid- Technique as shown at the exemple of the assessment of gender identity], Verlag fur empirische Padagogik, Landau. German. (Not in PubMed)

Althof SE, Lothstein LM, Jones P, Shen J. An MMPI subscale (Gd): to identify males with gender identity conflicts. *J Pers Assess.* 1983 Feb;47(1):42-9. PMID: 6834232.

American College of Obstetricians and Gynecologists (ACOG). Committee on Health Care for Underserved Women. Committee Opinion No. 512: Health care for transgender individuals. *Obstet Gynecol.* 2011 Dec;118(6):1454-8.

American Medical Association House of Delegates resolution 122 (A-08) proposal *Removing Financial Barriers to Care for Transgender Patients*. 2008.

American Psychological Association (APA). Guidelines for Psychological Practice with Transgender and Gender Nonconforming People. *American Psychologist*: 2015: Adopted by the Council of Representatives, August 5& 7, 2015. www.apa.org/practice/guidelines/transgender.pdf (publication pending).

Antoszewski B, Bratoś R, Sitek A, Fijałkowska M. Long-term results of breast reduction in female-to- male transsexuals. *Pol Przegl Chir.* 2012 Mar;84(3):144-51. PMID: 22659357.

Arcelus J, Bouman WP, Van Den Noortgate W, Claes L, Witcomb G, Fernandez-Aranda F. Systematic review and meta-analysis of prevalence studies in transsexualism. *Eur Psychiatry*. 2015 Sep;30(6):807-15. Epub 2015 May 26. PMID: 26021270.

Asscheman H, Gooren LJ, Eklund PL. Mortality and morbidity in transsexual patients with cross-gender hormone treatment. *Metabolism*. 1989 Sep;38(9):869-73. PMID: 2528051.

Asscheman H, Giltay EJ, Megens JA, de Ronde WP, van Trotsenburg MA, Gooren LJ. A long-term follow-up study of mortality in transsexuals receiving treatment with cross-sex hormones. *Eur J Endocrinol*. 2011 Apr;164(4):635-42. Epub 2011 Jan 25. PMID: 21266549.

Asscheman H, T'Sjoen G, Lemaire A, Mas M, Meriggiola M, Mueller A, Kuhn A, Dhejne C, Morel- Journel N, Gooren L. Venous thrombo-embolism as a complication of cross-sex hormone treatment of male-to-female transsexual subjects: a review. *Andrologia.* 2014 Sep;46(7):791-5. Epub 2013 Aug 15. PMID: 23944849.

Atkins D, Best D, Briss PA, Eccles M, Falck-Ytter Y, Flottorp S, Guyatt GH, Harbour RT, Haugh MC, Henry D, Hill S, Jaeschke R, Leng G, Liberati A, Magrini N, Mason J, Middleton P, Mrukowicz J, O'Connell D, Oxman AD, Phillips B, Schünemann HJ, Edejer T, Varonen H, Vist GE, Williams JW Jr, Zaza S; GRADE Working Group. Grading quality of evidence and strength of recommendations. *BMJ.* 2004 June;328(19):1490–4. PMID: 15205295.

Auer M, Fuss J, Stalla G, Athanasoulia A. Twenty years of endocrinologic treatment in transsexualism: analyzing the role of chromosomal analysis and hormonal profiling in the diagnostic work-up. *Fertil Steril* 2013 Oct;100(4):1103-10. Epub 2013 Jun 27.

Auerbach JD. The iPrEx results: lifting hopes, raising questions. *BETA.* 2010 Summer-Fall;22 (4):47-9. PMID: 21591604.

Baba T, Endo T, Ikeda K, Shimizu A, Honnma H, Ikeda H, Masumori N, Ohmura T, Kiya T, Fujimoto T, Koizumi M, Saito T. Distinctive features of female-to-male transsexualism and prevalence of gender identity disorder in Japan. *J Sex Med.* 2011 Jun;8(6):1686-93. Epub 2011 Apr 7. PMID: 21477021.

Balshem H, Helfand M, Schünemann HJ, Oxman AD, Kunz R, Brozek J, Vist GE, Falck-Ytter Y, Meerpohl J, Norris S, Guyatt GH. GRADE guidelines: 3. Rating the quality of evidence. *J Clin Epidemiol.* 2011 Apr;64(4):401-6. Epub 2011 Jan 5. PMID: 21208779.

Bandini E, Fisher AD, Ricca V, Ristori J, Meriggiola MC, Jannini EA, Manieri C, Corona G, Monami M, Fanni E, Galleni A, Forti G, Mannucci E, Maggi M. Childhood maltreatment in subjects with male-to-female gender identity disorder. *Int J Impot Res.* 2011 Nov-Dec;23(6):276-85. Epub 2011 Aug 11. PMID: 21833007.

Bao AM, Swaab DF. Sexual differentiation of the human brain: relation to gender identity, sexual orientation and neuropsychiatric disorders. *Front Neuroendocrinol*. 2011 Apr;32(2):214-26. Epub 2011 Feb 18. PMID: 21334362.

Baral S, Poteat T, Strömdahl S, Wirtz A, Guadamuz T, Beyrer C. Worldwide burden of HIV in transgender women: a systematic review and meta-analysis. *Lancet Infect Dis.* 2013 Mar;13(3):214- 22. Epub 2012 Dec 21. PMID: 23260128.

Barlow DH, Abel GG, Blanchard EB. Gender identity change in transsexuals. Follow-up and replications. *Arch Gen Psychiatry.* 1979 Aug;36(9):1001-7. PMID: 464738.

Barrett J. (1998) *Psychological and social function before and after phalloplasty.* University of London. Institute of Psychiatry. Thesis (MSc). King's College London. Catalogue #000457428 or *IJT*. 1998; 2:1 or http://gendertrust.org.uk/wp-content/uploads/2013/02/13-Psychological-and-Social-Function-Before-and-After-Phal..pdf.

Barrington C, Wejnert C, Guardado ME, Nieto AI, Bailey GP. Social network characteristics and HIV vulnerability among transgender persons in San Salvador: identifying opportunities for HIV prevention strategies. *AIDS Behav*. 2012 Jan;16(1):214-24. PMID: 464738.

Bartlett NH, Vasey PL. A retrospective study of childhood gender-atypical behavior in Samoan fa'afafine. *Arch Sex Behav.* 2006 Dec;35(6):659-66. Epub 2006 Aug 15. PMID: 16909317.

Bartolucci C, Gómez-Gil E, Salamero M, Esteva I, Guillamón A, Zubiaurre L, Molero F, Montejo A. Sexual quality of life in gender-dysphoric adults before genital sex reassignment surgery. *J Sex Med* .2015 Jan;12(1):180-8. Epub 2014 Nov 17. PMID: 25401972.

Baumeister S, Sohn M, Domke C, Exner K. [Phalloplasty in female-to-male transsexuals: experience from 259 cases]. *Handchir Mikrochir Plast Chir.* 2011 Aug;43(4):215-21. Epub 2011 Aug 11. PMID: 21837614.

Beatrice J. A psychological comparison of heterosexuals, transvestites, preoperative transsexuals, and postoperative transsexuals. *J Nerv Ment Dis.* 1985 Jun;173(6):358-65. PMID: 3998721.

Beck A, Ward C, Mendelson M, Mock J, Erbaugh J. An inventory for measuring depression. *Arch Gen Psychiatry* .1961 Jun;4:561-71. PMID: 13688369.

Bentz EK, Hefler LA, Kaufmann U, Huber JC, Kolbus A, Tempfer CB. A polymorphism of the CYP17 gene related to sex steroid metabolism is associated with female-to-male but not male-to- female transsexualism. *Fertil Steril*. 2008 Jul;90(1):56-9. Epub 2007 Sep 4. PMID: 17765230.

Bentz EK, Pils D, Bilban M, Kaufmann U, Hefler LA, Reinthaller A, Singer CF, Huber JC, Horvat R, Tempfer CB. Gene expression signatures of breast tissue before and after cross-sex hormone therapy in female-to-male transsexuals. *Fertil Steril.* 2010 Dec;94(7):2688-96. Epub 2010 May 26. PMID: 20537635.

Bem, S. L. (1974). The measurement of psychological androgyny. *Journal of Consulting and Clinical Psychology.* 1974; 42:155-162. (Not in PubMed)

Berry MG, Curtis R, Davies D. Female-to-male transgender chest reconstruction: a large consecutive, single-surgeon experience. *J Plast Reconstr Aesthet Surg.* 2012 Jun;65(6):711-9. Epub 2011 Dec 19. PMID: 22189204.

Besnier, N. (1994). Polynesian gender liminality through time and space. In G.Herdt (Ed.), *Third> sex, third gender: Beyond sexual dimorphism in culture and history*. New York: Zone Books.

Birtchnell J, Evans C, Kennard J. The total score of the Crown-Crisp Experiential Index: a useful and valid measure of psychoneurotic pathology. *Br J Med Psychol*. 1988 Sep;61 (Pt 3):255-66. PMID: 3179248.

Bith-Melander P, Sheoran B, Sheth L, Bermudez C, Drone J, Wood W, Schroeder K. Understanding sociocultural and psychological factors affecting transgender people of color in San Francisco. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):207-20. PMID: 20416495.

Bjerrome Ahlin H, Kölby L, Elander A, Selvaggi G. Improved results after implementation of the Ghent algorithm for subcutaneous mastectomy in female-to-male transsexuals. *J Plast Surg Hand Surg*. 2014 Dec;48(6):362-7. Epub 2014 Mar 11. PMID: 24611803.

A-Blanchard R, Steiner BW, Clemmensen LH. Gender dysphoria, gender reorientation, and the clinical management of transsexualism. *J Consult Clin Psychol*. 1985 Jun;53(3):295-304. PMID: 4008715.

B-Blanchard R. Typology of male-to-female transsexualism. *Arch Sex Behav.* 1985 Jun;14(3):247-61. PMID: 4004548.

C-Blanchard RJ, Blanchard DC, Flannelly KJ. Social desirability response set and systematic distortion in the self-report of adult male gender patients. *Behav Processes.* 1985 Aug;11(2):209-13. doi: 10.1016/0376-6357(85)90062-2. PMID: 24895927.

D-Blanchard, R. (1985). *Research methods for the typological study of gender disorders in males*. In B. W. Steiner (Ed.), Gender dysphoria: Development, research, management (pp. 227-257). New York: Plenum Press.

Blanchard R, Clemmensen LH, Steiner BW. Heterosexual and homosexual gender dysphoria. *Arch Sex Behav.* 1987 Apr;16(2):139-52. PMID: 3592961.

Blanchard R, Steiner BW, Clemmensen LH, Dickey R. Prediction of regrets in postoperative transsexuals. *Can J Psychiatry.* 1989 Feb;34(1):43-5. PMID: 2924248.

Bockting W, Coleman E, De Cuypere G. Care of transsexual persons. *N Engl J Med.* 2011 Jun 30;364 (26):2559-60; author reply 2560. PMID: 21714669.

Bodlund O, Armelius K. Self-image and personality traits in gender identity disorders: an empirical study. *J Sex Marital Ther.* 1994 Winter;20(4):303-17. PMID: 7897678.

Bodlund O, Kullgren G. Transsexualism general outcome and prognostic factors: a five-year follow- up study of nineteen transsexuals in the process of changing sex. *Arch Sex Behav.* 1996 Jun;25 (3):303-16. PMID: 8726553.

Boehmer AL, Brinkmann AO, Sandkuijl LA, Halley DJ, Niermeijer MF, Andersson S, de Jong FH, Kayserili H, de Vroede MA, Otten BJ, Rouwé CW, Mendonça BB, Rodrigues C, Bode HH, de Ruiter PE, Delemarre-van de Waal HA, Drop SL. 17Beta-hydroxysteroid dehydrogenase-3 deficiency: diagnosis, phenotypic variability, population genetics, and worldwide distribution of ancient and de novo mutations. *J Clin Endocrinol Metab.* 1999 Dec;84(12):4713-21. PMID: 10599740.

Boehmer U. Twenty years of public health research: inclusion of lesbian, gay, bisexual, and transgender populations. *Am J Public Health*. 2002 Jul;92(7):1125-30. PMID: 12084696.

Bonifacio HJ, Rosenthal SM. Gender Variance and Dysphoria in Children and Adolescents. *Pediatr Clin North Am*. 2015 Aug;62(4):1001-16. Epub 2015 Jun 11. PMID: 26210629.

Borsboom D, Mellenbergh GJ, van Heerden J. The theoretical status of latent variables. *Psychol Rev.* 2003 Apr;110(2):203-19. PMID: 12747522.

Bouman M, van Zeijl M, Buncamper M, Meijerink W, van Bodegraven A, Mullender M. Intestinal vaginoplasty revisited: a review of surgical techniques, complications, and sexual function. *J Sex Med*. 2014 Jul;11(7):1835-47. Epub 2014 Apr 4. PMID: 24697986.

Bowman E, Oprea G, Okoli J, Gundry K, Rizzo M, Gabram-Mendola S, Manne U, Smith G, Pambuccian S, Bumpers HL. Pseudoangiomatous stromal hyperplasia (PASH) of the breast: a series of 24 patients. *Breast J.* 2012 May-Jun;18(3):242-7. PMID: 22583194.

Broderick JP. Devices and clinical trials: overview and equipoise. *Stroke*. 2013 Jun;44(6 Suppl 1):S3-6. PMID: 23709721.

Brown L (Ed.). (1997) *Two Spirit People: American Indian, lesbian women and gay men*. Routledge.

Bye L, Gruskin E, Greenwood, G, Albright V, Krotki K. California Lesbians, Gays, Bisexuals, and Transgender (LGBT) Tobacco Use Survey – 2004. *Sacramento, CA: California Department of Health Services*, 2005. (Not in PubMed)

Byne, W, Bradley SJ, Coleman E, Eyler AE, Green R, Menvielle EJ, Meyer-Bahlburg HFL, Richard R. Pleak RR, Tompkins DA. American Psychiatric Association. Report of the American Psychiatric Association Task Force on Treatment of Gender Identity Disorder. *Arch Sex Behav* 2012 Aug;41(4):759-96. PMID: 22854940.

Callens N, De Cuypere G, Van Hoecke E, T'sjoen G, Monstrey S, Cools M, Hoebeke P. Sexual quality of life after hormonal and surgical treatment, including phalloplasty, in men with micropenis: a review. *J Sex Med*. 2013 Dec;10(12):2890-903. Epub 2013 Aug 23. PMID: 23981815.

Callens N, Hoebeke P. Phalloplasty: A panacea for 46, XY disorder of sex development conditions with penile deficiency? *Endocr Dev.* 2014;27:222-33. Epub 2014 Sep 9. PMID: 25247659.

Cameron D. Language, gender, and sexuality: Current issues and new directions. *Applied Linguistics.* 2005; 26(4):482-502. (Not in PubMed)

Casella R, Bubendorf L, Schaefer D, Bachmann A, Gasser T, Sulser T. Does the prostate really need androgens to grow? Transurethral resection of the prostate in a male-to-female transsexual 25 years after sex-changing operation. *Urol Int*. 2005;75(3):288-90. PMID: 16215322.

Cantor JM. New MRI studies support the Blanchard typology of male-to-female transsexualism. *Arch Sex Behav.* 2011 Oct;40(5):863-4. PMID: 21739338.

Cebula H, Pham TQ, Boyer P, Froelich S. Regression of meningiomas after discontinuation of cyproterone acetate in a transsexual patient. *Acta Neurochir (Wien).* 2010 Nov;152(11):1955-6. Epub 2010 Sep 3. PMID: 20811919.

Cerwenka S, Nieder T, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Kreukels B, Richter-Appelt H. Sexual behavior of gender-dysphoric individuals before gender-confirming interventions: a European multicenter study. *J Sex Marital Ther* 2014;40(5):457-71. PMID: 24846436.

Chan AW, Altman DG. Epidemiology and reporting of randomised trials published in PubMed journals. *Lancet*. 2005 Mar 26-Apr 1;365(9465):1159-62. PMID: 15794971.

Chen S, McFarland W, Thompson HM, Raymond HF. Transmen in San Francisco: what do we know from HIV test site data? *AIDS Behav.* 2011 Apr;15(3):659-62. PMID: 21153048.

Chinas, B. (1995). Isthmus Zapotec attitudes toward sex and gender anomalies. In S. O. Murray (Ed.), *Latin American male homosexualities* (pp. 293-302). Albuquerque,NM: University of New> Mexico Press.

Chiong W. The real problem with equipoise. *Am J Bioeth.* 2006 Jul-Aug;6(4):37-47. PMID: 16885104.

CHIS 2009: California Health Interview Survey, 2009. "AskCHIS" via the UCLA Center for Health Policy Research date website ask.chis.ucla.edu/.

Chong JM. Social assessment of transsexuals who apply for sex reassignment therapy. *Soc Work Health Care*. 1990;14(3):87-105. PMID: 2367927.

Claes L, Bouman W, Witcomb G, Thurston M, Fernandez-Aranda F, Arcelus J. Non-suicidal self- injury in trans people: associations with psychological symptoms, victimization, interpersonal functioning, and perceived social support. *J Sex Med.* 2015 Jan;12(1):168-79. Epub 2014 Oct 6. PMID: 25283073.

Clement U, Löwe B. [Validation of the FKB-20 as scale for the detection of body image distortions in psychosomatic patients]. *Psychother Psychosom Med Psychol.* 1996 Jul;46(7):254-9. German. PMID: 8765897.

Clements-Nolle K, Marx R, Katz M. Attempted suicide among transgender persons: The influence of gender-based discrimination and victimization. *J Homosex.* 2006;51(3):53-69. PMID: 17135115.

CMS Office of Minority Health. New Directions in CMS Disparities Research: Sexual Orientation & Gender Identity. 2015. Academy Health Annual Research Meeting, Minneapolis, Minnesota.

CMS Office of Minority Health. If You Build It, They Will Come: Accessing and Utilizing HHS LGBTI Data and Information Products. 2015. Gay and Lesbian Medical Association Meeting, Portland, Oregon.

Cohen-Kettenis PT, van Goozen SH. Sex reassignment of adolescent transsexuals: a follow-up study. *J Am Acad Child Adolesc Psychiatry.* 1997 Feb;36(2):263-71. PMID: 9031580.

A Cohen-Kettenis P. Psychological long-term outcome in intersex conditions. *Horm Res.* 2005;64 Suppl 2:27-30. PMID: 16286767.

B Cohen-Kettenis PT.Gender change in 46 XY persons with 5alpha-reductase-2 deficiency and 17beta-hydroxysteroid dehydrogenase-3 deficiency. *Arch Sex Behav*. 2005 Aug;34(4):399-410. PMID: 16010463.

Cohen-Kettenis P, Pfäfflin F. The DSM diagnostic criteria for gender identity disorder in adolescents and adults. *Arch Sex Behav.* 2010 Apr;39(2):499-513. PMID: 19838784.

Colizzi M, Costa R, Pace V, Todarello O. Hormonal treatment reduces psychobiological distress

in gender identity disorder, independently of the attachment style. *J Sex Med*. 2013 Dec;10(12):3049-58. Epub 2013 Apr 9. PMID: 23574768.

Colizzi M, Costa R, Todarello O. Transsexual patients' psychiatric comorbidity and positive effect of cross-sex hormonal treatment on mental health: results from a longitudinal study. *Psychoneuroendocrinology.* 2014 Jan;39:65-73. Epub 2013 Oct 10. PMID: 24275005.

Colizzi M, Costa R, Scaramuzzi F, Palumbo C, Tyropani M, Pace V, Quagliarella L, Brescia F, Natilla LC, Loverro G, Todarello O. Concomitant psychiatric problems and hormonal treatment induced metabolic syndrome in gender dysphoria individuals: a 2 year follow-up study. *J Psychosom Res*. 2015 Apr;78(4):399-406. Epub 2015 Feb 10. PMID: 25691225.

Coleman E, Colgan P, Gooren L. Male cross-gender behavior in Myanmar (Burma): A description of the acault. *Arch Sex Behav*. 1992 Jun;21(3):313-21. PMID: 1535191.

Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Lev AI, Mayer G, Meyer-Bahlburg H, Hall BP, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Kevan R. Wylie KR, Zucker K. World Professional Association for Transgender Health (formerly the Harry Benjamin International Gender Dysphoria Association). Standards of Care for the Health of Transsexual, Transgender, and Gender- Nonconforming People (Version 7). *Int J Transgend.* 2011;13:165–232. © 2012 World Professional Association for Transgender Health (WPATH). (not in Pubmed) www.wpath.org/uploaded_files/140/files/Standards%20of%20Care,%20V7%20Full%20Book.pdf.

Conron KJ, Scott G, Stowell GS, Landers SJ. Transgender health in Massachusetts: results from

a household probability sample of adults. *Am J Public Health.* 2012 Jan;102(1):118-22. Epub 2011 Nov 28. PMID: 22095354.

Corsello SM, Di Donna V, Senes P, Luotto V, Ricciato MP, Paragliola RM, Pontecorvi A. Biological aspects of gender disorders. *Minerva Endocrinol.* 2011 Dec;36(4):325-39. PMID: 22322655.

Costa L M, Matzner A. (2007). *Male bodies, women's souls: Personal narrative of Thailand's transgendered youth.* Routledge.

Costantino A, Cerpolini S, Alvisi S, Morselli P, Venturoli S, Meriggiola M. A prospective study on sexual function and mood in female-to-male transsexuals during testosterone administration and after sex reassignment surgery. *J Sex Marital Ther.* 2013;39(4):321-35. Epub 2013 Mar 7. PMID: 23470169.

Cregten-Escobar P, Bouman M, Buncamper M, Mullender M. Subcutaneous mastectomy in female-to-male transsexuals: a retrospective cohort-analysis of 202 patients. *J Sex Med* 2012 Dec;9(12):3148- 53. PMID: 23470169.

Crown S, Crisp AH. A short clinical diagnostic self-rating scale for psychoneurotic patients. The Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1966 Sep;112(490):917-23. PMID: 5970912.

Crown S, Duncan KP, Howell RW. Further evaluation of the Middlesex Hospital Questionnaire (M.H.Q.). *Br J Psychiatry.* 1970 Jan;116(530):33-7. PMID: 5411005.

Crown S. The Middlesex Hospital Questionnaire (MHQ) in clinical research. A review. *Mod Probl Pharmacopsychiatry*. 1974;7(0):111-24. PMID: 4607280.

Cupisti S, Giltay EJ, Gooren LJ, Kronawitter D, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. The impact of testosterone administration to female-to-male transsexuals on insulin resistance and lipid parameters compared with women with polycystic ovary syndrome. *Fertil Steril.* 2010 Dec;94 (7):2647-53. Epub 2010 May 7. PMID: 20451188.

Day P. Tech Brief Series. *Trans-gender reassignment surgery.* New Zealand Health technpology Assessment. (NZHTA). The clearinghouse forhealth outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

De Cuypere G, T'Sjoen G, Beerten R, Selvaggi G, De Sutter P, Hoebeke P, Monstrey S, Vansteenwegen A, Rubens R. Sexual and physical health after sex reassignment surgery. *Arch Sex Behav.* 2005 Dec;34(6):679-90. PMID: 16362252.

De Cuypere G, Elaut E, Heylens G, van Maele G, Selvaggi G, T'Sjoen G, Rubens R, Hoebeke R, Monstrey S. Long-

term follow-up: psychosocial outcome of Belgian transsexuals after sex reassignment surgery. J Sexol. 2006;15:126-33. (Not in PubMed)

De Cuypere G, Van Hemelrijck M, Michel A, Carael B, Heylens G, Rubens R, Hoebeke P, Monstrey S. Prevalence and demography of transsexualism in Belgium. *Eur Psychiatry.* 2007 Apr;22(3):137- 41. Epub 2006 Dec 26. PMID: 17188846.

Deeks JJ, Dinnes J, D'Amico R, Sowden AJ, Sakarovitch C, Song F, Petticrew M, Altman DG; International Stroke Trial Collaborative Group; European Carotid Surgery Trial Collaborative Group. Evaluating non-randomised intervention studies. *Health Technol Assess.* 2003;7(27):iii-x, 1-173. PMID: 14499048.

Deipolyi AR, Han SJ, Parsa AT. Development of a symptomatic intracranial meningioma in a male- to-female transsexual after initiation of hormone therapy. *J Clin Neurosci.* 2010 Oct;17(10):1324-6. Epub 2010 Jul 1. PMID: 20594855.

Derogatis LR, Lipman RS, Covi L. SCL-90: an outpatient psychiatric rating scale preliminary report. *Psychopharmacol Bull.* 1973 Jan;9(1):13-28. PMID: 4682398.

A-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL): a self-report symptom inventory. *Behav Sci*. 1974 Jan;19(1):1-15. PMID:

B-Derogatis LR, Lipman RS, Rickels K, Uhlenhuth EH, Covi L. The Hopkins Symptom Checklist (HSCL). A measure of primary symptom dimensions. *Mod Probl Pharmacopsychiatry.* 1974;7(0):79- 110. PMID: 4607278.

Derogatis LR, Cleary PA. Factorial invariance across gender for the primary symptom dimensions of the SCL-90. *Br J Soc Clin Psychol*. 1977 Nov;16(4):347-56 PMID: 588890.

Derogatis LR, Meyer JK, Vazquez N. A psychological profile of the transsexual. I. The male. *J Nerv Ment Dis.* 1978 Apr;166(4):234-54. PMID: 650186.

Deutsch M, Bhakri V, Kubicek K. Effects of cross-sex hormone treatment on transgender women and men. *Obstet Gyneco*. 2015 Mar;125(3):605-10. PMID: 25730222.

de Vries A, Kreukels B, Steensma T, Doreleijers T, Cohen-Kettenis P. Comparing adult and adolescent transsexuals: an MMPI-2 and MMPI-A study. *Psychiatry Res* 2011 Apr 30;186 (2-3):414-8. PMID: 20801524.

Dhejne C, Lichtenstein P, Boman M, Johansson A, Långström N, Landén M. Long-term follow-up of transsexual persons undergoing sex reassignment surgery: cohort study in Sweden. *PLoS One* 2011;6 (2):e16885. Epub 2011 Feb 22. PMID: 21364939.

Dhejne C, Öberg K, Arver S, Landén M. An analysis of all applications for sex reassignment surgery in Sweden, 1960-2010: prevalence, incidence, and regrets. *Arch Sex Behav.* 2014 Nov;43(8):1535-45. Epub 2014 May 29. PMID: 24872188.

Dhillon R, Bastiampillai T, Krishnan S, Opray N, Tibrewal P. Transgender late onset psychosis: the role of sex hormones. *Aust N Z J Psychiatry*. 2011 Jul;45(7):603. Epub 2011 May 5. PMID: 21542781.

Diamond M. Developmental, sexual and reproductive neuroendocrinology: historical, clinical and ethical considerations. *Front Neuroendocrinol.* 2011 Apr;32(2):255-63. Epub 2011 Feb 18. PMID: 21310174.

Dittrich R, Binder H, Cupisti S, Hoffmann I, Beckmann M, Mueller A. Endocrine treatment of male- to-female transsexuals using gonadotropin-releasing hormone agonist. *Exp Clin Endocrinol Diabetes.* 2005 Dec;113(10):586-92. PMID: 16320157.

Djordjevic ML, Stanojevic DS, Bizic MR. Rectosigmoid vaginoplasty: clinical experience and outcomes in 86 cases. *J Sex Med*. 2011 Dec;8(12):3487-94. Epub 2011 Oct 13. PMID: 21995738.

Djordjevic ML, Bizic MR. Comparison of two different methods for urethral lengthening in female to male (metoidioplasty) surgery. *J Sex Med*. 2013 May;10(5):1431-8. Epub 2013 Feb 27. PMID: 23444841.

Doorduin T, van Berlo W. Trans people's experience of sexuality in the Netherlands: a pilot study. *J Homosex*.2014;61(5):654-72. PMID: 24295055.

Doorn CD, Poortinga J, Verschoor AM. Cross-gender identity in transvestites and male transsexuals. *Arch Sex Behav.* 1994 Apr;23(2):185-201. PMID: 8018022.

Doornaert M, Hoebeke P, Ceulemans P, T'Sjoen G, Heylens G, Monstrey S. Penile reconstruction with the radial forearm flap: an update. *Handchir Mikrochir Plast Chir*. 2011 Aug;43(4):208-14. Epub 2011 Aug 11.

A-Dos Ramos Farías MS, Picconi MA, Garcia MN, González JV, Basiletti J, Pando Mde L, Avila MM. Human papilloma virus genotype diversity of anal infection among trans (male to female transvestites, transsexuals or transgender) sex workers in Argentina. *J Clin Virol.* 2011 Jun;51 (2):96-9. Epub 2011 Apr 20. PMID: 21511521.

B-Dos Ramos Farías MS, Garcia MN, Reynaga E, Romero M, Vaulet ML, Fermepín MR, Toscano MF, Rey J, Marone R, Squiquera L, González JV, Basiletti J, Picconi MA, Pando MA, Avila MM. First report on sexually transmitted infections among trans (male to female transvestites, transsexuals, or transgender) and male sex workers in Argentina: high HIV, HPV, HBV, and syphilis prevalence. *Int J Infect Dis.* 2011 Sep;15(9):e635-40. Epub 2011 Jul 13. PMID: 21742530.

DSM: American Psychiatric Association. (2013). *Diagnostic and statistical manual of mental disorders: DSM-5*. Washington, D.C: American Psychiatric Association.

Dubois L. Associations between transition-specific stress experience, nocturnal decline in ambulatory blood pressure, and C-reactive protein levels among transgender men. *Am J Hum Biol* 2012 Jan- Feb;24(1):52-61. Epub 2011 Nov 28. PMID: 22120883.

Duisin D, Nikolić-Balkoski G, Batinić B. Sociodemographic profile of transsexual patients. *Psychiatr Danub.* 2009 Jun;21(2):220-3. PMID: 19556952.

Duišin D, Batinić B, Barišić J, Djordjević ML, Vujović S, Bizić M. Personality disorders in persons with gender identity disorder. *ScientificWorldJournal.* 2014;2014:809058. Epub 2014 May 13. PMID: 24959629.

Dunn, OJ. Multiple Comparisons Among Means. *J Am Statis Assoc*. 1961 Mar; 56(293): 52- 64. (Not in PubMed) www.jstor.org/stable/2282330.

Elamin M, Garcia M, Murad M, Erwin P, Montori V. Effect of sex steroid use on cardiovascular risk in transsexual individuals: a systematic review and meta-analyses. *Clin Endocrinol (Oxf)*. 2010 Jan;72 (1):1-10. Epub 2009 May 16. PMID: 19473174.

Elaut E, Bogaert V, De Cuypere G, Weyers S, Gijs L, Kaufman J, T'Sjoen G. Contribution of androgen receptor sensitivity to the relation between testosterone and sexual desire: An exploration in male-to-female transsexuals. *J Endocrinol Invest*. 2010 Jan;33(1):37-41. Epub 2009 Jul 20. PMID: 19620824.

Eldh J, Berg A, Gustafsson M. Long-term follow up after sex reassignment surgery. *Scand J Plast Reconstr Surg Hand Surg.* 1997 Mar;31(1):39-45. PMID: 9075286.

Ettner R. Care of the elderly transgender patient. *Curr Opin Endocrinol Diabetes Obes* 2013 Dec;20 (6):580-4. PMID: 24468762.

Europe QOL 2010 Anderson R, Mikuliç B, Vermeylen G, Lyly-Yrjanainen M, Zigante V. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work -Overview.* EF0902. December 13, 2010. www.eurofound.europa.eu/publications/report/2009/quality-of-life/second-european-quality-of-life-survey-overview.

Europe QOL 2011 Kotowska IE, Matysiak A, Styrc M, Pailhe A, Solaz, A Vignoli D. European Foundation for the Improvement of Living and Working Conditions. *Second European Quality of Life Survey: Family life and work.* EF1002. August 22, 2011. NLM classification: WC 503.6. www.eurofound.europa.eu/publications/report/2010/quality-of-life-social-policies/second-european-quality-of-life-survey-family-life-and-work.

Fares WH. The availability bias: underappreciated but with major potential implications. *Crit Care*. 2014 Mar 12;18(2):118. PMID: 25029621.

Ferring D, Filipp SH. Messung des Selbstwertgefuhls: Befunde zu Reliabilitat, Validitat und Stabilitat der Rosenberg-Skala [Measurement of self-esteem: Findings on reliability, validity, and stability of the Rosenberg Scale]. *Diagnostica.* 1996; 42: 284–292. German. (Not in PubMed)

Ferron P, Young S, Boulanger C, Rodriguez A, Moreno J. Integrated care of an aging HIV-infected male-to-female transgender patient. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):278-82. Epub 2010 Mar 19. PMID: 20303795.

Fisher AD, Bandini E, Casale H, Ferruccio N, Meriggiola MC, Gualerzi A, Manieri C, Jannini E, Mannucci E, Monami M, Stomaci N, Delle Rose A, Susini T, Ricca V, Maggi M. Sociodemographic and clinical features of gender identity disorder: an Italian multicentric evaluation. *J Sex Med*. 2013 Feb;10(2):408-19. Epub 2012 Nov 21. PMID: 23171237.

Flanagan BM, Philpott S, Strosberg MA. Protecting participants of clinical trials conducted in the intensive care unit. *J Intensive Care Med.* 2011 Jul-Aug;26(4):237-49. PMID: 21764767.

Fleming M, Steinman C, Bocknek G. Methodological problems in assessing sex-reassignment surgery: a reply to Meyer and Reter. *Arch Sex Behav*. 1980 Oct;9(5):451-6. PMID: 7447685.

Fleming M, Cohen D, Salt P, Jones D, Jenkins S. A study of pre- and postsurgical transsexuals: MMPI characteristics. *Arch Sex Behav*. 1981 Apr;10(2):161-70. PMID: 7247725.

Flores A, Herman J, Gates G, Brown T. (2016) *How many adults identify as transgender in the United States?* Los Angeles, CA: The Williams Institute.

Frances AJ, Nardo JM. ICD-11 should not repeat the mistakes made by DSM-5. *Br J Psychiatry.* 2013 Jul;203(1):1 -2. PMID: 23818530.

Frade-Costa EM, Bilharinho Mendonca B. Clinical management of transsexual subjects. *Arq Bras Endocrinol Metab*. 2014;58(2):188-96. (Not in PubMed)

Franco T, Miranda L, Franco D, Zaidhaft S, Aran M. Male-to-female transsexualsurgery: experience at the UFRJ University Hospital. *Rev Col Bras Cir.* 2010 Dec;37(6):426-34. PMID: 21340258.

Fuss J, Biedermann S, Stalla G, Auer M. On the quest for a biomechanism of transsexualism: is there a role for BDNF? *J Psychiatr Res*. 2013 Dec;47(12):2015-7. Epub 2013 Sep 7. PMID: 23915300.

Futterweit W. Endocrine therapy of transsexualism and potential complications of long-term treatment. *Arch Sex Behav.* 1998 Apr;27(2):209-26. PMID: 9562902.

Garaffa G, Raheem AA, Ralph DJ. An update on penile reconstruction. *Asian J Androl*. 2011 May;13 (3):391-4. PMID: 22426595.

Garaffa G, Gentile V, Antonini G, Tsafrakidis P, Raheem AA, Ralph DJ. Penile reconstruction in the male. *Arab J Urol.* 2013 Sep;11(3):267-71. Epub 2013 Jun 12. PMID: 26558091.

Garcia-Falgueras A, Swaab DF. Sexual hormones and the brain: an essential alliance for sexual identity and sexual orientation. *Endocr Dev*. 2010;17:22-35. Epub 2009 Nov 24. PMID: 19955753.

Garcia-Falgueras A, Ligtenberg L, Kruijver FP, Swaab DF. Galanin neurons in the intermediate nucleus (InM) of the human hypothalamus in relation to sex, age, and gender identity. *J Comp Neurol.* 2011 Oct 15;519(15):3061 -84. PMID: 21618223.

García-Malpartida K, Martín-Gorgojo A, Rocha M, Gómez-Balaguer M, Hernández-Mijares A. Prolactinoma induced by estrogen and cyproterone acetate in a male-to-female transsexual. *Fertil Steril.* 2010 Aug;94(3):1097.e13-5. Epub 2010 Mar 12. PMID: 20227072.

Garrels L, Kockott G, Michael N, Preuss W, Renter K, Schmidt G, Sigusch V, Windgassen K. Sex ratio of transsexuals in Germany: the development over three decades. *Acta Psychiatr Scand.* 2000 Dec;102(6):445-8. PMID: 11142434.

Gaspari L, Paris F, Philibert P, Audran F, Orsini M, Servant N, Maïmoun L, Kalfa N, Sultan C. 'Idiopathic' partial androgen insensitivity syndrome in 28 newborn and infant males: impact of prenatal exposure to environmental endocrine disruptor chemicals? *Eur J Endocrinol*. 2011 Oct;165 (4):579-87. Epub 2011 Jul 25. PMID: 21788424.

Gates GJ. How many people are lesbian, gay, bisexual, and transgender? 2011. (Not in PubMed) williamsinstitute@law.ucla.edu.

Giami A, Le Bail J. HIV infection and STI in the trans population: a critical review. *Rev Epidemiol Sante Publique*. 2011 Aug;59(4):259-68. Epub 2011 Jul 20. PMID: 21767925.

Glezer A, McNiel D, Binder R. Transgendered and incarcerated: a review of the literature, current policies and laws, and ethics. *J Am Acad Psychiatry Law.* 2013;41(4):551-9. PMID: 24335329.

A-Goddard JC, Vickery RM, Terry TR. Development of feminizing genitoplasty for gender dysphoria. *J Sex Med.* 2007 Jul;4(4 Pt 1):981-9. Epub 2007 Apr 19. PMID: 17451484.

B-Goddard JC, Vickery RM, Qureshi A, Summerton DJ, Khoosal D, Terry TR. Feminizing genitoplasty in adult transsexuals: early and long-term surgical results. *BJU Int.* 2007 Sep;100(3):607- 13. PMID: 17669144.

Godlewski J. Transsexualism and anatomic sex ratio reversal in Poland. *Arch Sex Behav*. 1988 Dec;17(6):547-8. PMID: 3265612.

Goldberg DP, Blackwell B. Psychiatric illness in general practice. A detailed study using a new method of case identification. *Br Med J*. 1970 May 23;1(5707):439-43. PMID: 5420206.

Goldman M. Spring 2008 - Stat C141/ Bioeng C141 - Statistics for Bioinformatics. Course Website: http://www.stat.berkeley.edu/users/hhuang/141C-2008.html. Section Website: http://www.stat.berkeley.edu/users/mgoldman.

Gómez-Gil E, Trilla García A, Godás Sieso T, Halperin Rabinovich I, Puig Domingo M, Vidal Hagemeijer A, Peri Nogués JM. Estimation of prevalence, incidence and sex ratio of transsexualism in Catalonia according to health care demand. *Actas Esp Psiquiatr*. 2006 Sep-Oct;34(5):295-302. Spanish. PMID: 17117339.

Gómez-Gil E, Vidal-Hagemeijer A, Salamero M. MMPI-2 characteristics of transsexuals requesting sex reassignment: comparison of patients in prehormonal and presurgical phases. *J Pers Assess.* 2008 Jul;90(4):368-74. PMID: 18584445.

Gómez-Gil E, Trilla A, Salamero M, Godás T, Valdés M. Sociodemographic, clinical, and psychiatric characteristics of transsexuals from Spain. *Arch Sex Behav.* 2009 Jun;38(3):378-92. Epub 2008 Feb 21. PMID: 18288600.

Gómez-Gil E, Esteva I, Almaraz M, Pasaro E, Segovia S, Guillamon A. Familiality of gender identity disorder in non-twin siblings. *Arch Sex Behav.* 2010 Apr;39(2):546-52. Epub 2009 Jul 29. PMID: 19639402.

Gómez-Gil E, Esteva I, Carrasco R, Almaraz MC, Pasaro E, Salamero M, Guillamon A. Birth order and ratio of brothers to sisters in Spanish transsexuals. *Arch Sex Behav.* 2011 Jun;40(3):505-10. Epub 2010 Mar 16. PMID: 20232130.

A-Gómez-Gil E, Gómez A, Cañizares S, Guillamón A, Rametti G, Esteva I, Vázquez A, Salamero- Baró M. Clinical utility of the Bem Sex Role Inventory (BSRI) in the Spanish transsexual and nontranssexual population. *J Pers Assess*. 2012;94(3):304-9. Epub 2012 Jan 13. PMID: 22242861.

B-Gómez-Gil E, Zubiaurre-Elorza L, Esteva I, Guillamon A, Godás T, Cruz Almaraz M, Halperin I, Salamero M. Hormone-treated transsexuals report less social distress, anxiety and depression. *Psychoneuroendocrinology.*

2012 May;37(5):662-70. Epub 2011 Sep 19. PMID: 21937168.

Gómez-Gil E, Zubiaurre-Elorza L, de Antonio I, Guillamon A, Salamero M. Determinants of quality of life in Spanish transsexuals attending a gender unit before genital sex reassignment surgery. *Qual Life Res.* 2014 Mar;23(2):669-76. Epub 2013 Aug 13. PMID: 23943260.

Gooren L. Hormone treatment of the adult transsexual patient. *Horm Res.* 2005;64 Suppl 2:31-6. PMID: 16286768.

Gooren L. Clinical practice. Care of transsexual persons. *N Engl J Med.* 2011 Mar 31;364(13):1251-7. PMID: 21449788.

A-Gooren L, Giltay E. Men and women, so different, so similar: observations from cross-sex hormone treatment of transsexual subjects. *Andrologia*. 2014 Jun;46(5):570-5. Epub 2013 May 19. PMID: 23682909.

B-Gooren L. Management of female-to-male transgender persons: medical and surgical management, life expectancy. *Curr Opin Endocrinol Diabetes Obes.* 2014 Jun;21(3):233-8. PMID: 24755998.

C-Gooren LJ, Wierckx K, Giltay EJ. Cardiovascular disease in transsexual persons treated with cross- sex hormones: reversal of the traditional sex difference in cardiovascular disease pattern. *Eur J Endocrinol*. 2014 Jun;170(6):809-19. Epub 2014 Mar 10. PMID: 24616414.

D-Gooren L, Lips P. Conjectures concerning cross-sex hormone treatment of aging transsexual persons. *J Sex Med.* 2014 Aug;11(8):2012-9. Epub 2014 Apr 29. PMID: 24775178.

E-Gooren L, Morgentaler A. Prostate cancer incidence in orchidectomised male-to-female transsexual persons treated with oestrogens. *Andrologia.* 2014 Dec;46(10):1156-60. Epub 2013 Dec 12. PMID: 24329588.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Gebleux S, Penochet J, Pringuey D, Albarel F, Morange I, Loundou A, Berbis J, Auquier P, Lançon C, Bonierbale M. Is hormonal therapy associated with better quality of life in transsexuals? A cross-sectional study. *J Sex Med.* 2012 Feb;9 (2):531-41. Epub 2011 Dec 6. PMID: 22145968.

Gorin-Lazard A, Baumstarck K, Boyer L, Maquigneau A, Penochet J, Pringuey D, Albarel F, Morange I, Bonierbale M, Lançon C, Auquier P. Hormonal therapy is associated with better self- esteem, mood, and quality of life in transsexuals. *J Nerv Ment Dis.* 2013 Nov;201(11):996-1000. PMID: 24177489.

Grant JE, Flynn M, Odlaug BL, Schreiber LR. Personality disorders in gay, lesbian, bisexual, and transgender chemically dependent patients. *Am J Addict*. 2011 Sep-Oct;20(5):05-11. Epub 2011 Jul 18. PMID: 21838838.

Green R. Sexual functioning in post-operative transsexuals: male-to-female and female-to-male. *Int J Impot Res.* 1998 May;10 Suppl 1:S22-4. PMID: 9669217.

Greenberg G, Frank G. Response set in the Tennessee Department of Mental Health Self Concept Scale. *J Clin Psychol*. 1965 Jul;21:287-8. PMID: 14332192.

Greenberg RP, Laurence L. A comparison of the MMPI results for psychiatric patients and male applicants for transsexual surgery. *J Nerv Ment Dis.* 1981 May;169(5):320-3. PMID: 7217944.

Gurtman MB. Interpersonal Problems and the Psychotherapy Context: The Construct Validity of the Inventory of Interpersonal Problems. *Psychological Assessment.*1996; 8 (3):241-55. (Not in PubMed)

Guadamuz TE, Wimonsate W, Varangrat A, Phanuphak P, Jommaroeng R, McNicholl JM, Mock PA, Tappero JW, van Griensven F. HIV prevalence, risk behavior, hormone use and surgical history among transgender persons in Thailand. *AIDS Behav.* 2011 Apr;15(3):650-8. PMID: 21104008.

A-Guyatt GH, Oxman AD, Vist GE, Kunz R, Falck-Ytter Y, Alonso-Coello P, Schünemann HJ; GRADE Working Group. GRADE: an emerging consensus on rating quality of evidence and> strength of recommendations. *BMJ*. 2008 Apr 26;336(7650):924-6. PMID: 18436948.

B-Guyatt GH, Oxman AD, Kunz R, Vist GE, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. What is "quality of evidence" and why is it important to clinicians? *BMJ.* 2008 May 3;336 (7651):995-8. PMID: 18456631.

C-Guyatt GH, Oxman AD, Kunz R, Falck-Ytter Y, Vist GE, Liberati A, Schünemann HJ; GRADE Working Group. Going from evidence to recommendations. *BMJ*. 2008 May 10;336(7652): 1049-51. Erratum in: *BMJ*. 2008 Jun 21;336(7658). PMID: 18467413.

A-Guyatt GH, Oxman AD, Kunz R, Atkins D, Brozek J, Vist G, Alderson P, Glasziou P, Falck-Ytter Y, Schünemann HJ. GRADE guidelines: 2. Framing the question and deciding on important outcomes. *J Clin Epidemiol.* 2011 Apr;64(4):395-400. Epub 2010 Dec 30. PMID: 21194891.

B-Guyatt GH, Oxman AD, Vist G, Kunz R, Brozek J, Alonso-Coello P, Montori V, Akl EA, Djulbegovic B, Falck-Ytter Y, Norris SL, Williams JW Jr, Atkins D, Meerpohl J, Schünemann HJ. GRADE guidelines: 4. Rating the quality of evidence study limitations (risk of bias). *J Clin Epidemiol*. 2011 Apr;64(4):407-15. doi: 10.1016/j.jclinepi.2010.07.017. Epub 2011 Jan 19. PMID: 21247734.

C-Guyatt GH, Oxman AD, Montori V, Vist G, Kunz R, Brozek J, Alonso-Coello P, Djulbegovic B, Atkins D, Falck-Ytter Y, Williams JW Jr, Meerpohl J, Norris SL, Akl EA, Schünemann HJ. GRADE guidelines: 5. Rating the quality of evidence publication bias. *J Clin Epidemiol.* 2011 Dec;64 (12):1277-82. Epub 2011 Jul 30. PMID: 21802904.

D-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Glasziou P, Jaeschke R, Akl EA, Norris S, Vist G, Dahm P, Shukla VK, Higgins J, Falck-Ytter Y, Schünemann HJ; GRADE Working Group. GRADE guidelines: 7. Rating the quality of evidence inconsistency. *J Clin Epidemiol*. 2011 Dec;64(12):1294-302. Epub 2011 Jul 31. PMID: 21803546.

E-Guyatt GH, Oxman AD, Kunz R, Woodcock J, Brozek J, Helfand M, Alonso-Coello P, Falck-Ytter Y, Jaeschke R, Vist G, Akl EA, Post PN, Norris S, Meerpohl J, Shukla VK, Nasser M, Schünemann HJ; GRADE Working Group. GRADE guidelines: 8. Rating the quality of evidence indirectness. *J Clin Epidemiol*. 2011 Dec;64(12):1303-10. Epub 2011 Jul 30. PMID: 21802903.

Haas AP, Eliason M, Mays VM, Mathy RM, Cochran SD, D'Augelli AR, Silverman MM, Fisher PW, Hughes T, Rosario M, Russell ST, Malley E, Reed J, Litts DA, Haller E, Sell RL, Remafedi G, Bradford J, Beautrais AL, Brown GK, Diamond GM, Friedman MS, Garofalo R, Turner MS, Hollibaugh A, Clayton PJ. Suicide and suicide risk in lesbian,

gay, bisexual, and transgender populations: review and recommendations. *J Homosex.* 2011;58(1):10-51. PMID: 21213174.

Hage JJ, De Graaf FH. Addressing the ideal requirements by free flap phalloplasty: some reflections on refinements of technique. *Microsurgery.* 1993;14(9):592-8. PMID: 8289643.

Hage JJ, Karim RB. Ought GIDNOS get nought? Treatment options for nontranssexual gender dysphoria. *Plast Reconstr Surg*. 2000 Mar;105(3):1222-7. PMID: 10724285.

Hale JC. Ethical problems with the mental health evaluation standards of care for adult gender variant prospective patients. *Perspectives in Biology and Medicine*. 2007Autumn;50(4):491-505. (Not in PubMed)

Haraldsen IR, Dahl AA. Symptom profiles of gender dysphoric patients of transsexual type compared to patients with personality disorders and healthy adults. *Acta Psychiatr Scand.* 2000 Oct;102(4):276- 81. PMID: 11089727.

Hare L, Bernard P, Sánchez FJ, Baird PN, Vilain E, Kennedy T, Harley VR. Androgen receptor repeat length polymorphism associated with male-to-female transsexualism. *Biol Psychiatry.* 2009 Jan 1;65(1):93-6. Epub 2008 Oct 28. PMID: 18962445.

Hathaway S, Briggs P. Some normative data on new MMPI scales. *J Clin Psychol.* 1957 Oct;13 (4):364-8. PMID: 13463138.

Hathaway SR,Reynolds PC,Monachesi ED. Follow-up of the later careers and lives of 1,000 boys who dropped out of high school. *J Consult Clin Psychol*. 1969 Jun;33(3):370-80. PMID: 4389336.

Hebbar S, Pandey H, Chawla A. Understanding King“s Health Questionnaire (KHQ) in assessment of female urinary incontinence. Int J Res Med Sci 2015;3:531-8.

Hembree WC, Cohen-Kettenis P, Delemarre-van de Waal HA, Gooren LJ, Meyer WJ 3rd, Spack NP, Tangpricha V, Montori VM; Endocrine Society. Endocrine Treatment of Transsexual Persons: an Endocrine Society Clinical Practice Guideline. *J Clin Endocrinol Metab.* 2009;94:3132-54. PMID: 19509099.

Hembree WC. Guidelines for pubertal suspension and gender reassignment for transgender adolescents. *Child Adolesc Psychiatr Clin N Am.* 2011 Oct;20(4):725-32. PMID: 22051008.

Hepp U, Klaghofer R, Burkhard-Kübler R, Buddeberg C. [Treatment follow-up of transsexual patients. A catamnestic study]. *Nervenarzt.* 2002 Mar;73(3):283-8. German. PMID: 11963265.

Hepp U, Kraemer B, Schnyder U, Miller N, Delsignore A. Psychiatric comorbidity in gender identity disorder. *J Psychosom Res.* 2005 Mar;58(3):259-61. PMID: 15865950.

Herbst J, Jacobs E, Finlayson T, McKleroy V, Neumann M, Crepaz N. Estimating HIV prevalence and risk behaviors of transgender persons in the United States: a systematic review. *AIDS Behav*. 2008 Jan;12(1):1-17. Epub 2007 Aug 13. PMID: 17694429.

Heresová J, Pobisová Z, Hampl R, Stárka L. Androgen administration to transsexual women. II. Hormonal changes. *Exp Clin Endocrinol*. 1986 Dec;88(2):219-23. PMID: 3556412.

Hormonal changes. *Exp Clin Endocrinol.* 1986 Dec;88(2):219-23. PMID: 3556412.

Hess J, Rossi Neto R, Panic L, Rübben H, Senf W. Satisfaction with male-to-female gender reassignment surgery. *Dtsch Arztebl Int*. 2014 Nov 21;111(47):795-801. PMID: 25487762.

A-Heylens G, Verroken C, De Cock S, T'Sjoen G, De Cuypere G. Effects of different steps in gender reassignment therapy on psychopathology: a prospective study of persons with a gender identity disorder. *J Sex Med.* 2014 Jan;11(1):119-26. Epub 2013 Oct 28. PMID: 24344788.

B-Heylens G, Elaut E, Kreukels BP, Paap MC, Cerwenka S, Richter-Appelt H, Cohen-Kettenis PT, Haraldsen I, De Cuypere G. Psychiatric characteristics in transsexual individuals: multicentre study in four European countries. *Br J Psychiatry.* 2014 Feb;204(2):151-6. Epub 2013 May 9. PMID: 23869030.

HHS-HP: US Department of Health and Human Services. Lesbian, gay, bisexual and transgender health: objectives. Healthy People 2020. www.healthypeople.gov/2020/topics objectives2020/overview.aspx?topicid=25.

HHS-2011: US Department of Health and Human Services.Affordable Care Act to improve data collection, reduce health disparities. www.hhs.gov/news/press/2011pres/06/20110629a.html.

Hines M, Ahmed SF, Hughes IA. Psychological outcomes and gender-related development in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2003 Apr;32(2):93-101. PMID: 12710824.

Hoekzema E, Schagen SE, Kreukels BP, Veltman DJ, Cohen-Kettenis PT, Delemarre-van de Waal H, Bakker J. Regional volumes and spatial volumetric distribution of gray matter in the gender dysphoric brain. *Psychoneuroendocrinology.* 2015 May;55:59-71. Epub 2015 Jan 30. PMID: 25720349.

Hoenig J, Kenna J, Youd A. A follow-up study of transsexualists: social and economic aspects. *Psychiatr Clin (Basel).* 1970;3(2):85-100. PMID: 5424767.

Hoenig J, Kenna JC, Youd A. Surgical treatment for transsexualism. *Acta Psychiatr Scand.* 1971;47 (1):106-33 or 36. PMID: 5096332 or 5148350.

Hoenig J, Kenna J. Epidemiological aspects of transsexualism. *Psychiatr Clin (Basel).* 1973;6(2):65- 80. PMID: 4705331.

Hoffman B. An Overview of Depression among Transgender Women. *Depress Res Treat.* 2014;2014:394283. Epub 2014 Mar 13. PMID: 24744918.

Hopewell S, Loudon K, Clarke MJ, Oxman AD, Dickersin K. Publication bias in clinical trials due to statistical significance or direction of trial results. *Cochrane Database Syst Rev*. 2009 Jan 21; (1):MR000006. PMID: 19160345.

Hopewell S, Dutton S, Yu LM, Chan AW, Altman DG. The quality of reports of randomised trials in 2000 and 2006: comparative study of articles indexed in PubMed. *BMJ*. 2010 Mar 23;340:c723. PMID: 20332510.

Hopewell S, Hirst A, Collins GS, Mallett S, Yu LM, Altman DG. Reporting of participant flow diagrams in published reports of randomized trials. *Trials*. 2011 Dec 5;12:253. PMID: 22141446.

Horbach S, Bouman M, Smit J, Özer M, Buncamper M, Mullender M. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jun;12(6):1499-512. Epub 2015 Mar 26. PMID: 25817066.

Horowitz LM, Rosenberg SE, Baer BA, Ureño G, Villaseñor VS. Inventory of interpersonal problems: psychometric properties and clinical applications. *J Consult Clin Psychol.* 1988 Dec;56 (6):885-92. PMID: 3204198.

Hoshiai M, Matsumoto Y, Sato T, Ohnishi M, Okabe N, Kishimoto Y, Terada S, Kuroda S. Psychiatric comorbidity among patients with gender identity disorder. *Psychiatry Clin Neurosci.* 2010 Oct;64(5):514-9. Epub 2010 Aug 19. PMID: 20727112.

A-Hunt DD, Hampson JL. Follow-up of 17 biologic male transsexuals after sex-reassignment surgery. *Am J Psychiatry*. 1980 Apr;137(4):432-8. PMID: 7361928.

B-Hunt DD, Hampson JL. Transsexualism: a standardized psychosocial rating format for the evaluation of results of sex reassignment surgery. *Arch Sex Behav.* 1980 Jun;9(3):255-63. PMID: 7396697.

Hunt DD, Carr JE, Hampson JL. Cognitive correlates of biologic sex and gender identity in transsexualism. *Arch Sex Behav.* 1981 Feb;10(1):65-77. PMID: 7011255.

Inoubli A, De Cuypere G, Rubens R, Heylens G, Elaut E, Van Caenegem E, Menten B, T'Sjoen G. Karyotyping, is it worthwhile intranssexualism? *J Sex Med*. 2011 Feb;8(2):475-8. Epub 2010 Nov 29. PMID: 21114769.

A-Imperato-McGinley J. 5alpha-reductase-2 deficiency and complete androgen insensitivity: lessons from nature. *Adv Exp Med Biol*. 2002;511:121-31; discussion 131-4. PMID: 12575759.

B- Imperato-McGinley J, Zhu YS. Androgens and male physiology the syndrome of 5 alpha- reductase-2 deficiency. *Mol Cell Endocrinol*. 2002 Dec 30;198(1-2):51-9. PMID: 12573814.

Insel T. Director's Blog: Transforming Diagnosis. April 29, 2013. http://www.nimh.nih.gov/about/director/2013/transforming-diagnosis.shtml.

Insel T. The NIMH Research Domain Criteria (RDoC) Project: precision medicine for psychiatry. *Am J Psychiatry.* 2014 Apr;171(4):395-7. PMID: 24687194.

IOM 2011 Robert Graham (Chair); Committee on Lesbian, Gay, Bisexual, and Transgender Health Issues and Research Gaps and Opportunities. Institute of Medicine (IOM). (Study Sponsor: The National Institutes of Health). The Health of Lesbian, Gay, Bisexual, and Transgender People: Building a Foundation for Better Understanding. Issued March 31, 2011. http://thefenwayinstitute.org/documents/lgbthealthreportbriefembargoed.pdf.

Jackson PA. Thai research on male homosexuality and transgenderism and the cultural limits of Foucaultian analysis*. J Hist Sex.* 1997 Jul;8(1):52-85. PMID: 11619530.

Jackson, Peter A.. An explosion of Thai identities: peripheral genders and the limits of queer theory. *Culture, Health, & Sexuality*, 2000;2(4):405-24. Taylor & Francis. (Not in PubMed)

Jackson PA. Pre-gay, post-queer: Thai perspectives on proliferating gender/sex diversity in Asia. *J Homosex*. 2001;40(3-4):1-25. PMID: 11386329.

Jacobeit J, Gooren L, Schulte H. Safety aspects of 36 months of administration of long-acting intramuscular testosterone undecanoate for treatment of female-to-male transgender individuals. *Eur J Endocrinol.* 2009 Nov;161(5):795-8. Epub 2009 Sep 11. PMID: 19749027.

Jacobs, S-E, Thomas W, and Lang S (Eds.). (1997). *Two-spirit people: Native American gender identity, sexuality, and spirituality*. Urbana: University of Illinois Press.

Jain A, Bradbeer C. Gender identity disorder: treatment and post-transition care in transsexual adults. *Int J STD AIDS.* 2007 Mar;18(3):147-50. PMID: 17362542.

Jarolím L, Sedý J, Schmidt M, Nanka O, Foltán R, Kawaciuk I. Gender reassignment surgery in male-to-female transsexualism: A retrospective 3-month follow-up study with anatomical remarks. *J Sex Med.* 2009 Jun;6(6):1635-44. Epub 2009 Mar 30. PMID: 19473463.

Johansson A, Sundbom E, Höjerback T, Bodlund O. A five-year follow-up study of Swedish adults with gender identity disorder. *Arch Sex Behav. 2010* Dec;39(6):1429-37. Epub 2009 Oct 9. PMID: 19816764.

Jokić-Begić N, Lauri Korajlija A, Jurin T. Psychosocial adjustment to sex reassignment surgery: a qualitative examination and personal experiences of six transsexual persons in Croatia. *Scientific World Journal.* 2014;2014:960745. Epub 2014 Mar 25. PMID: 24790589.

Joseph A, Shabir I, Marumadi E, Dada R, Ammini A, Mehta M. Psychosexual outcomes in three siblings with partial androgen insensitivity syndrome: impact of nature versus nurture. *J Pediatr Endocrinol Metab.* 2013;26(9-10):915-20. PMID: 23729553.

Judge C, O'Donovan C, Callaghan G, Gaoatswe G, O'Shea D. Gender dysphoria - prevalence and co- morbidities in an Irish adult population. *Front Endocrinol (Lausanne)* 2014;5:87. Epub 2014 Jun 13. PMID: 24982651.

Jürgensen M, Hiort O, Holterhus PM, Thyen U. Gender role behavior in children with XX karyotype and disorders of sex development. *Horm Behav*. 2007 Mar;51(3):443-53. Epub 2007 Jan 12. PMID: 17306800.

Keenan JP, Wheeler MA, Gallup GG Jr, Pascual-Leone A. Self-recognition and the right prefrontal cortex. *Trends Cogn Sci*. 2000 Sep;4(9):338-344. PMID: 10962615.

Kelleher CJ, Cardozo LD, Khullar V, Salvatore S. A new questionnaire to assess the quality of life of urinary incontinent women. *Br J Obstet Gynaecol.* 1997 Dec;104(12):1374-9. PMID: 9422015.

Khan L. Transgender health at the crossroads: legal norms, insurance markets, and the threat of healthcare reform. *Yale J Health Policy Law Ethics*. 2011 Summer;11(2):375-418. PMID: 22136012.

Khandelwal A, Agarwal A, Jiloha RC. A 47,XXY female with gender identity disorder. *Arch Sex Behav.* 2010 Oct;39(5):1021-3. PMID: 20464469.

Knight R. Fragmentation, fluidity, and transformation: nonlinear development in middle childhood. *Psychoanal Study Child.* 2011;65:19-47. PMID: 26027138.

Kockott G, Fahrner EM. Transsexuals who have not undergone surgery: a follow-up study. *Arch Sex Behav.* 1987 Dec;16(6):511-22. PMID:> 3426393.

Kockott G, Fahrner EM. Male-to-female and female-to-male transsexuals: a comparison. *Arch Sex Behav.* 1988 Dec;17(6):539-46. PMID: 3223814.

Kohlberg, L. "A Cognitive-Developmental Analysis of Children's Sex-Role Concepts and Attitudes." In E. E. Maccoby (ed.). *The Development of Sex Differences.* Stanford, Calif.: Stanford University Press, 1966.

Kraemer B, Delsignore A, Schnyder U, Hepp U. Body image and transsexualism. *Psychopathology*. 2008;41(2):96-100. Epub 2007 Nov 23. PMID: 18033979.

Krege S, Bex A, Lümmen G, Rübben H. Male-to-female transsexualism: a technique, results and long-term follow -up in 66 patients. *BJU Int*. 2001 Sep;88(4):396-402. PMID: 11564029.

Kreukels B, Haraldsen, De Cuypere G, Richter-Appelt H, Gijs L, Cohen-Kettenis P. A European network for the investigation of gender incongruence: the ENIGI initiative. *Eur Psychiatry*. 2012 Aug;27(6):445-50. Epub 2010 Jul 9. PMID: 20620022.

Kröhn W, Bertermann H, Wand H, Wille R. [Transsexualism: a long-term follow-up after sex reassignment surgery (author's transl)]. *Nervenarzt*. 1981 Jan;52(1):26-31. PMID: 7219610.

Kronawitter D, Gooren LJ, Zollver H, Oppelt PG, Beckmann MW, Dittrich R, Mueller A. Effects of transdermal testosterone or oral dydrogesterone on hypoactive sexual desire disorder in transsexual women: results of a pilot study. *Eur J Endocrinol.* 2009 Aug;161(2): 363-8. Epub 2009 Jun 4. PMID: 19497984.

Kruijver FP, Fernández-Guasti A, Fodor M, Kraan EM, Swaab DF. Sex differences in androgen receptors of the human mamillary bodies are related to endocrine status rather than to sexual orientation or transsexuality. *J Clin Endocrinol Metab*. 2001 Feb;86(2):818-27. PMID: 11158052.

Kuiper B, Cohen-Kettenis P. Sex reassignment surgery: a study of 141 Dutch transsexuals. *Arch Sex Behav*. 1988 Oct;17(5):439-57. PMID: 3219066.

Kuhn A, Hiltebrand R, Birkhäuser M. Do transsexuals have micturition disorders? *Eur J Obstet Gynecol Reprod Biol.* 2007 Apr;131(2):226-30. Epub 2006 May 5. PMID: 16678333.

Kuhn A, Bodmer C, Stadlmayr W, Kuhn P, Mueller M, Birkhäuser M. Quality of life 15 years after sex reassignment surgery for transsexualism. *Fertil Steril.* 2009 Nov;92(5):1685-1689.e3. Epub

2008 Nov 6. PMID: 18990387.

Kuhn A, Santi A, Birkhäuser M. Vaginal prolapse, pelvic floor function, and related symptoms 16 years after sex reassignment surgery in transsexuals. *Fertil Steril*. 2011 Jun;95(7):2379-82. Epub 2011 Apr 2. PMID: 21458798.

Kunz R, Oxman AD. The unpredictability paradox: review of empirical comparisons of randomised and non-randomised clinical trials. *BMJ.* 1998 Oct 31;317(7167):1185-90. PMID: 9794851.

Kunz R, Vist G, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*. 2007 Apr 18;(2):MR000012. Update in: *Cochrane Database Syst Rev*. 2011; (4) MR000012. PMID: 17443633.

Kupfer DJ, Kuhl EA, Regier DA. Two views on the new DSM-5: DSM-5: a diagnostic guide relevant to both primary care and psychiatric practice. *Am Fam Physician.* 2013 Oct 15;88(8):Online. PMID: 24364581.

Kuper LE, Nussbaum R, Mustanski B. Exploring the diversity of gender and sexual orientation identities in an online sample of transgender individuals*. J Sex Res.* 2012;49(2-3):244-54. Epub 2011 Jul 28. PMID: 21797716.

Lader EW, Cannon CP, Ohman EM, Newby LK, Sulmasy DP, Barst RJ, Fair JM, Flather M, Freedman JE, Frye RL, Hand MM, Jesse RL, Van de Werf F, Costa F; American Heart Association. The clinician as investigator: participating in clinical trials in the practice setting: Appendix 2: statistical concepts in study design and analysis. *Circulation.* 2004 Jun 1;109(21):e305-7. PMID: 15173053.

Lament C. Transgender Children: Conundrums and Controversies A Introduction to the Section. *Psychoanal Study Child* 2014;68:13-27. PMID: 26173324.

Lancet Editorial-No Authors . Health of lesbian, gay, bisexual, and transgender populations. *Lancet.* 2011 April 9;377: 1211. PMID:2 1481690.

A - Landén M, Wålinder J, Hambert G, Lundström B. Factors predictive of regret in sex reassignment. *Acta Psychiatr Scand.* 1998 Apr;97(4):284-9. PMID: 9570489.

B – Landén M, Walinder J, Lundstrom B. Clinical characteristics of a total cohort of female and male applicants for sex reassignment: a descriptive study. Acta Psychiatr Scand 1998: 97: 189-194.

Lang, S. (1998). *Men as Women, Women as Men: Changing Gender in Native American Cultures*. Austin, TX: University of Texas Press.

Lang RJ, Vernon PE. Dimensionality of the perceived self: the Tennessee Self Concept Scale. *Br J Soc Clin Psychol.* 1977 Nov;16(4):363-71. PMID: 588892.

Lawrence AA. Changes in sexual orientation in six male-to-female (MtF) transsexuals. *Arch Sex Behav.* 1999 Dec;28(6):581-3. PMID:> 10650442.

Lawrence A. Factors associated with satisfaction or regret following male-to-female sex reassignment surgery. *Arch Sex Behav.* 2003 Aug;32(4):299-315. PMID: 12856892.

Lawrence A. Sexuality before and after male-to-female sex reassignment surgery. *Arch Sex Behav.* 2005 Apr;34(2):147-66. PMID: 15803249.

Lawrence A. Patient-reported complications and functional outcomes of male-to-female sex reassignment surgery. *Arch Sex Behav.* 2006 Dec;35(6):717-27. Epub 2006 Nov 16. PMID: 17109225.

A-Lawrence AA. Sexual orientation versus age of onset as bases for typologies (subtypes) for gender identity disorder in adolescents and adults. *Arch Sex Behav*. 2010 Apr;39(2):514-45. Epub 2010 Feb 6. PMID: 20140487.

B-Lawrence AA. Societal individualism predicts prevalence of nonhomosexual orientation in male-to-female transsexualism. *Arch Sex Behav*. 2010 Apr;39(2):573-83. Epub 2008 Dec 9. PMID: 19067152.

Leavitt F, Berger JC, Hoeppner JA, Northrop G. Presurgical adjustment in male transsexuals with and without hormonal treatment. *J Nerv Ment Dis.* 1980 Nov;168(11):693-7. PMID: 6255090.

A-Leclère F, Casoli V, Weigert R. Outcome of Vaginoplasty in Male-to-Female Transgenders: A Systematic Review of Surgical Techniques. *J Sex Med.* 2015 Jul;12(7):1655-6. Epub 2015 Jun 11. PMID: 26096230.

B-Leclère FM, Casoli V, Weigert R. Vaginoplasty in Male-to-Female Transsexual Surgery: A Training Concept Incorporating Dissection Room Experience to Optimize Functional and Cosmetic Results. *J Sex Med.* 2015 Oct;12(10):2074-83. PMID: 26481600.

Leinung M, Urizar M, Patel N, Sood S. Endocrine treatment of transsexual persons: extensive personal experience. *Endocr Pract*. 2013 Jul-Aug;19(4):644-50. PMID: 23512380.

Lief HI, Hubschman L. Orgasm in the postoperative transsexual. *Arch Sex Behav.* 1993 Apr;22 (2):145-55. PMID: 8476334.

Lindemalm G, Körlin D, Uddenberg N. Long-term follow-up of "sex change" in 13 male-to-female transsexuals. *Arch Sex Behav.* 1986 Jun;15(3):187-210. PMID: 3729700.

Lindemalm G, Körlin D, Uddenberg N. Prognostic factors vs. outcome in male-to-female transsexualism. A follow-up study of 13 cases. *Acta Psychiatr Scand.* 1987 Mar;75(3):268-74. PMID: 3591409.

Lindgren TW, Pauly IB. A body image scale for evaluating transsexuals. *Arch Sex Behav*. 1975 Nov;4(6):639-56. PMID: 1212093.

Lioudaki E, Ganotakis ES, Mikhailidis DP, Nair DR. The estrogenic burden on vascular risk in male-to-female transsexuals. *Curr Pharm Des.* 2010;16(34):3815-22. PMID: 21128891

Lobato MI, Koff WJ, Manenti C, da Fonseca Seger D, Salvador J, da Graça Borges Fortes M, Petry AR, Silveira E, Henriques AA. Follow-up of sex reassignment surgery in transsexuals: a Brazilian cohort. *Arch Sex Behav*. 2006 Dec;35(6):711-5. PMID: 17075731.

Lothstein LM. The aging gender dysphoria (transsexual) patient. *Arch Sex Behav.* 1979 Sep;8 (5):431-44. PMID: 496624.

Lothstein LM, Roback H. Black female transsexuals and schizophrenia: a serendipitous finding? *Arch Sex Behav.* 1984 Aug;13(4):371-86. PMID: 6487080.

Lothstein LM. Psychological testing with transsexuals: a 30-year review. *J Pers Assess.* 1984 Oct;48 (5):500-7. PMID: 6389823.

Lundström B, Pauly I, Wålinder J. Outcome of sex reassignment surgery. *Acta Psychiatr Scand.* 1984 Oct;70(4):289-94. PMID: 6388248.

Maccoby EE. The role of gender identity and gender constancy in sex-differentiated development. *New Dir Child Dev.* 1990 Spring;(47):5-20. PMID: 2194142.

Maimoun L, Philibert P, Cammas B, Audran F, Bouchard P, Fenichel P, Cartigny M, Pienkowski C, Polak M, Skordis N, Mazen I, Ocal G, Berberoglu M, Reynaud R, Baumann C, Cabrol S, Simon D,

Kayemba-Kay's K, De Kerdanet M, Kurtz F, Leheup B, Heinrichs C, Tenoutasse S, Van Vliet G, Grüters A, Eunice M, Ammini AC, Hafez M, Hochberg Z, Einaudi S, Al Mawlawi H, Nuñez CJ, Servant N, Lumbroso S, Paris F, Sultan C. Phenotypical, biological, and molecular heterogeneity of 5α-reductase deficiency: an extensive international experience of 55 patients. *J Clin Endocrinol Metab.* 2011 Feb;96(2):296-307. Epub 2010 Dec 8. PMID: 21147889.

Marks I, Green R, Mataix-Cols D. Adult gender identity disorder can remit. *Compr Psychiatry*. 2000 Jul-Aug;41(4):273-5. PMID: 10929795.

Marshall E, Claes L, Bouman WP, Witcomb GL, Arcelus J. Non-suicidal self-injury and suicidality in trans people: A systematic review of the literature. *Int Rev Psychiatry*. 2015 Sep 2:1-12. [Epub ahead of print]. PMID: 26329283.

Matarazzo B, Barnes S, Pease J, Russell L, Hanson J, Soberay K, Gutierrez P. Suicide risk among lesbian, gay, bisexual, and transgender military personnel and veterans: what does the literature tell us? *Suicide Life Threat Behav.* 2014 Apr;44(2):200-17. Epub 2014 Feb 3. PMID: 24494604.

Mate-Kole C, Freschi M, Robin A. Aspects of psychiatric symptoms at different stages in the treatment of transsexualism. *Br J Psychiatry.* 1988 Apr;152:550-3. PMID: 3167409.

Mate-Kole C, Freschi M, Robin A. A controlled study of psychological and social change after surgical gender reassignment in selected male transsexuals. *Br J Psychiatry.* 1990 Aug;157:261-4. PMID: 2224377.

Maycock L, Kennedy H. Breast care in the transgender individual. *J Midwifery Womens Health.* 2014 Jan-Feb;59(1):74-81. Epub 2013 Nov 13. PMID: 24224502.

McHorney CA, Ware JE, Raczek AE. The MOS 36-Item Short-Form Health Survey (SF-36): II. Psychometric and clinical tests of validity in measuring physical and mental health constructs. *Med Care*. 1993 Mar;31(3):247-63. PMID: 8450681.

McHugh PR, Slavney PR. Mental illness comprehensive evaluation or checklist? *N Engl J Med.* 2012 May 17;366(20):1853-5. PMID: 22591291.

Meads C, Pennant M, McManus J, Bayliss S. West Midlands Health Technology Assessment Collaboration. A systematic review of lesbian, gay, bisexual and transgender health in the West Midlands region of the UK compared to published UK research. *Health Technology Assessment Database.* 2009. No.3. www.birmingham.ac.uk/Documents/college-

Medraś M, Jóźków P. Transsexualism diagnostic and therapeutic aspects. *Endokrynol Pol.* 2010 Jul-Aug;61(4):412-6. PMID: 20806188.

Megeri D, Khoosal D. Anxiety and depression in males experiencing gender dysphoria. *Sexual and Relationship Therapy*. 2007 Feb; 22(1):77-81. (Not in PubMed)

Melendez RM, Exner TA, Ehrhardt AA, Dodge B, Remien RH, Rotheram-Borus MJ, Lightfoot M, Hong D. Health and health care among male-to-female transgender persons who are HIV positive. *Am J Public Health.* 2006 Jun;96(6):1034-7. Epub 2005 Aug 30. PMID: 16131645.

Mepham N, Bouman W, Arcelus J, Hayter M, Wylie K. People with gender dysphoria who self- prescribe cross-sex hormones: prevalence, sources, and side effects knowledge. *J Sex Med.* 2014 Dec;11(12):2995-3001. Epub 2014 Sep 11. PMID: 25213018.

Meriggiola M, Jannini E, Lenzi A, Maggi M, Manieri C. Endocrine treatment of transsexual persons: an Endocrine Society Clinical Practice Guideline: commentary from a European perspective. *Eur J Endocrinol.* 2010 May;162(5):831-3. Epub 2010 Feb 11. PMID: 20150325.

Meriggiola M, Berra M. Long-term cross-sex hormone treatment is safe in transsexual subjects. *Asian J Androl.* 2012 Nov;14(6):813-4. Epub 2012 Aug 27. PMID: 22922319.

Meriggiola M, Berra M. Safety of hormonal treatment in transgenders. *Curr Opin Endocrinol Diabetes Obes*. 2013 Dec;20(6):565-9. PMID: 24468759.

A-Meriggiola MC, Gava G. Endocrine care of transpeople part I. A review of cross-sex hormonal treatments, outcomes and adverse effects in transmen. *Clin Endocrinol (Oxf)*. 2015 Nov;83(5):597-606. Epub 2015 Mar 25. PMID: 25692791.

B-Meriggiola MC, Gava G. Endocrine care of transpeople part II. A review of cross-sex hormonal treatments, outcomes and adverse effects in transwomen. *Clin Endocrinol (Oxf).* 2015 Nov;83(5):607- 15. Epub 2015 Mar 25. PMID: 25692882.

Meyer J, Knorr N, Blumer D. Characterization of a self-designated transsexual population. *Arch Sex Behav* 1971 Sep;1(3):219-30. PMID: 24179067.

A-Meyer JK. Sex assignment and reassignment: intersex and gender identity disorders. Foreword. *Clin Plast Surg*. 1974 Apr;1(2):199-200. PMID: 4426156.

B-Meyer JK. Psychiatric considerations in the sexual reassignment of non-intersex individuals. *Clin Plast Surg*. 1974 Apr;1(2):275-83. PMID: 4426161.

C-Meyer JK, Hoopes JE. The gender dysphoria syndromes. A position statement on so-called "transsexualism". *Plast Reconstr Surg*. 1974 Oct;54(4):444-51. PMID: 4416283.

D- Meyer JK. Clinical variants among applicants for sex reassignment. *Arch Sex Behav.* 1974 Nov;3 (6):527-58. PMID: 4429437.

Meyer JK, Reter DJ. Sex reassignment. Follow-up. *Arch Gen Psychiatry*. 1979 Aug;36(9): 1010-5. PMID: 464739.

Meyer WJ, Finkelstein JW, Stuart CA, Webb A, Smith ER, Payer AF, Walker PA. Physical and hormonal evaluation of transsexual patients during hormonal therapy. *Arch Sex Behav*. 1981 Aug;10 (4):347-56. PMID: 6794543.

Meyer WJ, Webb A, Stuart CA, Finkelstein JW, Lawrence B, Walker PA. Physical and hormonal evaluation of transsexual patients: a longitudinal study. *Arch Sex Behav* 1986 Apr;15(2):121-38. PMID: 22051002.

Meyer-Bahlburg HF. Gender outcome in 46,XY complete androgen insensitivity syndrome: comment on T'Sjoen et al. (2010). *Arch Sex Behav.* 2010 Dec;39(6):1221-4. PMID: 20552263.

Meyer-Bahlburg HF. Gender monitoring and gender reassignment of children and adolescents with a somatic disorder of sex development. *Child Adolesc Psychiatr Clin N Am.* 2011 Oct;20(4):639-49. PMID: 22051002. Epub 2011 Sep 23.

Miach PP, Berah EF, Butcher JN, Rouse S. Utility of the MMPI-2 in assessing gender dysphoric patients. *J Pers Assess*. 2000 Oct;75(2):268-79. PMID: 11020144.

Michel A, Mormont C, Legros JJ. A psycho-endocrinological overview of transsexualism. *Eur J Endocrinol*. 2001 Oct;145(4):365-76. PMID: 11580991.

Michel A, Ansseau M, Legros J, Pitchot W, Cornet J, Mormont C. Comparisons of two groups of sex-change applicants based on the MMPI. *Psychol Rep* 2002 Aug;91(1):233-40. PMID: 12353786.

Miles C, Green R, Hines M. Estrogen treatment effects on cognition, memory and mood in male-to- female transsexuals. *Horm Behav.* 2006 Dec;50(5):708-17. Epub 2006 Aug 1. PMID: 16884726.

Miller FG, Brody H. A critique of clinical equipoise: Therapeutic misconception in the ethics of clinical trials. *Hastings Center Report*. 2003; May-June. Report 33, No. 3: 19-28. PMID: 12854452.

Miller FG. Equipoise and the Ethics of Clinical Research Revisited. *The American Journal of Bioethics.* 2006; 6:4, 59-61. PMID: 16885110.

Miller PB, Weijer C. Trust based obligations of the state and physician-researchers to patient- subjects. *J Med Ethics.* 2006 Sep;32(9):542-7. PMID: 16943338.

A-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG. CONSORT 2010 explanation and elaboration: updated guidelines for reporting parallel group randomised trials. *BMJ*. 2010 Mar 23;340:c869. PMID: 20332511.

B-Moher D, Hopewell S, Schulz KF, Montori V, Gøtzsche PC, Devereaux PJ, Elbourne D, Egger M, Altman DG; Consolidated Standards of Reporting Trials Group. CONSORT 2010 Explanation and elaboration: Updated guidelines for reporting parallel group randomised trials. *J Clin Epidemiol.* 2010 Aug;63(8):e1-37. Epub 2010 Mar 25. Erratum in *J Clin Epidemiol.* 2012 Mar;65(3):351. PMID: 20346624.

Monstrey S, Hoebeke P, Selvaggi G, Ceulemans P, Van Landuyt K, Blondeel P, Hamdi M, Roche N, Weyers S, De Cuypere G. Penile reconstruction: is the radial forearm flap really the standard technique? *Plast Reconstr Surg*. 2009 Aug;124(2):510-8. PMID: 19644267.

Monstrey S, Ceulemans P, Hoebeke P. Sex Reassignment Surgery in the Female-to-Male Transsexual. *Semin Plast Surg.* 2011 Aug;25(3):229-44. PMID: 22851915.

Moreno-Pérez O, Esteva De Antonio I; Grupo de Identidad y Diferenciación Sexual de la SEEN (GIDSEEN). [Clinical practice guidelines for assessment and treatment of transsexualism. SEEN Identity and Sexual Differentiation Group (GIDSEEN)]. *Endocrinol Nutr.* 2012 Jun-Jul;59(6):367-82. Epub 2012 Apr 26. Spanish. PMID: 22542505.

Moser C. Blanchard's Autogynephilia Theory: a critique. *J Homosex*. 2010;57(6):790-809. PMID: 20582803.

Motmans J, Meier P, Ponnet K, T'Sjoen G. Female and male transgender quality of life: socioeconomic and medical differences. *J Sex Med.* 2012 Mar;9(3):743-50. Epub 2011 Dec 21. PMID: 22188877.

Motmans J, Ponnet K, De Cuypere G. Sociodemographic characteristics of trans persons in Belgium: A secondary data analysis of medical, state, and social data. *Arch Sex Behav.* 2015 Jul;44(5):1289-99. Epub 2014 Oct 10. PMID: 25300904.

Mueller A, Haeberle L, Zollver H, Claassen T, Kronawitter D, Oppelt P, Cupisti S, Beckmann M, Dittrich R. Effects of intramuscular testosterone undecanoate on body composition and bone mineral density in female-to-male transsexuals. *J Sex Med.* 2010 Sep;7(9):3190-8. PMID: 20584125.

Murad MH, Elamin MB, Garcia MZ, Mullan RJ, Murad A, Erwin PJ, Montori VM. Hormonal therapy and sex reassignment: a systematic review and meta-analysis of quality of life and psychosocial outcomes. *Clin Endocrinol (Oxf)*. 2010 Feb;72(2):214-31. Epub 2009 May 16. PMID: 19473181.

Nanda S. The hijras of India: cultural and individual dimensions of an institutionalized third gender role. *J Homosex*. 1985 Summer;11(3-4):35-54. PMID: 4093603.

Nanda, S. (1999). *Neither man nor woman: The hijras of India*. Belmont, CA: Wadsworth Publishing.

Nanda S. (2014, 2nd edition) *Gender Diversity: Cross cultural variations*. Long Grove, IL: Waveland Press.

NIH FY 2016-2020 Strategic Plan to Advance Research on the Health and Well-being of Sexual and Gender Minorities. 2015 http://edi.nih.gov/sites/default/files/EDI_Public_files/sgm-strategic-plan.pdf

NIH-LGBT 2013: National Institutes of Health Lesbian, Gay, Bisexual, and Transgender (LGBT) Research Coordinating Committee. Consideration of the Institute of Medicine (IOM) report on the health of lesbian, gay, bisexual, and transgender (LGBT) individuals. Bethesda, MD: National Institutes of Health; 2013. http://report.nih.gov/UploadDocs/LGBT%20Health%20Report_FINAL_2013-01-03-508%20compliant.pdf.

Nemoto T, Iwamoto M, Perngparn U, Areesantichai C, Kamitani E, Sakata M. HIV-related risk behaviors among kathoey (male-to-female transgender) sex workers in Bangkok, Thailand. *AIDS Care.* 2012;24(2):210-9. Epub 2011 Jul 25. PMID: 21780964.

Newfield E, Hart S, Dibble S, Kohler L. Female-to-male transgender quality of life. *Qual Life Res.* 2006 Nov;15(9):1447-57. Epub 2006 Jun 7. PMID: 16758113.

Newsom J. Latent variable. *USP 655 SEM. Winter 2015.* (Portland State quantitative methods)www.upa.pdx.edu/IOA/newsom/semclass/ho_latent.pdf.

Nieder T, Herff M, Cerwenka S, Preuss W, Cohen-Kettenis P, De Cuypere G, Haraldsen I, Richter- Appelt H. Age of onset and sexual orientation in transsexual males and females. *J Sex Med.* 2011 Mar;8(3):783-91. Epub 2010 Dec 8. PMID: 21143416.

Nuttbrock L, Hwahng S, Bockting W, Rosenblum A, Mason M, Macri M, Becker J. Lifetime risk factors for HIV/sexually transmitted infections among male-to-female transgender persons. J *Acquir Immune Defic Syndr.* 2009 Nov 1;52(3):417-21. PMID: 19550351.

Nuttbrock L, Bockting W, Rosenblum A, Hwahng S, Mason M, Macri M, Becker J. Gender abuse, depressive symptoms, and HIV and other sexually transmitted infections among male-to-female transgender persons: a three-year prospective study. *Am J Public Health* 2013 Feb;103(2):300-7. Epub 2012 Jun 14. Erratum in: *Am J Public Health.* 2015 Feb;105(2):e5. PMID: 22698023.

NZHTA 2002: Day P. Tech Brief Series. *Trans-gender reassignment surgery.* New Zealand Health technpology Assessment. (NZHTA). The clearinghouse forhealth outcomes and health technology assessment. February 2002 Volume 1 Number 1. http://nzhta.chmeds.ac.nz/publications/trans_gender.pdf.

Odgaard-Jensen J, Vist GE, Timmer A, Kunz R, Akl EA, Schünemann H, Briel M, Nordmann AJ, Pregno S, Oxman AD. Randomisation to protect against selection bias in healthcare trials. *Cochrane Database Syst Rev*.2011 Apr 13;(4):MR000012. PMID: 21491415.

O'Gorman EC. A preliminary report on transsexualism in Northern Ireland. *Ulster Med J.* 1981;50 (1):46–9. PMID: 7233635.

Okabe N, Sato T, Matsumoto Y, Ido Y, Terada S, Kuroda S. Clinical characteristics of patients with gender identity disorder at a Japanese gender identity disorder clinic. *Psychiatry Res*. 2008 Jan 15;157 (1-3):315-8. Epub 2007 Oct 23. PMID: 17959255.

Olson J, Forbes C, Belzer M. Management of the transgender adolescent. *Arch Pediatr Adolesc Med.* 2011 Feb;165(2):171-6. PMID: 21300658.

Olsson SE, Jansson I, Moller A. Men as women. Experiences from five case after administrative, hormonal, and

surgical treatment. *Nord J Psychiatry.* 1996;50(5):395-9. (Not in PubMed)

Olsson S, Möller A. On the incidence and sex ratio of transsexualism in Sweden, 1972-2002. *Arch Sex Behav.* 2003 Aug;32(4):381-6. PMID: 12856899.

Olsson S, Möller A. Regret after sex reassignment surgery in a male-to-female transsexual: a long- term follow-up. *Arch Sex Behav.* 2006 Aug;35(4):501-6. Epub 2006 Aug 11. PMID: 16900416.

Operario D, Nemoto T. HIV in transgender communities: syndemic dynamics and a need for multicomponent interventions. *J Acquir Immune Defic Syndr.* 2010 Dec;55 Suppl 2:S91-3. PMID: 21406995.

Operario D, Nemoto T, Iwamoto M, Moore T. Unprotected sexual behavior and HIV risk in the context of primary partnerships for transgender women. *AIDS Behav.* 2011 Apr;15(3):674-82. PMID: 21604064.

Orel N. Investigating the needs and concerns of lesbian, gay, bisexual, and transgender older adults: the use of qualitative and quantitative methodology. *J Homosex.* 2014;61(1):53-78. PMID: 24313253.

Oster JM, Shastri P, Geyer C. Cerebral venous sinus thrombosis after gender reassignment surgery. *Gend Med*. 2010 Jun;7(3):270-5. PMID: 20638632.

Ott J, van Trotsenburg M, Kaufmann U, Schrögendorfer K, Haslik W, Huber JC, Wenzl R. Combined hysterectomy/salpingo-oophorectomy and mastectomy is a safe and valuable procedure for female-to- male transsexuals. *J Sex Med.* 2010 Jun;7(6):2130-8. Epub 2010 Mar 3. PMID: 20233279.

Paap MC, Meijer RR, Cohen-Kettenis PT, Richter-Appelt H, de Cuypere G, Kreukels BP, Pedersen G, Karterud S, Malt UF, Haraldsen IR. Why the factorial structure of the SCL-90-R is unstable: comparing patient groups with different levels of psychological distress using Mokken Scale Analysis. *Psychiatry Res.* 2012 Dec 30;200(2-3):819-26. Epub 2012 Apr 9. PMID: 22494703.

Palmer D, Dietsch A, Searl J. Endoscopic and stroboscopic presentation of the larynx in male-to- female transsexual persons. *J Voice.* 2012 Jan;26(1):117-26. Epub 2011 Apr 7. PMID: 21477987.

Palmer JR, Wise LA, Robboy SJ, Titus-Ernstoff L, Noller KL, Herbst AL, Troisi R, Hoover RN. Hypospadias in sons of women exposed to diethylstilbestrol in utero. *Epidemiology.* 2005 Jul;16 (4):583-6. PMID: 15951681.

Palmer JR, Herbst AL, Noller KL, Boggs DA, Troisi R, Titus-Ernstoff L, Hatch EE, Wise LA, Strohsnitter WC, Hoover RN. Urogenital abnormalities in men exposed to diethylstilbestrol in utero: a cohort study. *Environ Health.* 2009 Aug 18;8:37. PMID: 19689815.

Pauly IB. The current status of the change of sex operation. *J Nerv Ment Dis.* 1968 Nov;147(5):460- 71. PMID: 5726920.

Pauly IB. Outcome of sex reassignment surgery for transsexuals. *Aust N Z J Psychiatry* 1981 Mar;15 (1):45-51. PMID: 6942832.

Pelusi C, Costantino A, Martelli V, Lambertini M, Bazzocchi A, Ponti F, Battista G, Venturoli S, Meriggiola M. Effects of three different testosterone formulations in female-to-male transsexual persons. *J Sex Med.* 2014 Dec;11(12):3002-11. Epub 2014 Sep 24. PMID: 25250780.

Perez KM, Titus-Ernstoff L, Hatch EE, Troisi R, Wactawski-Wende J, Palmer JR, Noller K, Hoover RN; National Cancer Institute's DES Follow-up Study Group. Reproductive outcomes in men with prenatal exposure to diethylstilbestrol. *Fertil Steril.* 2005 Dec;84(6):1649-56. PMID: 16359959.

Perrone A, Cerpolini S, Maria Salfi N, Ceccarelli C, De Giorgi L, Formelli G, Casadio P, Ghi T, Pelusi G, Pelusi C, Meriggiola M. Effect of long-term testosterone administration on the endometrium of female-to-male (FtM) transsexuals. *J Sex Med.* 2009 Nov;6(11):3193-200. Epub 2009 Jun 29. PMID: 19570144.

Persson D. Unique challenges of transgender aging: implications from the literature. *J Gerontol Soc Work.* 2009 Aug-Sep;52(6):633-46. PMID: 19598043.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 1: conceptual and definitional issues in psychiatric diagnosis. *Philos Ethics Humanit Med.* 2012 Jan 13;7:3. PMID: 22243994.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 2: Issues of conservatism and pragmatism in psychiatric diagnosis. *Philos Ethics Humanit Med*. 2012 Jul 5;7:8. PMID: 22512887.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue part 3: issues and alternative approaches in psychiatric diagnosis. *Philos Ethics Humanit Med.* 2012 May 23;7:9. PMID: 22621419.

Phillips J, Frances A, Cerullo MA, Chardavoyne J, Decker HS, First MB, Ghaemi N, Greenberg G, Hinderliter AC, Kinghorn WA, LoBello SG, Martin EB, Mishara AL, Paris J, Pierre JM, Pies RW, Pincus HA, Porter D, Pouncey C, Schwartz MA, Szasz T, Wakefield JC, Waterman GS, Whooley O, Zachar P. The six most essential questions in psychiatric diagnosis: a pluralogue. Part 4: general conclusion. *Philos Ethics Humanit Med*. 2012 Dec 18;7:14. PMID: 23249629.

PRO Guidance 2009: U.S. Department of Health and Human Services; Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER), Center for Devices and Radiological Health (CDRH). *Guidance for Industry. Patient-reported outcome measures: Use in medical product development to support labeling claims.* December 2009. http://www.fda.gov/downloads/Drugs/.../Guidances/UCM193282.pdf.

Quirós C, Patrascioiu I, Mora M, Aranda GB, Hanzu FA, Gómez-Gil E, Godás T, Halperin I. Effect of cross-sex hormone treatment on cardiovascular risk factors in transsexual individuals. Experience in a specialized unit in Catalonia. *Endocrinol Nutr*. 2015 May;62(5):210-6. Epub 2015 Mar 16. PMID: 25790747.

Rachlin Katherine. Factors Which Influence Individual's Decisions When Considering Female-To- Male Genital Reconstructive Surgery. *IJT.* 1999 Jul-Sept;3(3). (Not in PubMed) http://www.symposion.com/ijt/ijt990302.htm

Rakic Z, Starcevic V, Maric J, Kelin K. The outcome of sex reassignment surgery in Belgrade: 32 patients of both sexes. *Arch Sex Behav*. 1996 Oct;25(5):515-25. PMID: 8899143.

A-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Segovia S, Gomez Á, Guillamon A. White matter microstructure in female to male transsexuals before cross-sex hormonal treatment. A diffusion tensor imaging study. *J Psychiatr Res.* 2011 Feb;45(2):199-204. Epub 2010 Jun 8. PMID: 20562024.

B-Rametti G, Carrillo B, Gómez-Gil E, Junque C, Zubiarre-Elorza L, Segovia S, Gomez Á, Guillamon A. The microstructure of white matter in male to female transsexuals before cross-sex hormonal treatment. A DTI study. *J Psychiatr Res.* 2011 Jul;45(7):949-54. Epub 2010 Dec 30. PMID: 21195418.

Randell JB. Transvestitism and trans-sexualism. A study of 50 cases. *Br Med J*. 1959 Dec 26; 2 (5164): 1448–52. PMID: 14436154.

Randell J. Indications for reassignment surgery. *Archives of Sexual Behavior*. 1971; 1(2):153-61. (Not in PubMed)

Randell J. (1969). *Pre-operative and post-operative status of transsexuals* (Chapter 26) in Green R, Money J (eds):Trans-sexualism and Sex reassignment. Baltimore: Johns Hopkins Press.

Rappaport R. Intersex management: what is achieved and what is needed. Commentary to Thyen et al.: epidemiology and initial management of ambiguous genitalia at birth in Germany (*Horm Res.* 2006;66:195-203). *Horm Res*. 2006;66(4):204-5. Epub 2006 Jul 27. PMID: 16877871.

Reed HM. Aesthetic and functional male to female genital and perineal surgery: feminizing vaginoplasty. *Semin Plast Surg*. 2011 May;25(2):163-74. PMID: 22547974.

Rehman J, Lazer S, Benet AE, Schaefer LC, Melman A. The reported sex and surgery satisfactions of 28 postoperative male-to-female transsexual patients. *Arch Sex Behav.* 1999 Feb;28(1):71-89. PMID: 10097806.

Reisner S, Poteat T, Keatley J, Cabral M, Mothopeng T, Dunham E, Holland C, Max R, Baral S. Global heath burden and needs of transgender populations: a review. *Lancet*. Epub 16 June 2016. http://dx.doi.org/10.1016/S0140-6736(16)00684-X

Roback HB, Lothstein LM. The female mid-life sex change applicant: a comparison with younger female transsexuals and older male sex change applicants. *Arch Sex Behav*. 1986 Oct;15(5):401-15. PMID: 3789904.

Roscoe W. (1991). *The Zuni Man-Woman*. Albuquerque: University of New Mexico Press.

Roscoe, W. (1998). *Changing Ones: Third and Fourth Genders in Native North America*. New York: St. Martin's Press.

Rosen R, Brown C, Heiman J, Leiblum S, Meston C, Shabsigh R, Ferguson D, D'Agostino R Jr. The Female Sexual Function Index (FSFI): a multidimensional self-report instrument for the assessment of female sexual function. *J Sex Marital Ther*. 2000 Apr-Jun;26(2):191-208. PMID: 10782451.

Rosenberg, M. (1965). *Society and the Adolescent Self-Image*, Princeton University Press, Princeton.

Ross MW, Wålinder J, Lundström B, Thuwe I. Cross-cultural approaches to transsexualism. A comparison between Sweden and Australia*. Acta Psychiatr Scand.* 1981 Jan;63(1):75-82. PMID: 7234467.

Ross MW, Need JA. Effects of adequacy of gender reassignment surgery on psychological adjustment: a follow-up of fourteen male-to-female patients. *Arch Sex Behav.* 1989 Apr;18(2):145-53. PMID: 2712690.

Rubin SO. Sex-reassignment surgery male-to-female. Review, own results and report of a new technique using the glans penis as a pseudoclitoris. *Scand J Urol Nephrol Suppl.* 1993;154:1-28. PMID: 8140401.

Ruppin U, Pfäfflin F. Long-term follow-up of adults with gender identity disorder. *Arch Sex Behav.* 2015 Jul;44(5):1321-9. Epub 2015 Feb 18. PMID: 25690443.

Russell ST, Ryan C, Toomey RB, Diaz RM, Sanchez J. Lesbian, gay, bisexual, and transgender adolescent school victimization: implications for young adult health and adjustment. *J Sch Health.* 2011 May;81(5):223-30. PMID: 21517860.

Safer J, Tangpricha V. Out of the shadows: it is time to mainstream treatment for transgender patients. *Endocr Pract.* 2008 Mar;14(2):248-50. PMID: 18308667.

Salkind MR. Beck depression inventory in general practice. *J R Coll Gen Pract*. 1969 Nov;18 (88):267-71. PMID: 5350525.

Salvador J, Massuda R, Andreazza T, Koff WJ, Silveira E, Kreische F, de Souza L, de Oliveira MH, Rosito T, Fernandes BS, Lobato MI. Minimum 2-year follow up of sex reassignment surgery in Brazilian male-to-female transsexuals. *Psychiatry Clin Neurosci.* 2012 Jun;66(4):371-2. PMID: 22624747.

Savic I, Garcia-Falgueras A, Swaab DF. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Prog Brain Res*. 2010;186:41-62. PMID: 21094885.

Schaeffer CE. The Kutenai female berdache: Courier, guide, prophetess, and warrior. *Ethnohistory*. 1965;12 (3): 193–236. (Not in PubMed)

Schlatterer K, Yassouridis A, von Werder K, Poland D, Kemper J, Stalla GK. A follow-up study for estimating the effectiveness of a cross-gender hormone substitution therapy on transsexual patients. *Arch Sex Behav*. 1998 Oct;27(5):475-92. PMID: 9795728.

Schroder M, Carroll RA. New Women: Sexological outcomes of male-to-female gender reassignment surgery. JSET. 1999;24(3):137-46. (Not in PubMed)

Seal L, Franklin S, Richards C, Shishkareva A, Sinclaire C, Barrett J. Predictive markers for mammoplasty and a comparison of side effect profiles in transwomen taking various hormonal regimens. *J Clin Endocrinol Metab.* 2012 Dec;97(12):4422-8. Epub 2012 Oct 9. PMID: 23055547.

Selvaggi G, Monstrey S, Ceulemans P, T'Sjoen G, De Cuypere G, Hoebeke P. Genital sensitivity after sex reassignment surgery in transsexual patients. *Ann Plast Surg*. 2007 Apr;58(4):427-33. PMID: 17413887.

Selvaggi G, Bellringer J. Gender reassignment surgery: an overview. *Nat Rev Urol.* 2011 May;8 (5):274-82. Epub 2011 Apr 12. PMID: 21487386.

Selvaggi G, Dhejne C, Landen M, Elander A. The 2011 WPATH Standards of Care and Penile Reconstruction in Female-to-Male Transsexual Individuals. *Adv Urol*. 2012;2012:581712. Epub 2012 May 14. PMID: 22654902.

Shao T, Grossbard ML, Klein P. Breast cancer in female-to-male transsexuals: two cases with a review of physiology and management. *Clin Breast Cancer.* 2011 Dec;11(6):417-9. Epub 2011 Aug 10. PMID: 21831723.

Shechner T. Gender identity disorder: a literature review from a developmental perspective. *Isr J Psychiatry Relat Sci*. 2010;47(2):132-8. PMID: 20733256.

Shields J, Cohen R, Glassman J, Whitaker K, Franks H, Bertolini I. Estimating population size and demographic characteristics of lesbian, gay, bisexual, and transgender youth in middle school. *J Adolesc Health*. 2013 Feb;52(2):248-50. Epub 2012 Aug 15. PMID: 23332492.

Simopoulos E, Khin Khin E. Fundamental principles inherent in the comprehensive care of transgender inmates. *J Am Acad Psychiatry Law.* 2014;42(1):26-36. PMID: 24618516.

Slabbekoorn D, van Goozen SH, Sanders G, Gooren LJ, Cohen-Kettenis PT. The dermatoglyphic characteristics of transsexuals: is there evidence for an organizing effect of sex hormones. *Psychoneuroendocrinology.* 2000 May;25(4):365-75. PMID: 10725613.

Slabbekoorn D., Van Goozen S., Gooren L., Cohen-Kettenis P. Effects of Cross-Sex Hormone Treatment on Emotionality in Transsexuals. *IJT.* 2001 Jul-Sept; 5(3):20 pages.http://www.symposion.com/ijt/ijtvo05no03_02.htm.

Slaby RG, Frey KS. Development of gender constancy and selective attention to same-sex models. *Child Dev.* 1975 Dec;46(4):849-56. PMID: 1201664.

Smilkstein G. The family APGAR: a proposal for a family function test and its use by physicians. *J Fam Pract.* 1978 Jun;6(6):1231-9. PMID: 660126.

Smilkstein G, Ashworth C, Montano D. Validity and reliability of the family APGAR as a test of family function. *J Fam Pract.* 1982 Aug;15(2):303-11. PMID:7097168.

Smith YL, van Goozen SH, Cohen-Kettenis PT. Adolescents with gender identity disorder who were accepted or rejected for sex reassignment surgery: a prospective follow-up study. *J Am Acad Child Adolesc Psychiatry.* 2001 Apr;40(4):472-81. PMID: 11314574.

A-Smith YL, Van Goozen SH, Kuiper AJ, Cohen-Kettenis PT. Sex reassignment: outcomes and predictors of treatment for adolescent and adult transsexuals. *Psychol Med.* 2005 Jan;35(1):89-99. PMID: 15842032.

B-Smith Y, van Goozen S, Kuiper A, Cohen-Kettenis P. Transsexual subtypes: clinical and theoretical significance. *Psychiatry Res.* 2005 Dec 15;137(3):151-60. Epub 2005 Nov 17. PMID: 16298429.

A-Sørensen T. A follow-up study of operated transsexual males. *Acta Psychiatr Scand.* 1981 May;63 (5):486-503. PMID: 7315491.

B-Sørensen T. A follow-up study of operated transsexual females. *Acta Psychiatr Scand.* 1981 Jul;64 (1):50-64. PMID: 7315494.

Sørensen T, Hertoft P. Male and female transsexualism: the Danish experience with 37 patients. *Arch Sex Behav* 1982 Apr;11(2):133-55. PMID: 7125885.

Steensma TD, McGuire JK, Kreukels BP, Beekman AJ, Cohen-Kettenis PT. Factors associated with desistence and persistence of childhood gender dysphoria: a quantitative follow-up study. *J Am Acad Child Adolesc Psychiatry*. 2013 Jun;52(6):582-90. Epub 2013 May 3. PMID: 23702447.

Stieglitz KA. Development, risk, and resilience of transgender youth. *J Assoc Nurses AIDS Care.* 2010 May-Jun;21(3):192-206Epub 2010 Mar 29. PMID: 20347346.

Steinle K. Hormonal management of the female-to-male transgender patient. *J Midwifery Womens Health.* 2011 May-Jun;56(3):293-302. PMID: 21535376.

Stephens SC, Bernstein KT, Philip SS. Male to female and female to male transgender persons have different sexual risk behaviors yet similar rates of STDs and HIV. *AIDS Behav.* 2011 Apr;15(3):683-6. PMID: 20694509.

Stinson B. A study of twelve applicants for transsexual surgery. *Ohio State Med J.* 1972 Mar;68 (3):245-9. PMID: 4401539.

Stojanovic B, Djordjevic ML. Anatomy of the clitoris and its impact on neophalloplasty (metoidioplasty) in female transgenders. *Clin Anat.* 2015 Apr;28(3):368-75. Epub 2015 Mar 4. PMID: 25740576.

Strauss B, Richter-Appelt H (1995) *Fragebogen zur Beurteilung des eigenen Körpers (FBeK), Handanweisung*. Hogrefe, Göttingen Bern Toronto Seattle.

Stroumsa D. The state of transgender health care: policy, law, and medical frameworks. *Am J Public Health .* 2014 Mar;104(3):e31-8. Epub 2014 Jan 16. PMID: 24432926.

Sultan B. Transsexual prisoners: how much treatment is enough? *New Engl Law Rev.* 2003 Summer;37(4):1195-230. PMID: 15295855.

Sundbom E, Bodlund O. Prediction of outcome in transsexualism by means of the Defense Mechanism Test and multivariate modeling: a pilot study. *Percept Mot Skills.* 1999 Feb;88(1):3-20. PMID: 10214627.

Swaab DF. Sexual differentiation of the human brain: relevance for gender identity, transsexualism and sexual orientation. *Gynecol Endocrinol.* 2004 Dec;19(6):301-12. PMID: 15724806.

Swaab DF, Garcia-Falgueras A. Sexual differentiation of the human brain in relation to gender identity and sexual orientation. *Funct Neurol.* 2009 Jan-Mar;24(1):17-28. PMID: 19403051.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Suicidal ideation among patients with gender identity disorder. *Psychiatry Res.* 2011 Nov 30;190(1):159-62. Epub 2011 May 25. PMID: 21612827.

Terada S, Matsumoto Y, Sato T, Okabe N, Kishimoto Y, Uchitomi Y. Factors predicting psychiatric co-morbidity in gender-dysphoric adults. *Psychiatry Res.* 2012 Dec 30;200(2-3):469-74. Epub 2012 Aug 9. PMID: 22884214.

Titus-Ernstoff L, Perez K, Hatch EE, Troisi R, Palmer JR, Hartge P, Hyer M, Kaufman R, Adam E, Strohsnitter W, Noller K, Pickett KE, Hoover R. Psychosexual characteristics of men and women exposed prenatally to diethylstilbestrol. *Epidemiology*. 2003 Mar;14(2):155-60. PMID: 12606880.

Torres A, Gómez-Gil E, Vidal A, Puig O, Boget T, Salamero M. Gender differences in cognitive functions and influence of sex hormones. *Actas Esp Psiquiatr*. 2006 Nov-Dec;34(6):408-15. Spanish. PMID: 17117339.

Tourbach SA, Hunter-Smith D, Morrison WA. Long anterior urethral reconstruction using a jejunal free flap. *J Plast Surg Hand Surg*. 2011 Feb;45(1):54-6. PMID: 21446801.

Traish AM, Gooren LJ. Safety of physiological testosterone therapy in women: lessons from female- to-male transsexuals (FMT) treated with pharmacological testosterone therapy. *J Sex Med*. 2010 Nov;7(11):3758-64. Epub 2010 Aug 16. PMID: 20722789.

Trentacosti AM. *Epoietin alpha: FDA overview of patient reported outcome (PRO) claims*. 2007. www.fda.gov/ohrms/dockets/ac/07/slides/2007-4315s1-09-FDA-Trentacosti.ppt.

Trum H, Hoebeke P, Gooren L. Sex reassignment of transsexual people from a gynecologist's and urologist's perspective. *Acta Obstet Gynecol Scand.* 2015 Jun;94(6):563-7. Epub 2015 Mar 29. PMID: 25721104.

T'Sjoen G, Weyers S, Taes Y, Lapauw B, Toye K, Goemaere S, Kaufman J. Prevalence of low bone mass in relation to estrogen treatment and body composition in male-to-female transsexual persons. *J Clin Densitom.* 2009 Jul-Sep;12(3):306-13. Epub 2009 Jan 3. PMID: 19121966.

T'Sjoen G, De Cuypere G, Monstrey S, Hoebeke P, Freedman F, Appari M, Holterhus P, Van Borsel J, Cools M. Male gender identity in complete androgen insensitivity syndrome. *Arch Sex Behav.* 2011 Jun;40(3):635-8. Epub 2010 Apr 1. PMID: 20358272.

TSjoen G, Van Caenegem E, Wierckx K. Transgenderism and reproduction. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):575-9. PMID: 24468761.

Tsoi WF, Kok LP, Long FY. Male transsexualism in Singapore: a description of 56 cases. *Br J Psychiatry*. 1977 Oct;131:405-9. PMID: 922268.

Tsoi WF. The prevalence of transsexualism in Singapore. *Acta Psychiatr Scand.* 1988 Oct;78 (4):501-4. PMID: 3265846.

Tsoi WF. Male and female transsexuals: a comparison. *Singapore Med J.* 1992 Apr;33(2):182-5. PMID: 1621125.

Tsoi WF. Follow-up study of transsexuals after sex-reassignment surgery. *Singapore Med J.* 1993 Dec;34(6):515-7. PMID: 8153713.

Tsoi WF, Kok LP, Yeo KL, Ratnam SS. Follow-up study of female transsexuals. *Ann Acad Med Singapore.* 1995 Sep;24(5):664-7. PMID: 8579306.

Tsushima WT, Wedding D. MMPI results of male candidates for transsexual surgery. *J Pers Assess.* 1979. Aug;43(4):385-7. PMID: 383946.

Tugnet N, Goddard JC, Vickery RM, Khoosal D, Terry TR. Current management of male-to-female gender identity disorder in the UK. *Postgrad Med J*. 2007 Oct;83(984):638-42. PMID: 17916872.

Udeze B, Abdelmawla N, Khoosal D, Terry T. Psychological functions in male-to-female people before and after surgery. *Sexual and Relationship Therapy*. 2008 May; 23(2):141-5. (Not in PubMed)

Urban R, Teng N, Kapp D. Gynecologic malignancies in female-to-male transgender patients: the need of original gender surveillance. *Am J Obstet Gynecol.* 2011 May;204(5):e9-e12. Epub 2011 Feb 26. PMID: 21354550.

Vacchiano RB, Strauss PS. The construct validity of the Tennessee self concept scale. *J Clin Psychol.* 1968 Jul;24(3):323-6. PMID: 5661752.

Van Caenegem E, Wierckx K, Taes Y, Dedecker D, Van de Peer F, Toye K, Kaufman J, T'Sjoen G. Bone mass, bone geometry, and body composition in female-to-male transsexual persons after long-term cross-sex hormonal therapy. *J Clin Endocrinol Metab.* 2012 Jul;97(7):2503-11. Epub 2012 May 7. PMID: 22564669.

A-Van Caenegem E, Taes Y, Wierckx K, Vandewalle S, Toye K, Kaufman J, Schreiner T, Haraldsen I, T'Sjoen G. Low bone mass is prevalent in male-to-female transsexual persons before the start of cross-sex hormonal therapy and gonadectomy. *Bone*. 2013 May;54(1):92-7. Epub 2013 Jan 28. PMID: 23369987.

B-Van Caenegem E, Verhaeghe E, Taes Y, Wierckx K, Toye K, Goemaere S, Zmierczak H, Hoebeke P, Monstrey S, T'Sjoen G. Long-term evaluation of donor-site morbidity after radial forearm flap phalloplasty for transsexual men. *J Sex Med.* 2013 Jun;10(6):1644-51. Epub 2013 Mar 27. PMID: 23534878.

Van Caenegem E, Wierckx K, Taes Y, Schreiner T, Vandewalle S, Toye K, Lapauw B, Kaufman J, T'Sjoen G. Body composition, bone turnover, and bone mass in trans men during testosterone treatment: 1-year follow-up data from a prospective case-controlled study (ENIGI). *Eur J Endocrinol*. 2015 Feb;172(2):163-71. PMID: 25550352.

Van Caenegem E, Wierckx K, Elaut E, Buysse A, Dewaele A, Van Nieuwerburgh F, De Cuypere G, T'Sjoen G. Prevalence of Gender Nonconformity inFlanders, Belgium. *Arch Sex Behav.* 2015 Jul;44 (5):1281-7. Epub 2015 Jan 15. PMID: 25588709.

VanderLaan DP, Vokey JR, Vasey PL. Is Transgendered Male Androphilia Familial in Non-Western Populations? The Case of a Samoan Village. *Arch Sex Behav.* 2013; 42:361–70. PMID: 23187702.

Van Kesteren PJ, Gooren LJ, Megens JA. An epidemiological and demographic study of transsexuals in The Netherlands. *Arch Sex Behav.* 1996 Dec;25(6):589-600. PMID: 8931882.

Van Kesteren PJ, Asscheman H, Megens JA, Gooren LJ. Mortality and morbidity in transsexual subjects treated with cross-sex hormones. *Clin Endocrinol (Oxf).* 1997 Sep;47(3):337-42. PMID: 9373456.

Vasey PL, Bartlett NH. What can the Samoan "Fa'afafine" teach us about the Western concept of gender identity disorder in childhood? *Perspect Biol Med.* 2007 Autumn;50(4):481-90. PMID: 17951883.

Veatch RM. Indifference of subjects: An alternative to equipoise in randomized clinical trials. *Soc Phil Policy*. 2002; 19:295-323. PMID: 12678091.

Veale J. Prevalence of transsexualism among New Zealand passport holders. *Aust N Z J Psychiatry*. 2008 Oct;42(10):887-9. PMID: 18777233.

Vrouenraets LJ, Fredriks AM, Hannema SE, Cohen-Kettenis PT, de Vries MC. Early Medical Treatment of Children and Adolescents With Gender Dysphoria: An Empirical Ethical Study. *J Adolesc Health*. 2015 Oct;57(4):367-73. Epub 2015 Jun 25. PMID: 26119518.

Vujovic S, Popovic S, Sbutega-Milosevic G, Djordjevic M, Gooren L. Transsexualism in Serbia: a twenty-year follow-up study. *J Sex Med.* 2009 Apr;6(4):1018-23. Epub 2008 Mar 4. PMID: 18331254.

Vujović S, Popović S, Mrvošević Marojević L, Ivović M, Tančić-Gajić M, Stojanović M, Marina LV, Barać M, Barać B, Kovačević M, Duišin D, Barišić J, Djordjević ML, Micić D. Finger length ratios in Serbian transsexuals. *Scientific World Journal.* 2014 May 20;2014:Article 763563. 4 pages. PMID: 24982993.

Walinder J, Thuwe I. *A social-psychiatric follow- up study of 24 sex-reassigned transsexuals*. Gothenburg: Scandinavian University Books, Akademiforlaget. 1975.

Walinder J, Lundstrom B, Thuwe I. Prognostic factors in the assessment of male transsexuals for sex reassignment. *Br J Psychiatry.* 1978:132: 16-20. (Not in PubMed)

Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care.* 1992 Jun;30(6):473-83. PMID: 1593914.

Watson D, Friend R. Measurement of social-evaluative anxiety. *J Consult Clin Psychol*. 1969 Aug;33(4):448-57. PMID: 5810590.

Winter S, Diamond M, Green J, Karasic D, Reed T, Whittle S, Wylie K. Transgender people: health at the margins of society. *Lancet*. Epub 16 June 2016 http://dx.doi.org/10.1016/S0140-6736(16)00683-8

Weigert R, Frison E, Sessiecq Q, Al Mutairi K, Casoli V. Patient satisfaction with breasts and psychosocial, sexual, and physical well-being after breast augmentation in male-to-female transsexuals. *Plast Reconstr Surg*. 2013 Dec;132(6):1421-9. PMID: 24281571.

A-Weyers S, Elaut E, De Sutter P, Gerris J, T'Sjoen G, Heylens G, De Cuypere G, Verstraelen H. Long-term assessment of the physical, mental, and sexual health among transsexual women. *J Sex Med.* 2009 Mar;6(3):752-60. Epub 2008 Nov 17. PMID: 19040622.

B-Weyers S, Decaestecker K, Verstraelen H, Monstrey S, T'Sjoen G, Gerris J, Hoebeke P, Villeirs G. Clinical and transvaginal sonographic evaluation of the prostate in transsexual women. *Urology.* 2009 Jul;74(1):191-6. Epub 2009 Apr 23. PMID: 19395005.

WHO 1996: Harper A. Manual for World Health Organization Quaility of Life Abbreviated. Director Dr. J. Orley. http://www.who.int/mental_health/media/en/76.pdf.

WHO 2011: Carlos F. Caceres CF, GerbaseA, Ying-Ru Lo Y-R, Rodolph M (key drafters). *Prevention and treatment of HIV and other sexually transmitted infections among men who have sex with other men and transgender people.Recommendations for a public health approach*. World Health Organization. 2011. http://www.who.int/hiv/pub/guidelines/msm_guidelines2011/en/.

WHO 2014: Chris Beyrer C, Kamarulzaman A (co-chairs.) World Health Organization. *Consolidated guidelines on HIV prevention, diagnosis, treatment, and care for key populations*. July 2014. www.who.int/hiv/pub/guidelines/keypopulations/en/.

WHO 2015: Poteat T, Keatley J. (key drafters). *Policy Brief: Transgender People and HIV.* World Health Organization. July 2015. http://www.who.int/hiv/pub/transgender/transgender-hiv-policy/en/.

Wiegel M, Meston C, Rosen R. The female sexual function index (FSFI): cross-validation and development of clinical cutoff scores. *J Sex Marital Ther.* 2005 Jan-Feb;31(1):1-20. PMID: 15841702.

A-Wierckx K, Elaut E, Van Caenegem E, Van De Peer F, Dedecker D, Van Houdenhove E, T'Sjoen G. Sexual desire in female-to-male transsexual persons: exploration of the role of testosterone administration. *Eur J Endocrinol*. 2011 Aug;165(2):331-7. Epub 2011 May 20. PMID: 21602316.

B-Wierckx K, Van Caenegem E, Elaut E, Dedecker D, Van de Peer F, Toye K, Weyers S, Hoebeke P, Monstrey S, De Cuypere G, T'Sjoen G. Quality of life and sexual health after sex reassignment surgery in transsexual men. *J Sex Med*. 2011 Dec;8(12):3379-88. Epub 2011 Jun 23. PMID: 21699661.

Wylie K, Knudson G, Khan S, Bonierbale M, Watanyusakul S, Baral S. Serving transgender people: clinical care considerations and service delivery models in transgender health. *Lancet*. Epub 16 June 2016. http://dx.doi.org/10.1016/S0140-6736(16)00682-6

A-Wierckx K, Van Caenegem E, Pennings G, Elaut E, Dedecker D, Van de Peer F, Weyers S, De Sutter P, T'Sjoen G. Reproductive wish in transsexual men. *Hum Reprod.* 2012 Feb;27(2):483-7. Epub 2011 Nov 28. PMID: 22128292.

B-Wierckx K, Mueller S, Weyers S, Van Caenegem E, Roef G, Heylens G, T'Sjoen G. Long-term evaluation of cross -sex hormone treatment in transsexual persons. *J Sex Med.* 2012 Oct;9(10):2641- 51. Epub 2012 Aug 20. PMID: 22906135.

C-Wierckx K, Stuyver I, Weyers S, Hamada A, Agarwal A, De Sutter P, T'Sjoen G. Sperm freezing in transsexual women. *Arch Sex Behav*. 2012 Oct;41(5):1069-71. PMID: 22968492.

Wierckx K, Elaut E, Declercq E, Heylens G, De Cuypere G, Taes Y, Kaufman J, T'Sjoen G. Prevalence of cardiovascular disease and cancer during cross-sex hormone therapy in a large cohort of trans persons: a case-control study. *Eur J Endocrinol*. 2013 Oct;169(4):471-8. Epub 2013 Sep 13. PMID: 23904280.

A-Wierckx K, Elaut E, Van Hoorde B, Heylens G, De Cuypere G, Monstrey S, Weyers S, Hoebeke P, T'Sjoen G. Sexual desire in trans persons: associations with sex reassignment treatment. *J Sex Med.* 2014 Jan;11(1):107-18. Epub 2013 Oct 24. PMID: 24165564.

B-Wierckx K, Gooren L, T'Sjoen G. Clinical review: Breast development in trans women receiving cross-sex hormones. *J Sex Med.* 2014 May;11(5):1240-7. Epub 2014 Mar 12. PMID: 24618412.

Williamson C. Providing care to transgender persons: a clinical approach to primary care, hormones, and HIV management. *J Assoc Nurses AIDS Care*. 2010 May-Jun;21(3):221-9. Epub 2010 Apr 3. PMID: 20363651.

Wilson CA, Davies DC. The control of sexual differentiation of the reproductive system and brain. *Reproduction.* 2007 Feb;133(2):331-59. PMID: 17307903.

Wilson EC, Garofalo R, Harris DR, Belzer M. Sexual risk taking among transgender male-to-female youths with different partner types. *Am J Public Health*. 2010 Aug;100(8):1500-5. Epub 2009 Nov 12. PMID: 20622176.

Wilson E, Pant SB, Comfort M, Ekstrand M. Stigma and HIV risk among Metis in Nepal. *Cult Health Sex.* 2011 Mar;13(3):253-66. PMID: 21058085.

Wilson P, Sharp C, Carr S.The prevalence of gender dysphoria in Scotland: a primary care study. *Brit J Gen Pract*. 1999; 49 (449): 991–2. PMID: 10824346.

Wilson RC, Nimkarn S, Dumic M, Obeid J, Azar MR, Najmabadi H, Saffari F, New MI. Ethnic- specific distribution of mutations in 716 patients with congenital adrenal hyperplasia owing to 21- hydroxylase deficiency. *Mol Genet Metab.* 2007 Apr;90(4):414-21. Epub 2007 Feb 1. Erratum in: *Mol Genet Metab*. 2008 Feb;93(2):219. Azar, Maryam [corrected to Azar, Maryam Razzaghy]. PMID: 17275379.

A-Wise LA, Palmer JR, Hatch EE, Troisi R, Titus-Ernstoff L, Herbst AL, Kaufman R, Noller KL, Hoover RN. Secondary sex ratio among women exposed to diethylstilbestrol in utero*. Environ Health Perspect*. 2007 Sep;115(9):1314-9. PMID: 17805421.

B-Wise LA, Titus-Ernstoff L, Palmer JR, Hoover RN, Hatch EE, Perez KM, Strohsnitter WC, Kaufman R, Anderson D, Troisi R. Time to pregnancy and secondary sex ratio in men exposed prenatally to diethylstilbestrol. *Am J Epidemiol.* 2007 Oct 1;166(7):765-74. Epub 2007 Jun 27. PMID: 17596265.

Wise TN, Meyer JK. The border area between transvestism and gender dysphoria: transvestitic applicants for sex reassignment. *Arch Sex Behav.* 1980 Aug;9(4):327-42. PMID: 7416946.

Wolfradt U, Engelmann S. Depersonalization, fantasies, and coping behavior in clinical context. *J Clin Psychol.* 1999 Feb;55(2):225-32. PMID: 10100823.

Wolfradt U, Neumann K. Depersonalization, self-esteem and body image in male-to-female transsexuals compared to male and female controls. *Arch Sex Behav.* 2001 Jun;30(3):301-10 PMID: 11330119.

WPATH 2001 Meyer III W, Bockting WO, Cohen-Kettenis P, Coleman E, DiCeglie D, Devor H, Gooren L, Hage JJ, Kirk S, Kuiper B., Laub D., Lawrence A., Menard Y., Monstrey S, Patton J, Schaefer L., Webb A, Wheeler CC .*The Harry Benjamin International Gender Dysphoria Association's Standards Of Care For Gender Identity Disorders.* (6th version) February, 2001. http://www.wpath.org/site_page.cfm?pk_association_webpage_menu=1351&pk_association_webpage=4655.

WPATH 2012 Coleman E, Bockting W, Botzer M, Cohen-Kettenis P, DeCuypere G, Feldman J, Fraser L, Green J, Knudson G, Meyer WJ, Monstrey S, Adler RK, Brown GR, Devor AH, Ehrbar R, Ettner R, Eyler E, Garofalo R, Karasic DH, Istar Lev A, Mayer G, Meyer-Bahlburg H, Paxton Hall B, Pfäfflin F, Rachlin K, Robinson B, Schechter LS, Tangpricha V, van Trotsenburg M, Vitale A, Winter S, Whittle S, Wylie KR, Zucker K. *Standards of care for the health of transsexual, transgender, and gender-nonconforming people*. (7th version) 2012. http://www.wpath.org/site_page.cfm? pk_association_webpage_menu=1351&pk_association_webpage=3926.

Wroblewski P, Gustafsson J, Selvaggi G. Sex reassignment surgery for transsexuals. *Curr Opin Endocrinol Diabetes Obes.* 2013 Dec;20(6):570-4. PMID: 24468760.

Wyler J, Battegay R, Krupp S, Rist M, Rauchfleisch U. [Transsexualism and its therapy]. *Schweiz Arch Neurol Neurochir Psychiatr.* 1979;124(1):43-58. PMID: 482895.

Yahyaoui R, Esteva I, Haro-Mora J, Almaraz M, Morcillo S, Rojo-Martínez G, Martínez J, Gómez- Zumaquero J, González I, Hernando V, Soriguer F. Effect of long-term administration of cross-sex hormone therapy on serum and urinary uric acid in transsexual persons. *J Clin Endocrinol Metab.* 2008 Jun;93(6):2230-3. Epub 2008 Mar 18. PMID: 18349066.

Yik Koon, T. (2002). *The Mak Nyahs: Malaysian Male to Female Transsexuals*. (Chapter 4) Eastern Universities Press.

Zhu, Y, Imperato-McGinley, J, Male Sexual Differentiation Disorder and 5α-Reductase-2 Deficiency. *Glob. libr. women's med*., (ISSN: 1756-2228) 2008; DOI 10.3843/GLOWM.10350. (Not in PubMed.)

Zigmond AS, Snaith RP. The hospital anxiety and depression scale. *Acta Psychiatr Scand.* 1983 Jun;67(6):361-70. PMID: 6880820.

Zimmermann A, Zimmer R, Kovacs L, Einödshofer S, Herschbach P, Henrich G, Tunner W, Biemer E, Papadopulos N. [Transsexuals' life satisfaction after gender transformation operations]. *Chirurg*. 2006 May;77(5):432-8. German. Erratum in *Chirurg*. 2006 Jun;77(6):530. PMID: 16437228.

Zoni AC, González MA, Sjögren HW. Syphilis in the most at-risk populations in Latin America and the Caribbean: a systematic review. *Int J Infect Dis*. 2013 Feb;17(2):e84-92. Epub 2012 Oct 12. PMID: 23063547.

Zucker KJ, Bradley SJ, Hughes HE. Gender dysphoria in a child with true hermaphroditism. *Can J Psychiatry.* 1987 Oct;32(7):602-9. PMID: 3676994.

A-Zucker KJ, Bradley SJ, Kuksis M, Pecore K, Birkenfeld-Adams A, Doering RW, Mitchell JN, Wild J. Gender constancy judgments in children with gender identity disorder: evidence for a developmental lag. *Arch Sex Behav*. 1999 Dec;28(6):475-502. PMID: 10650437.

B-Zucker KJ. Intersexuality and gender identity differentiation. *Annu Rev Sex Res.* 1999;10:1-69. PMID: 10895247.

Zucker K, Cohen-Kettenis P, Drescher J, Meyer-Bahlburg H, Pfäfflin F, Womack W. Memo outlining evidence for change for gender identity disorder in the DSM-5. *Arch Sex Behav*. 2013 Jul;42(5):901- 14. PMID: 23868018.