**Lean InClusion: Ensuring Sex/Gender Representation from Cells to Selves**

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Women’s Health Research Institute 8th Anniversary
Northwestern University Feinberg School of Medicine
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NIH Office of Research on Women’s Health

- Founded in 1990
- 1991: Women’s Health Initiative
- 1993: NIH Mandate to include women and minority groups in clinical trials
- 2013: NIH focal point for research on sex/gender influences on health

... Research across the lifespan of girls and women
Consumer: “For so long women’s health issues were not discussed. You would go to the doctor, get diagnosed and you didn’t question it because you trusted them. But now we know we can do more and educate ourselves.”

Consumer, on What does women’s health mean to you?: “There are two different type of sexes, or maybe it means LGBT, I don’t know really.”

Media Professional: “I love a scientist’s perspective, but I’m always looking for personal experiences [from a women’s health portal]”

Researcher: “The most important thing is this: women’s health research needs to educate people that women’s health is not just reproductive health”
Why Do We Need Research on Women’s Health?

- Many significant sex factors in diseases/organs related to reproduction
- Many significant sex factors in diseases/organs unrelated to reproduction
- Sex differences not always differences: “sex factors”
- **What are we missing** by not including sex and gender in investigations at all levels?
- **What harm are we doing** by not including sex and gender in investigations at all levels?
Office of Research on Women’s Health

- Enhance, stimulate, and expand efforts to improve the health of women through biomedical and behavioral research, across NIH
- Examine the role of sex/gender in health and disease, across NIH
- Promote recruitment, retention, reentry, and advancement of women in biomedical careers
ORWH Trans-NIH Strategy

ORWH Biennial Report

- Prepared in early 2013
- Includes contributions from each NIH IC
- Highlights research that specifically fulfills major goals and objectives of the NIH/ORWH Strategic Plan
- Research already interwoven throughout the fabric of the NIH research agenda
ORWH Co-Funds Grants and Partners With NIH ICs

Possible approaches:

- Addition of another group of subjects (human or animal) of the opposite sex when subjects of only one sex were used in the original study.
- Addition of more subjects (human or animal) of both sexes to sufficiently power a study that was insufficiently powered to conduct a sex/gender analysis.
- Analyses of pre-existing data where sex-specific data are included and power is sufficient, but a sex/gender analysis was not performed as part of the original study.

- 100% participation from all eligible NIH components.
- Enthusiastic response from scientific community: 250 applications.
- Funded 35 supplements.
Administrator Supplements: Extending Our Reach

Selected Topics
- Resources, Parent-Child Communication and Adjustment to Pediatric Cancer
- Molecular Biomarkers of Airway and Lung Linking COPD and Lung Cancer
- Sleep Duration Required to Restore Performance During Chronic Sleep Restriction
- Influenza A Virus Infection of Human Nasal Epithelial Cells
- Sex-Dependent Expression and Utilization of Spinal mu- and kappa-Opioid Systems
- Mechanisms of Asthma-Dietary Interventions against Environmental Triggers
- An Intercross Between the Circadian and NFkB Pathways
- Anticipating Personalized Genomic Medicine: Impact and Implications

Selected Approaches
“... add a second group of animals of the opposite sex (female) for comparative analyses of gender mediated effects and treatment outcomes”
“... analyze changes in cost-related non-adherence, drug utilization, treatment, and patient drug cost burden, by gender”
“... sex-dependent vulnerability and biomarkers for predicting subsequent adverse consequences”
“... testing methodological issues for understanding sex differences”
Multi-Disciplinary vs. Interdisciplinary

Women’s Health

NIH National Institutes of Health
Office of Research on Women's Health
Specialized Centers of Research on Sex Differences (SCOR)

- ORWH/FDA
- Interdisciplinary collaborations
- Research on sex/gender factors underlying a priority women’s health issue
- Bridges basic and clinical research
- $89 million investment over last decade

11 Funded SCOR Centers

- Sex-Specific Risk for Vascular Dysfunction and Cognitive Decline
- Sex and Gender Differences in Addictions and Stress Response
- Genes, Androgens and Intrauterine Environment in PCOS
- Sex Differences in Musculoskeletal Diseases
- Sex Differences in Pain
- Metabolic Consequences of Loss of Gonadal Function
- Birth, Muscle Injury, and Pelvic Floor Dysfunction
- Sex Differences and Progesterone effects on Impulsivity, Smoking, and Cocaine Stress
- Pre-pubertal Stress, Windows of Risk and Sex Bias for Affective Disturbance
- Molecular and Epidemiologic Basis of UTI in Women
- Gender-Sensitive Treatment for Tobacco Dependence
Building Interdisciplinary Research Careers in Women’s Health (BIRCWH)

- Main goal is support for transition to research independence
- Aims to reduce fragmentation in women’s health issues
- 542 scholars trained to date
  - ~ 80 percent women
  - ~ 20 percent men
- Scholars successful at getting NIH funding
BIRCWH Scholars: NIH Funding Success

- “Nearly 80 percent of BIRCWH scholars who have completed training have submitted at least one competitive application for an NIH grant.”
- “Of those who applied, almost two-thirds received at least one funded grant.”
- “Though not the original intention, BIRCWH also provides a platform for women, in particular, to be professionally successful.”
- “The BIRCWH program appears to provide incentive and support for women to stay in academic careers.”

Specialized Center Of Interdisciplinary Research (SCOR) on Sex And Gender Factors Affecting Women’s Health

Nonhuman primate models of polycystic ovary syndrome

David H. Abbott a,c,e, Lindsey E. Nicol b, Jon E. Levine c,d, Ning Xu e, Mark O. Goodarzi e,f, Daniel A. Dumesic g

Familial aggregation of circulating c-reactive protein in polycystic ovary syndrome

Arunachalam Sasidevi 1,*, Priyathama Vellanki 1,*, Allen R. Kunselman 1, Nazia Raza-Khan 2, Andrea Dunai 3 and Richard S. Legro 3

Evidence for Chromosome 2p16.3 Polycystic Ovary Syndrome Susceptibility Locus in Affected Women of European Ancestry


Serum Soluble Urokinase-Type Plasminogen Activator Receptor Levels and Idiopathic FSGS in Children: A Single-Center Report

Margret E. Bock *,†, Heather E. Price *,†, Lorenzo Gallon †, Craig B. Langman †

Contribution of evening macronutrient intake to total caloric intake and body mass index *

Kelly Glazer Baron b,*, Equivalent, Kathryn J. Reid b, Linda Van Horn b, Phyllis C. Zez b
- Enhance, stimulate, and expand efforts to improve the health of women through biomedical and behavioral research, across NIH
- Examine the role of sex/gender in health and disease, across NIH
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Liver is sexually dimorphic:
- Male rats: higher hydroxylating activity than females
- Females: express higher 5α-reductase than males
- Growth hormone release differences
- P450s sexually dimorphic
  - Female: CYP2C12 (15β-hydroxylase)
  - Male: CYP2C11 (16α-hydroxylase)
- Sex significantly influences how the body metabolizes Ambien, although details remain unclear
  - At any given dose, women will have more Ambien “in their system,” as indicated by AUC (area under the curve)
What We Know ... CVD-Related Sex Differences

- Preventive aspirin: different effects in men and women
- Women more prone than men to spontaneous coronary artery dissection (women 82% of diagnosed cases)
- Statins in women
  - Unlike men, no statistically significant risk reduction of all-cause mortality or any type of stroke
  - Like men, women with previous cardiovascular disease had a lower risk for a second heart attack
- Sex-specific risk of cardiovascular disease and cognitive decline
  - ORWH-funded SCOR project in progress

What We Should Know ... Sex-Specific Reporting of Results in CVD Trials Lower than in General

- Of the 628 studies reviewed, only 153 (24%) provided sex-specific results
- Studies reporting sex-specific results:
  - 37% (23/62) for general medical journals
  - 23% (130/566) for cardiovascular journals
- Among NIH-supported trials
  - 51% (31/61) analyzed outcomes by sex
  - 22% (125/567) of trials not NIH-sponsored

What We Know: Discovery Science of Sex Factors

- Gene expression differences in male and female animals as well as in male and female humans
- Sex differences in DNA methylation after exposure to prenatal famine

What We Could Know: How Sex-Specific eQTLs Contribute to Disease Risk

What We Know: Sex Differences in Hepatitis

- Life-threatening condition that often requires transplantation
- Autoimmune hepatitis: more common in women
- Higher risk:
  - Castrated males
  - Females without ovaries
- Estrogen triggers inflammatory damage
  - T-reg cells: possible future therapy
What We Could Know: Sex-Specific iPS Cells?
NIH Revitalization Act 1993 (PL 103-43)

NIH Inclusion Guidelines

- Women and Minorities **must be included** in all clinical research studies
- Women and Minorities **must be included** in Phase III clinical trials, and the trial must be designed to permit valid analysis
- Cost is **not allowed** as an acceptable reason for exclusion
- NIH to support outreach efforts to recruit and retain women, minorities, and their subpopulations in clinical studies

Enrollment by Sex/Gender: NIH Clinical Research
Percent Enrollment by Sex/Gender: NIH Clinical Research FY 2011, FY 2012

Excluding Male-Only and Female-Only Studies
Enrollment by Sex/Gender: NIH-Defined Phase III Clinical Trials

![Graph showing enrollment by sex/gender over fiscal years from 2003 to 2012. The graph displays data on the percentage of total enrollment for females and males. The graph indicates a general trend of decreasing enrollment over the years, with a slight increase in recent years for females.]
Percent Enrollment by Sex/Gender: NIH-Defined Phase III Clinical Trials FY 2011, FY 2012

Excluding Male-Only and Female-Only Studies
Sex-Based Under-Reporting in NIH-Funded Clinical Trials

- All NIH-defined phase 3 clinical research studies that reported enrollment to the NIH Tracking and Inclusion System
- ~4,000 unique NIH-funded phase 3 grants or cooperative agreements that completed enrollment 1994–2007
- 268 trial publications reviewed and summarized (enrollment completion reports)
Beyond Inclusion: Sex-Specific Reporting

U.S. Population

NIH-funded clinical trial sex/gender inclusion (average enrollment of women): 37 percent\(^1\)

NIH-funded clinical trial sex/gender reporting: 28 percent\(^1\) (of the above group)

\(^{1}\)Foulkes MA. After inclusion, information and inference: reporting on clinical trials results after 15 years of monitoring inclusion of women. *J Womens Health*. 2011;20:829-36
Why Sex/Gender Matters in Pre-Clinical Research

Animal Studies: Six fields relied on rodents in 80% or more of animal studies (general biology, immunology, neuroscience, physiology, pharmacology, and endocrinology)

- Male emphasis in 8 of 10 biological disciplines
  - Neuroscience (5.5/1)
  - Pharmacology (5/1)
  - Physiology (3.7/1)

“… after I understand the phenomenon in males, I’ll check whether it’s there in females.”

“In so many studies, information concerning the sex and/or number of animals was not provided. … we were told by almost every investigator that because of the estrus cycle, female animals did not give the same results as male animals.”

“All disciplines, but cardiology (22%), demonstrated an underrepresentation of research about gender differences in management, which ranges from 3 to 14%.

“Because only male mice were used, findings in this study may be more applicable to male OCD patients. This is relevant because there is evidence for gender differences in OCD.”

“In response to [the] question about whether [this researcher] was using male or females rats, s/he replied, “Male rats. I don’t go near female rats!” … s/he explained that, in essence, the nice story [that] was developing in male rats did not hold up well, if at all, in female rats.”
A Step Forward

Preparation Your Manuscript

Note: Before submitting your manuscript, please conduct a careful review of the information below to familiarize yourself with the structure you will need to apply to your manuscript to meet our editorial specifications. This page contains very useful information to help you prepare your content so that it flows smoothly through our peer review process, as well as important information to help you understand our editorial policies and procedures.

Materials and Methods

Describe techniques, cell/animal models used (including species, strain, and sex), and lists of reagents, chemicals, and equipment, as well as the names of manufacturers and suppliers, including URLs for those supplies obtained online, so that your study can be most easily replicated by others. For studies involving humans, the sex and/or gender of participants must be reported. Also in this section, describe the statistical methods that were used to evaluate the data. If clinical trials were used, a statement of registration is required; also, for all investigations involving humans or animals, a statement of protocol approval from an IRB or IACUC, or an equivalent statement, must be included (see Guiding Principles for Research Involving Animals and Human Beings). All animal or human studies must contain an explicit statement that the protocols were submitted to, and approved by, an institutional review board or committee or that the protocols were performed under a license obtained from such a committee, board, or governing office.
Four themes for advancing sex-specific reporting:

- Identifying the sex of populations in journal populations (include sex of origin cells, tissues and animals in basic research)
- Share sex-identified raw data to facilitate meta analyses
- “Extra credit” in review for manuscripts that include sex-specific information
- Requiring sex-stratified analyses

Intersecting roles:

- Journal editors
- Government funding agencies
- Industry
- Basic researchers
- Professional societies
- Other stakeholders
Progress: Sex/Gender in Professional School Curricula

ADEA Report recommends adding to curriculum for:
- Medical Schools
- Dental Schools
- Nursing Schools
- Pharmacy Schools
- Allied Health Schools

ORWH/FDA Online Course: The Science of Sex and Gender in Human Health

May 2013: HRSA Report on Women’s Health Curricula:
- Expert Panel Recommendations for Inter-professional Collaboration across the Health Professions
Office of Research on Women’s Health

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NIH Working Group on Women in Biomedical Careers

- Established in 2007 to consider recommendations from the National Academies report Beyond Bias and Barriers: Fulfilling the Potential of Women in Academic Science and Engineering
- Seeks innovative strategies to address concerns of NIH intramural and extramural communities
- Pays special attention to issues of barriers, minority women scientists, and mentoring
Causal Factors and Interventions Affecting Women in Biomedical Careers

Key Findings

- Bias is powerful, often unconscious, can be measured, and can be altered
- The NIH can lead by example to “de-silo” diversity and inclusion
- Mentor networks are more effective than mentor dyads
- Culture affects career satisfaction and performance, and can be measured
- Institutional flexibility policies are under-recognized and under-used, in part due to ingrained academic culture and lack of leadership buy-in

Causal Factors and Interventions Affecting Women in Biomedical Careers

Work–Life Balance in Academic Medicine: Narratives of Physician-Researchers and Their Mentors

Erin A. Strong, MS¹, Rochelle De Castro, MS²,³, Dana Sambuco, MPA²,³, Abigail Stewart, PhD⁴,⁵, Peter A. Ubel, MD⁶,⁷, Kent A. Griffith, MS⁸, and Reshma Jagsi, MD, DPhil²,³

A Culture Conducive to Women’s Academic Success: Development of a Measur
Alyssa Friede Westring, PhD, Rebecca M. Speck, MPH, Mary Dupu Patricia Scott, Lucy Wolf Tuton, PhD, Jeane Ann Grisso, MD, MSc, and Stephanie Abbuhi, MD

Changing the Culture of Academic Medicine to Eliminate the Gender Leadership Gap: 50/50 by 2020
Hannah Valantine, MD, and Christy I. Sandborg, MD

A qualitative study of work-life choices in academic internal medicine

Sponsorship: A Path to the Academic Medicine C-suite for Women Faculty?
Elizabeth L. Travis, PhD, Leilani Doty, PhD, and Deborah L. Helitzer, ScD

Physicians and Implicit Bias: How Doctors May Unwittingly Perpetuate Health Care Disparities
Elizabeth N. Chapman, MD¹,⁵, Anna Kaatz, MA, MPH, PhD⁴, and Molly Carnes, MD, MS¹,²,⁴,⁵
A New Lens for Research on Women’s Health

- Advance understanding of biological sex differences
- Apply new technologies to maximize research potential and impact
- Expand understanding of health and disease in women
- Foster partnerships to conduct and translate research

THANK YOU!