Barriers Which Impede Sex Differences Research and How To Overcome Them

Sex Differences and Implications for Translational Neuroscience Research – A Workshop
Institute of Medicine
San Francisco, March 2010

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A Basic Fact of Biology...

Males & Females Are Different!!!
Men and women are different – in ways beyond anatomy. A push to explore the chasm that separates research could give primary care more insight into the variations…

Vive la difference…’

‘…what (research scientists) uncover could help make …office visits more productive for primary care physicians and their patients…’
The NIH Policy: Inclusion of Women & Minorities as Subjects in Clinical Research
Recent attention directed to ‘inclusion’ policies to determine sex differences began in late 1980’s because of concern that clinical research on conditions that affect both women & men was being conducted primarily in a homogeneous white male population, but results applied in medical practice to both men and women of all races...
Changing Research Design at NIH in 1990 to Determine Sex & Gender Differences in Clinical Research Studies

Advocacy Demand
(Inclusion of women in clinical research)

Attention of Women in Congress

Establishment of ORWH to ensure that women are included in NIH funded clinical studies; Government Attention to Scientific Design of Research to address Sex/Gender factors in health and disease
Inclusion Policies for Clinical Research
Incorporated into Public Law

S.1 - National Institutes of Health Revitalization Act of 1993
Subtitle B--Clinical Research Equity Regarding Women and Minorities

PART I--WOMEN AND MINORITIES AS SUBJECTS IN CLINICAL RESEARCH

SEC. 131. REQUIREMENT OF INCLUSION IN RESEARCH.
Part G of title IV of the Public Health Service Act, as amended by section 101 of this Act, is amended by inserting after section 492A the following section:

INCLUSION OF WOMEN AND MINORITIES IN CLINICAL RESEARCH
SEC. 492B. (a) REQUIREMENT OF INCLUSION--
(1) IN GENERAL--In conducting or supporting clinical research for purposes of this title, the Director of NIH shall, subject to subsection (b), ensure that--
(A) women are included as subjects in each project of such research; and
(B) members of minority groups are included as subjects in such research.
(2) OUTREACH REGARDING PARTICIPATION AS SUBJECTS--The Director of NIH, in consultation with the Director of the Office of Research on Women's Health and the Director of the Office of Research on Minority Health, shall conduct or support outreach programs for the recruitment of women and members of minority groups as subjects in projects of clinical research.
NIH REVITALIZATION ACT OF 1993
(PL 103-43)
NIH Policies on Inclusion

NIH must:

- Ensure that women and members of minority groups and their subpopulations are included in all human subject research;
- For Phase III clinical trials, ensure that women and minorities and their subpopulations must be included such that valid analysis of differences in intervention effect can be accomplished;
- Not allow cost as an acceptable reason for excluding these groups; and
- Initiate programs and support for outreach efforts to recruit these groups into clinical studies.

It is the policy of NIH that women and members of minority groups ... must be included in all NIH-supported biomedical and behavioral research projects involving human subjects, unless a clear and compelling rationale and justification establishes... that inclusion is inappropriate with respect to the health of the subjects or the purposes of the research...

Federal Register March 1994
INTENT:
To insure that scientific norms for health, disease, treatments and other medical interventions are applicable to all populations (men & women, diverse racial/ethnic groups), based upon scientific evidence established by studying those populations; i.e., are there biological or other differences in effect based upon sex or race/ethnicity?...
**Valid Analysis**

The term "valid analysis" means an unbiased assessment. Such an assessment will, on average, yield the correct estimate of the difference in outcomes between two groups of subjects. Valid analysis can and should be conducted for both small and large studies. A valid analysis does not need to have a high statistical power for detecting a stated effect. The principal requirements for ensuring a valid analysis of the question of interest are:

- allocation of study participants of both sexes/genders (males and females) and different racial/ethnic groups to the intervention and control groups by an unbiased process such as randomization,
- unbiased evaluation of the outcome(s) of study participants, and
- use of unbiased statistical analyses and proper methods of inference to estimate and compare the intervention effects among the sex/gender and racial/ethnic groups.

**Significant Difference**

For purposes of this policy, a "significant difference" is a difference that is of clinical or public health importance, based on substantial scientific data. This definition differs from the commonly used "statistically significant difference," which refers to the event that, for a given set of data, the statistical test for a difference between the effects in two groups achieves statistical significance. Statistical significance depends upon the amount of information in the data set. With a very large amount of information, one could find a statistically significant, but clinically small difference that is of very little clinical importance. Conversely, with less information one could find a large difference of potential importance that is not statistically significant.

CARDIOVASCULAR RESEARCH:
Importance of Knowing About Sex Differences

‘Understanding more about the factors that cause sex differences in mortality from coronary heart disease has important public health implications…’

Although coronary heart disease (CHD) is the cause of more than 250,000 deaths in women each year, much of the research in the last 20 years on the diagnosis and treatment of CHD has either excluded women entirely or included only limited numbers of women and minorities… Even in studies that include women, *the published research often does not provide findings specific to women*, according to two evidence reviews on CHD in women, conducted for the Agency for Healthcare Research and Quality and the National Institutes of Health's Office of Research on Women's Health by researchers at the University of California at San Francisco/Stanford Evidence-based Practice Center. _Only 20 percent of the articles reviewed for this project provided separate findings on women._
The researchers conclude that even though funding agencies appear to have succeeded in ensuring that some women and minorities are included in randomized trials, data about these populations often are not made clear in the published findings.

They recommend that in addition to requiring participation of women and minorities in research, funding and regulatory agencies should request that outcome data by gender and race/ethnicity be published or made easily available.

ORIGINAL ARTICLE

Low Rate of Sex-Specific Result Reporting in Cardiovascular Trials

LORI A. BLAUWET, MD; SHARONNE N. HAYES, MD

OBJECTIVE: To explore the extent to which sex-specific result (SSR) reporting appears in recently published clinical trials.

METHODS: All original adult cardiovascular clinical trials reported in Annals of Internal Medicine, Archives of Internal Medicine, Journal of the American Medical Association, The Journal of the American College of Cardiology, The American Journal of Cardiology, and Circulation from July 1 through December 31, 2004, were reviewed. SSR result reporting was defined as presenting primary results in women in a format to allow the data to be abstracted for meta-analysis.

RESULTS: Of the 645 studies reviewed, 17 were excluded because they were appropriately single-sex trials. Of the remaining 628 studies, only 153 (24%) provided SSRs. The percentage of studies reporting SSRs was 37% (23/62) for general medical journals and 23% (130/566) for cardiovascular journals (P=.10). Among National Institutes of Health (NIH)-sponsored research, 31 (51%) of 61 trials analyzed outcomes by sex compared with 125 (22%) of 567 trials not sponsored by the NIH (P<.001).

CONCLUSION: Only a few current cardiovascular trials provide sex-specific data. Sex differences remain poorly understood, and this deficiency limits our ability to optimize medical care for both sexes. The stipulation that SSRs be investigated has led to significantly more SSR reporting in NIH-funded research. A parallel mandate by journal editors that requires authors to provide sex-specific data and analysis may help to bridge this knowledge gap.
Excerpt from Instructions to Authors from JNCI, Section 3

Methods
For clinical trials, authors should clearly define and explain the purpose of the study, study design, numbers of patients, clinical staging of disease, type and sequence of treatments given before and during the study, time points for evaluation of response, duration of follow-up, end points used (e.g., overall survival, disease-free survival), specific outcomes assessed, and methods of assessment. This requirement should be met, even when the major focus of a study is not the clinical trial to which it is related (e.g., association of gene, messenger RNA, or protein expression with disease therapy or prognosis). (See also "Clinical Trials".)

Where appropriate, clinical and epidemiologic studies should be analyzed to see if there is an effect of sex or any of the major ethnic groups. If there is no effect, it should be so stated in Results.
Sex/Gender Appropriate Medicine

- As research is defining conditions that affect both women and men, and discovering where sex/gender differences occur in presentation, diagnosis, treatment or response to therapy, medical care can be improved for both women and men.

- Yet – there is still much to be studied, new tools are enabling new discoveries that challenge the status quo for how clinicians approach male and female patients for diagnosis or treatment, but there is still much to learn before the process for moving discovery to treatment.

- The ethical and social implications of this new medicine, especially genetic based, still are challenges, but progress is at hand in assuring both women and men of sex-specific advances to improve their health and healthcare.
Today the reference is to ‘gender appropriate Personalized Medicine’…
Basic Research:
Needed to provide data that can guide the design of clinical research, translational research & applications in practice...
How can we best stress the importance of sex differences research on researchers and clinicians???

Most convincing argument appears to be stressing the potential or demonstrated role in improving clinical care

Sex and Gender Factors in Medical Studies: Implications for Health and Clinical Practice

Victor W. Pinn, MD

ACTA-RWinter 2003

The importance of sex differences research on researchers and clinicians appears to be demonstrated by an American Health Report released in June 2003.

1. Definitions

Sex-related differences refer to differences in responses to biological or environmental influences that are related to sex differences in anatomy, physiology, behavior, or psychological characteristics.

Gender-related differences refer to differences in responses to social or cultural influences that are related to cultural or social norms, values, or expectations.

2. Understanding the Role of Sex

Understanding the role of sex in health care requires an understanding of the biology of sex and gender.

Sex is a biological characteristic that is determined by the presence or absence of the SRY gene, which is present only in males. Sex is usually defined as male or female at birth, based on the presence or absence of the SRY gene.

Gender is a social construct that is determined by the roles, behaviors, and expectations associated with being male or female. Gender is usually defined as male or female at birth, based on the presence or absence of the SRY gene.

3. Expanding the Frontiers of Women's Health Research — US Style

Sex analyses in studies can have clinical implications.

For more recent, biologically based, and biologically oriented research, sex has provided biological benefits for the study of sex differences in women's health.

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Sex Differences Research and Analyses by Sex: Clinical Studies versus Basic Research Studies

Clinical studies funded by NIH are covered by policy & law.

What can facilitate designing basic research such that implications for clinical determinations of sex/gender differences are addressed or clinical studies supported by other sources?
Sex Differences Research and Analyses by Sex: Clinical Studies versus Basic Research Studies

- The 2001 IOM study of Sex Differences in basic biological students was seen as a valuable scientific impetus for emphasizing the importance of sex differences research in basic biological studies...
In recent years, considerable attention has been given to the differences and similarities between females and males (1) at the societal level by researchers evaluating how individual behaviors, lifestyles, and surroundings affect one’s biological development and health and (2) at the level of the whole organism by clinicians and applied researchers investigating the component organs and systems of humans. However, scientists have paid much less attention to the direct and intentional study of these differences at the basic cellular and molecular levels. Where data are available, they have often been a by-product of other areas of research. Historically, the research community assumed that beyond the reproductive system such differences do not exist or are not relevant.

The critical questions to be answered are

- How can information on sex differences be translated into preventive, diagnostic, and therapeutic practice?
- How can the new knowledge about and understanding of biological sex differences and similarities most effectively be used to positively affect patient outcomes and improve health and health care?
The Institute of Medicine of the National Academy of Science’s Report on Sex & Gender in Basic Biological Research 2001

Clarify use of the terms sex and gender:

- **SEX**: MALE or FEMALE according to reproductive organs and functions assigned by chromosomal complement.

- **GENDER**: Person’s self representation in response to/by social institutions; rooted in biology and shaped by environment & experience.
Does Sex Matter? Yes...

“Being male or female is an important basic human variable that affects health and illness throughout the lifespan... Sound medical treatment and research must account for sex and gender differences and similarities.”

From Exploring the Biological Contributions to Human Health: Does Sex Matter?
Institute of Medicine
SUMMARY OF MAJOR RECOMMENDATIONS

- Every cell has a sex: sexual genotype may explain reasons for heterogeneous expressions of some diseases between sexes
- Sex affects behavior and perception
- Sex affects health
“An additional and more general reason for studying differences between the sexes is that these differences, like other forms of **biological variation**, can offer important insights into underlying biological mechanisms.”

Wizemann, TM and Pardue, ML.

*Exploring the Biological Contributions to Human Health: Does Sex Matter?*

National Academy Press, 2001
“Scientists conducting research on sex differences are confronted with an array of barriers to progress, including ethical, financial, sociological, and scientific factors”.

**BOX 1**
Summary of Barriers to Progress in Research on Sex Differences

**Terminology**
- There is inconsistent and often confusing use of the terms *sex* and *gender* in the scientific literature and popular press.

**Research Tools and Resources**
- The conduct of research on sex differences and longitudinal research may require more complex studies and additional resources.
- Information on sex differences can be difficult to glean from the published literature.
- Useful information on the sex of origin of cell and tissue culture material is often lacking in the literature.
- There is a lack of data from longitudinal studies encompassing different diseases, disorders, and conditions across the life span.
- There is a lack of consideration of hormonal variability.

**Interdisciplinary and Collaborative Research**
- The application of federal regulations is not uniform.
- Opportunities for interdisciplinary collaboration have been underused.

**Non-Health-Related Implications of Research on Sex Differences in Health**
- There is a lack of awareness that the consequences of genetics and physiology may be amenable to change.
- The finding of sex differences can lead to discriminatory practices.
BOX 2
Summary of Recommendations

Recommendations for Research

- Promote research on sex at the cellular level.
- Study sex differences from womb to tomb.
- Mine cross-species information.
- Investigate natural variations.
- Expand research on sex differences in brain organization and function.
- Monitor sex differences and similarities for all human diseases that affect both sexes.

Recommendations for Addressing Barriers to Progress

- Clarify use of the terms \textit{sex} and \textit{gender}.
- Support and conduct additional research on sex differences.
- Make sex-specific data more readily available.
- Determine and disclose the sex of origin of biological research materials.
- Conduct and construct longitudinal studies so that the results can be analyzed by sex.
- Identify the endocrine status of research subjects.
- Encourage and support interdisciplinary research on sex differences.
- Reduce the potential for discrimination based on identified sex differences.
Sex and Gender in Biomedical Research

- It is important for physicians to understand the role of sex and gender in research and health, and the role of policies requiring this approach and their clinical applications.

- Both FDA and NIH have requirements for sex and gender research applicable to studies submitted to the FDA or funded by the NIH, but only NIH has this requirement in Public Law.
Pharmacodynamics and Pharmacokinetics

- The physiologic basis for the need to explore sex-specific characteristics relates to pharmacokinetic and pharmacodynamic effects of drugs.
- There are known and suspected sex-specific aspects of pharmacokinetics and factors that can influence absorption, metabolism, and excretion of drugs.
The FDA “Guideline for the Study and Evaluation of Gender Differences in the Clinical Evaluation of Drugs” calls for data analysis for sex-related variations in response to drug treatment to enable relevant assessment of pharmacodynamic differences or relationships.
Sex Differences in Drug Treatment

- Sex differences in drug metabolism may be important in determining dosages of drugs with narrow therapeutic ranges.
- Sex differences may be involved in higher adverse drug reactions in women than in men.
Sex Differences in Responses to Medications

- Women have increased risk of drug-induced cardiac arrhythmia (*torsades de pointes*, a potentially fatal arrhythmia) ([Drug Safety 2001;24:575-85; JAMA 1993;270:2590-7])

- Antipsychotics provide greater improvement for women than for men—but also greater risk of side effects. ([Life Sci 2003;72:2675-88; Drugs 1995:50:222-239; Am J Psychiatry 1992;149:587-595])
Online Course:
http://sexandgendercourse.od.nih.gov

• Developed by the NIH and FDA to provide a basic scientific understanding of the major physiological sex differences, the influence of these differences on health, and the policy, research and health care implications
• Online course with six 30-40 minute lessons
• Self-paced with quizzes to measure mastery
• Up to four AMA PRA Category I Credits™ can be awarded for successful completion

The Science of Sex and Gender in Human Health
Online Course Site

Welcome
The Science of Sex and Gender in Human Health Online Course Web Site was developed as a collaborative effort between the Office of Research on Women’s Health, Office of the Director, National Institutes of Health (NIH), Food and Drug Administration (FDA), Viwan W. Finn, M.D., Associate Director for Health, Director, Office of Research on Women’s Health, NIH, and Kathleen Unni, M.D., Assistant Health Director, Office of Women’s Health. Welcome you to the course web site.

This site was developed for researchers, clinicians, and members of academia to gain a basic understanding of the major physiological differences between the sexes, the influence of these differences on health and the implications for policy, medical research, and health care. Unless otherwise noted, the information is in the public domain and can be duplicated. However, a citation is appreciated.

The site currently offers one course titled, The Basic Science and the Biological Basis for Sex... and... The course includes six lessons, each of which will take from 20 minutes to an hour to complete and contain educational content. Credit can be awarded for successful completion of the course. To receive credit, you must complete all six lesson quizzes with a score of at least 70 percent, and to complete the form. Partial credit will not be awarded to participants who complete only selected lessons and see the continuing education page for more information.
Module I Lessons

- Sex and Gender in Biomedical Research
- Legislative Process Framework
- Cell Physiology
- Developmental Biology
- Pharmacodynamics/Pharmacokinetics
- Clinical Applications of Genomics

Module II Lessons and Authors (under development)

- Cardiovascular Disease: Dr. Ileana Piña
- Autoimmunity: Dr. Michael Lockshin
- Bone Metabolism: Dr. Lori Tosi and Dr. Mary O’Connor
- Pregnancy (Reproduction/Fertility): Dr. Don Mattison
- Mental Health: Dr. Donna Stewart
- Irritable Bowel Syndrome: Dr. Margaret Heitkemper
- PCOS/Metabolic Syndrome: Dr. Kathryn Sharif
- HIV/AIDS: Dr. Kathleen Squire
- Pharmacokinetics/Pharmacodynamics: Dr. Emmanuel Fadiran
- Biostatistics: Dr. Ameeta Parekh
- Biostatistics: Dr. Pamela Scott

http://sexandgendercourse.od.nih.gov/
Challenges to Future Progress in Sex Differences Research

- **Clinical trials**: Getting sex differences research accomplished and results reported
- **Basic Research**: Making “sex matter” more to basic scientists
- **Translational Research**: Getting basic and clinical researchers to make connections, and understand the relevance of sex differences research
- **Interdisciplinary research**: Bridges basic and translational but is complex, expensive and does not fit the typical academic silos
- **Education/communication**: Making the case for importance of sex differences research to health without stigma
- **Research resources and emerging technologies**: What’s XX got to do with them?
Challenges: Clinical Research and Clinical Trials: Inclusion Issues and Sex Differences Analysis

- Law/Policy does not allow for exclusions to implementation, i.e., for foreign populations, etc., and issues related to OMB categories of race/ethnicity.
- Continuing need to emphasize importance of analyses by sex.
- Publication of sex/gender results in scientific journals.
- Recruitment & retention of diverse populations, including the elderly and ethnic minorities.
- Inclusion of pregnant women in clinical trials still an issue.
- Law/Policy only relates to NIH funded studies and does not include industry or other studies funded by other sources.
Challenge: Basic Sex Differences Research

• Researchers are not aware of the pervasiveness of sex differences, or of the proper subtleties inherent in studying them.

• Investigators believe they must control all experimental factors, and accounting for variables such as cyclical differences in hormones may create an impossibly large experiment.

• Experimental standards and phenotypes have been mostly defined using male animals, making it difficult to evaluate behavior that may differ in females depending on the cycle.
Methodological Advances:
Develop clinical trial methodology, including novel recruitment strategies and statistical analysis methodology that addresses ethical and study design issues specific to studies of women. Develop new methodologies for animal model studies of diseases and normal development of women, including use of female animals, and methodological studies related to the conceptualization, distinction and detection of sex and gender differences in basic and clinical biomedical research.
Challenge: Interdisciplinary Research on Sex Differences

• Interdisciplinary Research: Bridge between Basic & Clinical Science

• Inherently translational: essential for advances in complex areas that cross traditional disciplinary boundaries

• Requires new models of collaboration, institutional support and ways of evaluating those who conduct it

• Organization challenges to Interdisciplinary Research are training of scientists, academic silos; funding
Overcoming Challenges to Sex Differences Research

Targeted funding initiatives help!
ORWH Sponsored RFA with NIH Institutes & FDA
(administered through NIAMS)

**SCOR**

SPECIALIZED CENTERS OF RESEARCH on SEX and GENDER FACTORS AFFECTING WOMEN’S HEALTH

The requirement that the SCOR necessarily include both basic science and clinical (interdisciplinary) projects, and advance translation of scientific discoveries out of the lab & into a clinical environment.
The Institute of Medicine report, "Exploring the Biological Contributions to Human Health, Does Sex Matter?"

"An Agenda for Research on Women's Health for the 21st Century." This outline represents the recommendations from three national topic meetings examining research needs for women's health: (1) Scientific Areas, (2) Sex and Gender Perspectives Throughout the Life Cycle; and (3) Differences Among Populations of Women Throughout the Life Cycle.

NIH Research Priorities for Women's Health Research
Examples of SCOR Research Areas on Sex Differences Research


- M U S C: *Response to corticotropin-releasing hormone infusion in cocaine-dependent individuals.* Arch General Psychiatry, 2009 Apr;66(4):422-30 Brady KT, et al. (Participants were male and female controls and cocaine-dependent men and cocaine-dependent women.)

- Yale: *Sex chromosome complement regulates habit formation.* Nat Neurosci. 2007 Nov;10(11):1398-400. Epub 2007 Oct. Quinn JJ, et al. (Authors used mice in which sex chromosome complement (XX versus XY) and gonadal sex (ovaries versus testes) were independent, and found that XX mice showed faster food-reinforced instrumental habit formation than XY mice, regardless of gonadal phenotype.)
ANSWHR: Advancing Novel Science in Women's Health Research.

A recently implemented ORWH program announcements ANSWHR, Advancing Novel Science in Women's Health Research:


‘The purpose of this Funding Opportunity Announcement issued by the Office of Research on Women’s Health and co-sponsoring NIH institutes and centers, is to promote innovative, interdisciplinary research that will advance new concepts in women’s health research and the study of sex/gender differences. Recent research reports have established the importance of studying issues specific to women, including the scientific and clinical importance of analyzing data separately for females and males. ORWH is particularly interested in encouraging extramural investigators to undertake new interdisciplinary research to advance studies on how sex and gender factors affect women's health; however, applications in all areas of women’s health and/or sex/gender research are invited.’
Examples of Sex Differences Research from ANSWHR: FY2009

- **Gender-Specific Complications of Diabetic Autonomic Neuropathy: A New Mouse Model**, Jonas Galper, MD, Tufts University
  This project to test the hypothesis that the female Akita mouse might serve as a model for the study of gender-(SEX) specific complications of DAN, and the protective effects of estrogens against the development of diabetes and its secondary heart complications.

- **Sex Differences in Acute Pain and Analgesic Responses**; Barbara A. Hastie, PhD, University of Florida

- **Sex Differences in Myocardial Ischemia Triggered by Emotional Factors after MI**; Viola Vaccarino, MD, PhD; Emory University

- **Role of Sex Differences in the Expression & Function of Regulatory T cells in SLE**; Ram Singh, PhD., UCLA
Examples of Sex Differences Research from ANSWHR: FY2009

- Identification and Validation of Human Hypothalamic Nuclei in-vivo and ex-vivo (to understand sex differences): Nikolaos Makris, PhD; MGH

- Gender Selectivity to Colon Cancer Chemoprevention by Nonsteroidal anti-inflammatory drugs (NSAIDS): Ramesh Wali, PhD, Northshore University Health System (Chicago)
MOVING INTO THE FUTURE: NEW DIMENSIONS AND STRATEGIES FOR WOMEN’S HEALTH RESEARCH

Office of Research on Women’s Health/NIH/DHHS
Northwestern University, Feinberg School of Medicine, and Northwestern Memorial Hospital

Neuroscience Working Group
October 15, 2009
Sex differences in brain development, structure and function are well-recognized. The best characterized of these are related to sexually differentiated reproductive behavior and neurohormone secretions. It is increasingly clear, however, that neuronal development and function are sexually differentiated in many other ways, such as stress responsiveness, body weight regulation, nocioception, mood and affect, and aspects of social behaviors and cognition. Basic science studies of these processes, however, remain largely focused on male animal subjects, and do not address adequately the specific neurobiological principles that govern the processes in females. In addition to sex differences in normal physiological and behavioral processes, there are differences in prevalence of and/or other aspects of many human neural disorders.
From the Conference
Moving Into the Future:
New Dimensions and Strategies for Women’s Health Research
Chicago
October 14-16, 2009
External Co-Chairs:
John DeLancey, M.D.
Teresa K. Woodruff, Ph.D.
Underexploited technologies are not applicable to all women because their development and standardization have been based primarily on studies conducted in male subjects and animals. The effect of sex on biological responses to drugs and disease treatment regimens is now clearer than ever. Many routinely performed medical technologies and procedures (e.g. cardiovascular disease imaging and joint replacements) were originally designed, tested, executed and standardized using male models; this has become an issue demanding improvement due to increased awareness of physiological differences between the sexes.
Challenge: Research Resources and Emerging Technologies

- Build sex differences into ground floor of resource creation, technology development
  - Know sex of biological materials donor
  - Most tissues display sex-dependent differences, but existing references and simulations are derived from male models and are therefore improperly applied to the understanding of female physiology
  - Stem cells: sex of cells may affect properties
  - Use high throughput screening to identify clinically relevant sex differences in biologic materials
• The next generation of technological innovations need to be exploited to define sex-specific characteristics at multiple levels, from atoms to entire populations.
  - Existing references and simulations in the laboratory and the clinic (such as phantoms) are largely derived from male models and generalized to both sexes. These should be updated to reflect the physiology of both sexes.
Challenge: Educating Scientists

- There is a need to educate the scientific community that data analyses by sex/gender reflect quality science and that the findings can enhance the understanding of neurobiology and its implications for clinical medicine
  - Study sections
  - Basic, clinical and translational researchers
  - Sex differences in brain function as an integral topic in neuroscience graduate programs and medical school neuroscience courses
Brain & Psychiatric Working Group

- Progress in research on sex and/or gender differences has been impeded by a number of challenges. They include methodological attention to designing studies focused on sex/gender differences, not just separating data by sex/gender after data collection... there is a need for methodological development that takes into consideration the complexity of the domains of sex and gender in the initial design of the study.

- Second, there is a need to educate the scientific community that data analyses by sex/gender reflect quality science and that the findings can enhance the understanding of neurobiology and its implications for clinical medicine. This understanding should underlie the training of the next generation of leaders in women’s mental health.

- Furthermore, education regarding the importance of sex and gender differences in clinical medicine is important not only for the scientific community, but also for policy makers and the public if funding of these important arenas is to be sustained.
• A lack of significant focus on sex and gender differences in chronic pain, as the majority of the animal models of pain use male animals only. This situation is, in large part, due to the increased cost of studying sex-related differences, and to the technical challenges in controlling for cyclical hormonal variations in female animals.

• Problems identified with regard to current and future clinical research of chronic pain include a lack of rigor in studies in which, because of the higher prevalence of women with chronic pain, an insufficient or unrepresentative male sample affects the assessment of sex and gender differences in the treatment of pain.
Sex differences are important considerations in most areas of research... Consideration of these variables is critical to the accurate interpretation and validation of research. Moreover, these variables determine how similar or different health or disease processes may be between women or between men and women. Now to face the barriers and overcome them...