



Advancing NIH Research on the Health of Women: A 2021 Conference

BURDEN OF CHRONIC DISEASE: WHY IS THERE A SEX & GENDER GAP?

Marjorie R. Jenkins, MD MEDHP FACP

Dean, School of Medicine Greenville

Associate Provost, University of South Carolina

Chief Academic Officer, Prisma Health—Upstate

October 20, 2021

Disclosure

No relationship or financial conflicts of interests to disclose.

The statements and opinions expressed are those of the speaker
and do not represent
NIH or the University of South Carolina policies or official stance.

Overview

Terminology

National Impact of Chronic Illness

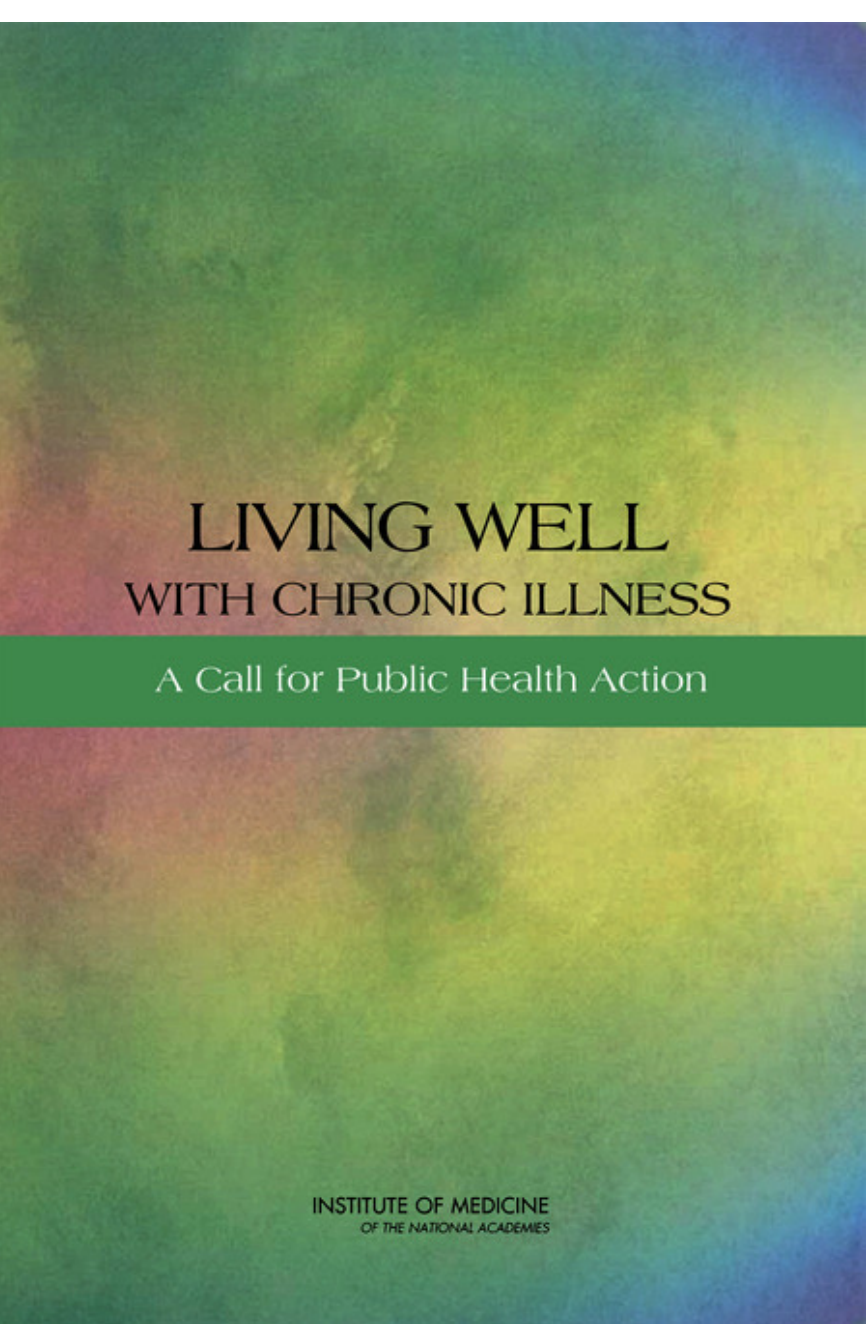
Limitations in Current Health Policies

Bias and Biology

Call to Action

Terminology Matters

Those who forget history are destined to repeat it



US Department of Health and Human Services (HHS), 2010

Definition	Chronic illnesses are “conditions that last a year or more and require ongoing medical attention and/or limit activities of daily living.”
Key components	Duration: ≥ 1 year Functional limitation: yes Need for ongoing medical care: yes
Comments	This definition, adapted from other sources, incorporates elements of duration, medical requirements, and functional status. It also has the advantage of being compact. The HHS Strategic Framework also adopts the definition of “multiple” used in another source as 2 or more concurrent chronic conditions.

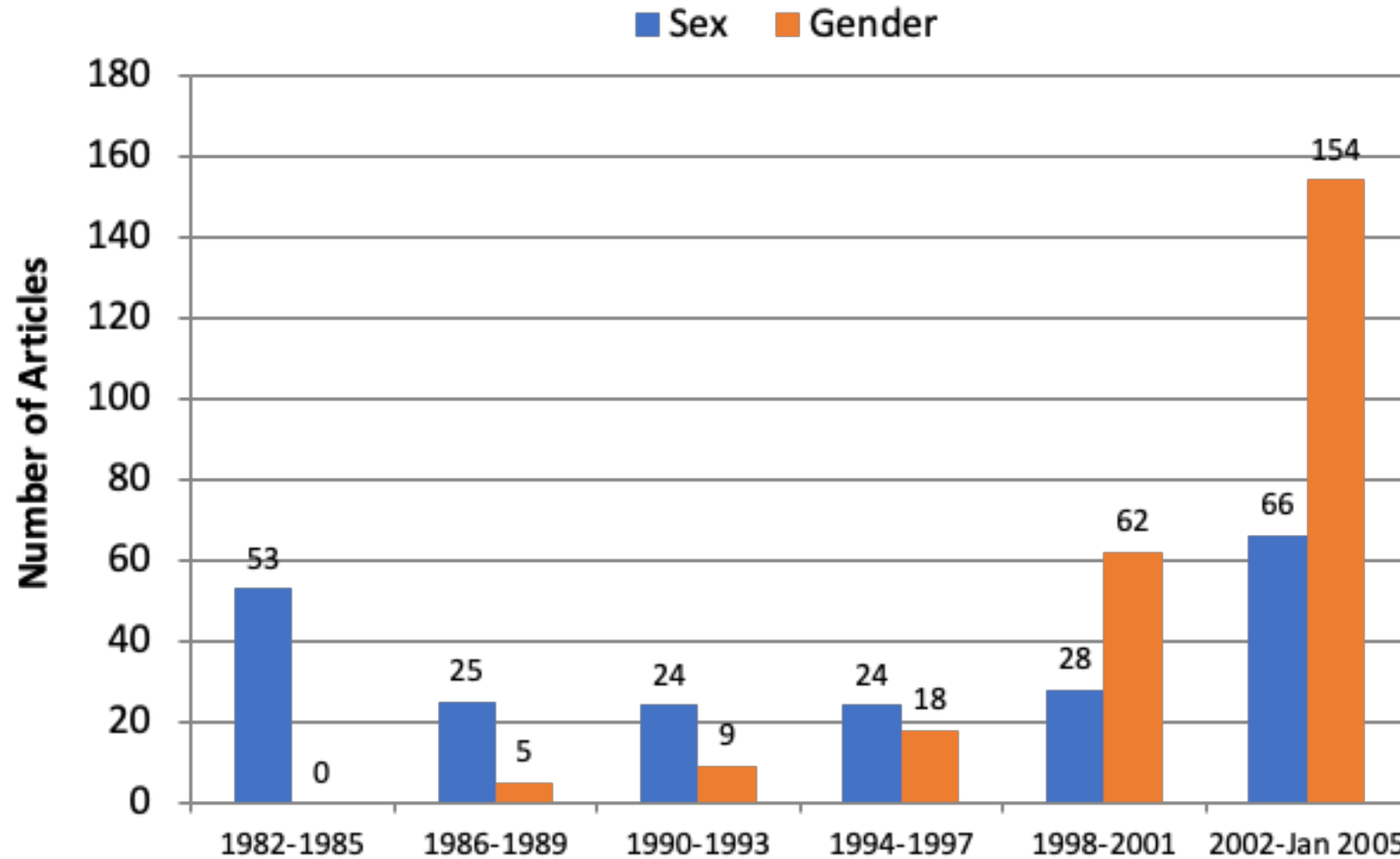
An NIH-wide definition of chronic debilitating conditions in women does not currently exist.

Sex and Gender are Unique Terms

Sex is the classification of living things, generally as male or female according to their reproductive organs and functions assigned by the chromosomal complement.

Gender is defined as a person's self-representation, or how that person is responded to by social institutions on the basis of the individual's gender presentation.

Frequency of the term Gender Interchanged with Sex



Number of article titles from 1960 to 2004 examined by the authors in which the term gender was used as an equivalent term for sex in sex-based research publications in the Journal of Applied Physiology and journals of the American Physiological Society

Impact of Chronic Illness

CDC's National Center for Chronic Disease Prevention and Health Promotion (NCCDPHP)

CHRONIC DISEASES IN AMERICA

6 IN 10

Adults in the US
have a **chronic disease**



4 IN 10

Adults in the US
have **two or more**

THE LEADING CAUSES OF DEATH AND DISABILITY
and Leading Drivers of the Nation's **\$3.8 Trillion** in Annual Health Care Costs



THE KEY LIFESTYLE RISKS FOR CHRONIC DISEASE

Leading Causes of Death, by Sex

All races and origins¹, Male, All ages²

All races and origins, Male, All ages	Percent
1) Heart disease	24.2%
2) Cancer	21.9%
3) Unintentional injuries	7.6%
4) Chronic lower respiratory diseases	5.2%
5) Stroke	4.3%
6) Diabetes	3.2%
7) Alzheimer's disease	2.6%
8) Suicide	2.6%
9) Influenza and pneumonia	1.8%
10) Chronic liver disease	1.8%

All races and origins¹, Female, All ages²

All races and origins, Female, All ages	Percent
1) Heart disease	21.8%
2) Cancer	20.7%
3) Chronic lower respiratory diseases	6.2%
4) Stroke	6.2%
5) Alzheimer's disease	6.1%
6) Unintentional injuries	4.4%
7) Diabetes	2.7%
8) Influenza and pneumonia	2.1%
9) Kidney disease	1.8%
10) Septicemia	1.6%

<https://www.cdc.gov/women/lcod/index.htm>



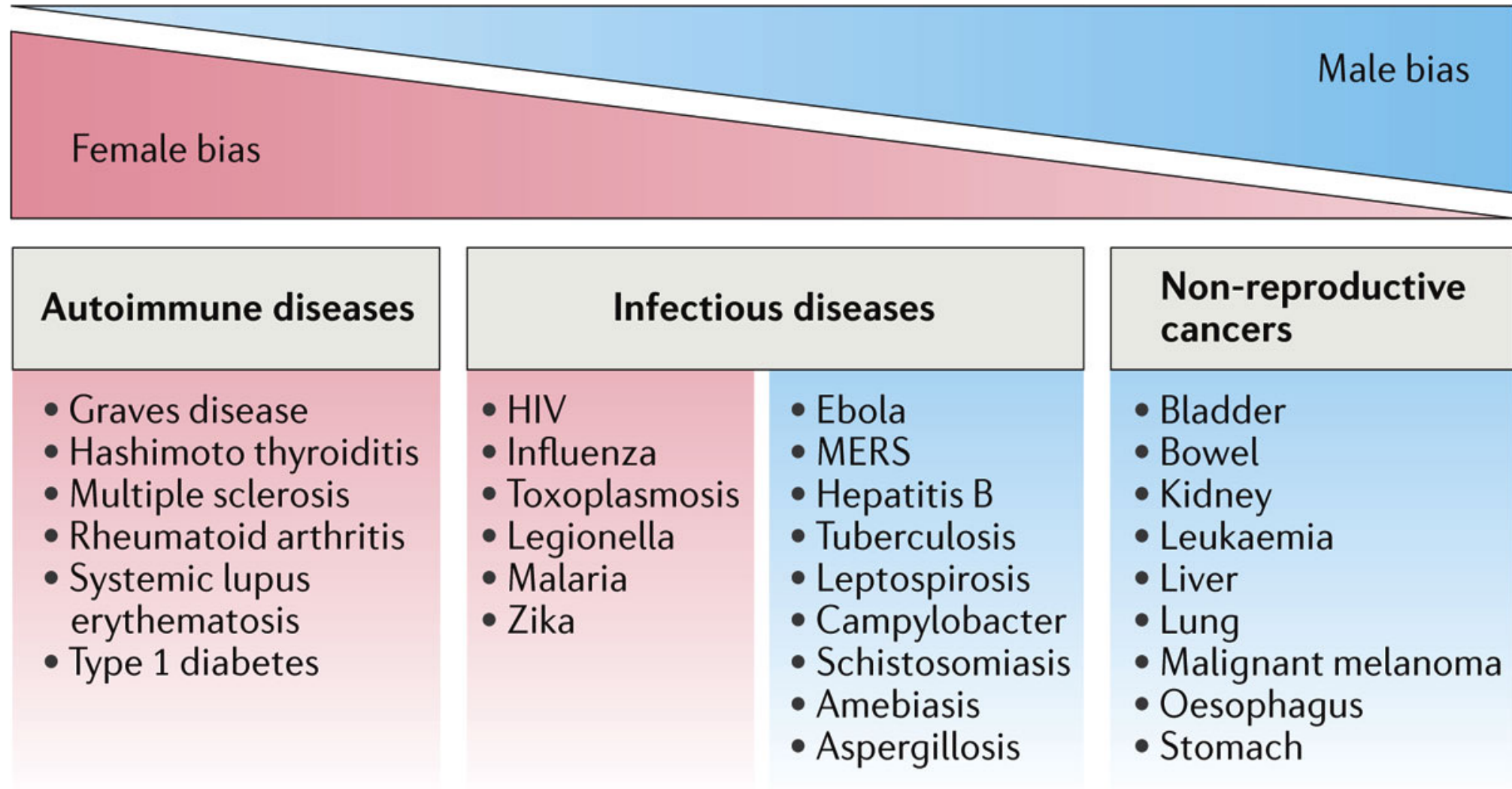
Evidence is provided through well-designed, well-conducted, and optimal reporting of research.

Healthcare is evidence-based.

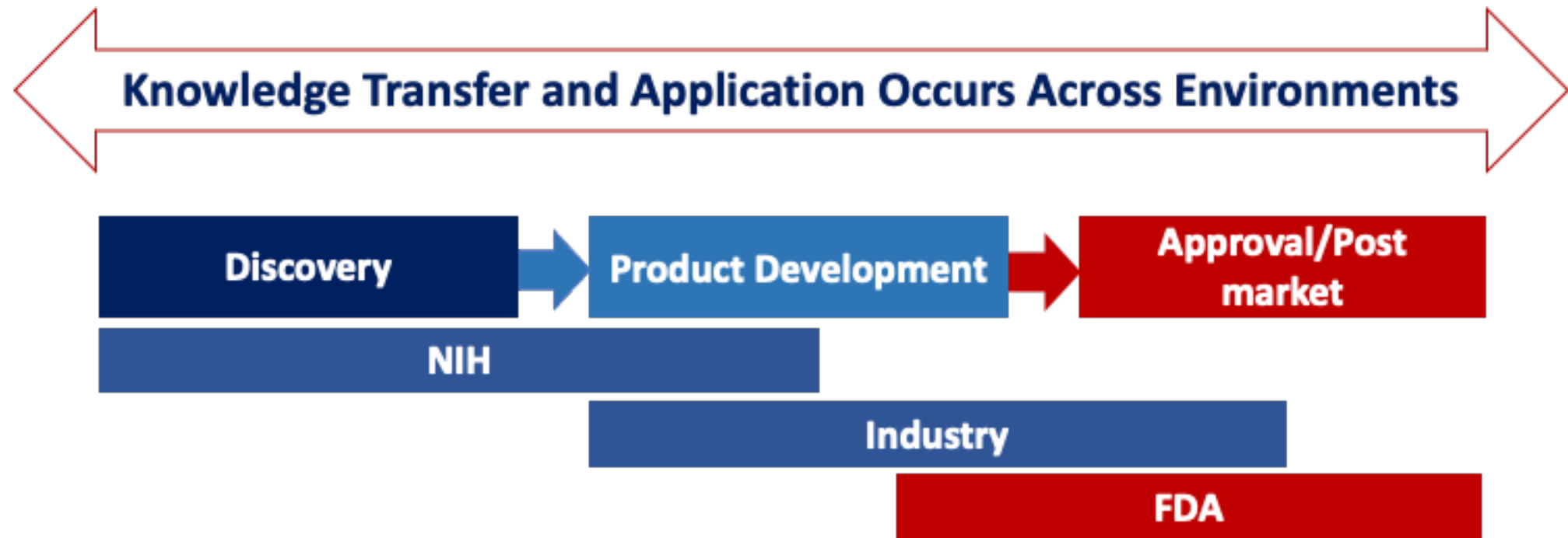
Without the data, cannot find the answer.

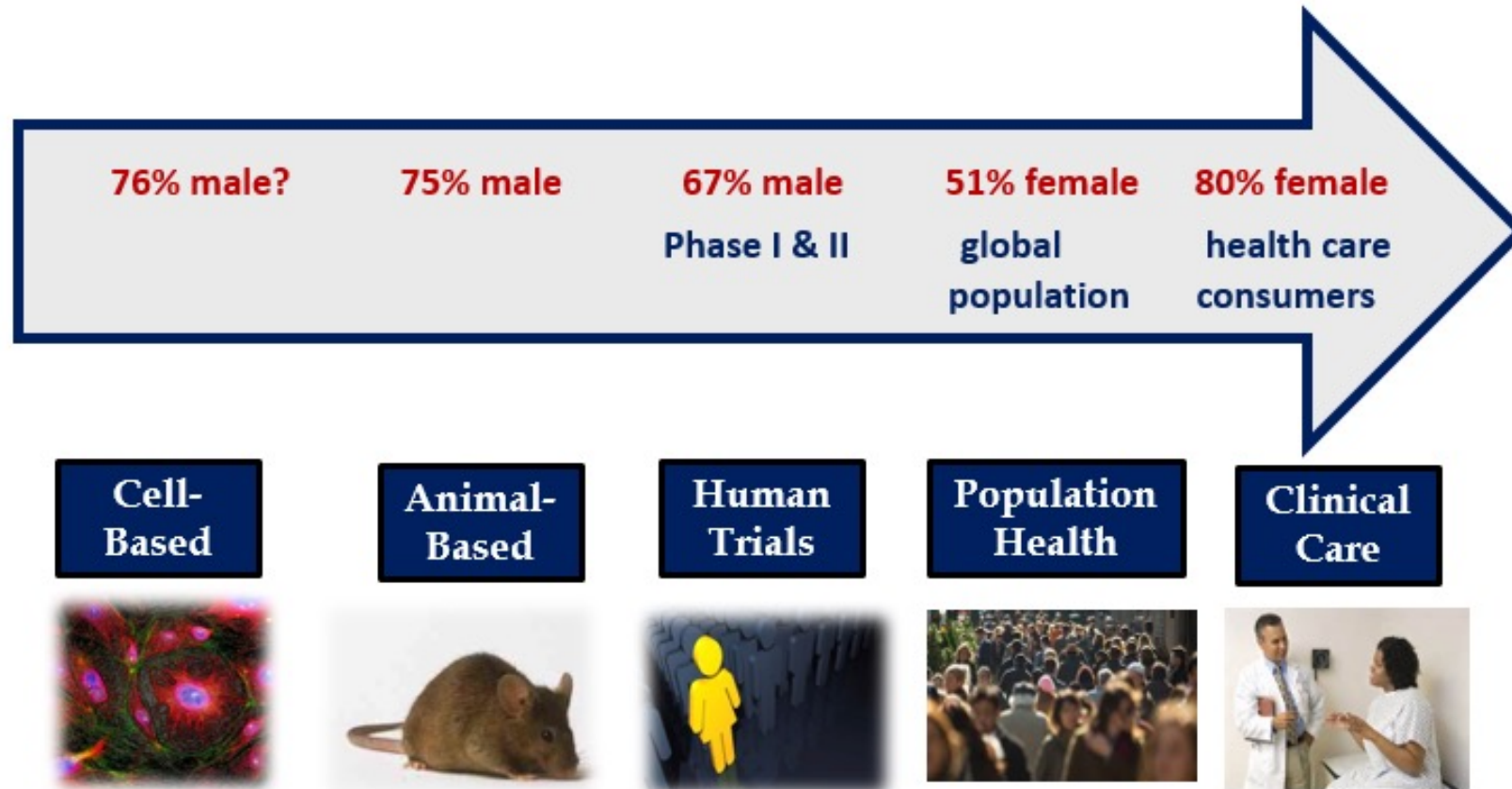
Biological Plausibility

Sex bias in infectious diseases, inflammatory diseases, and cancers



Research Environments and Research Expenditures Directly Impact the Burden of Chronic Diseases



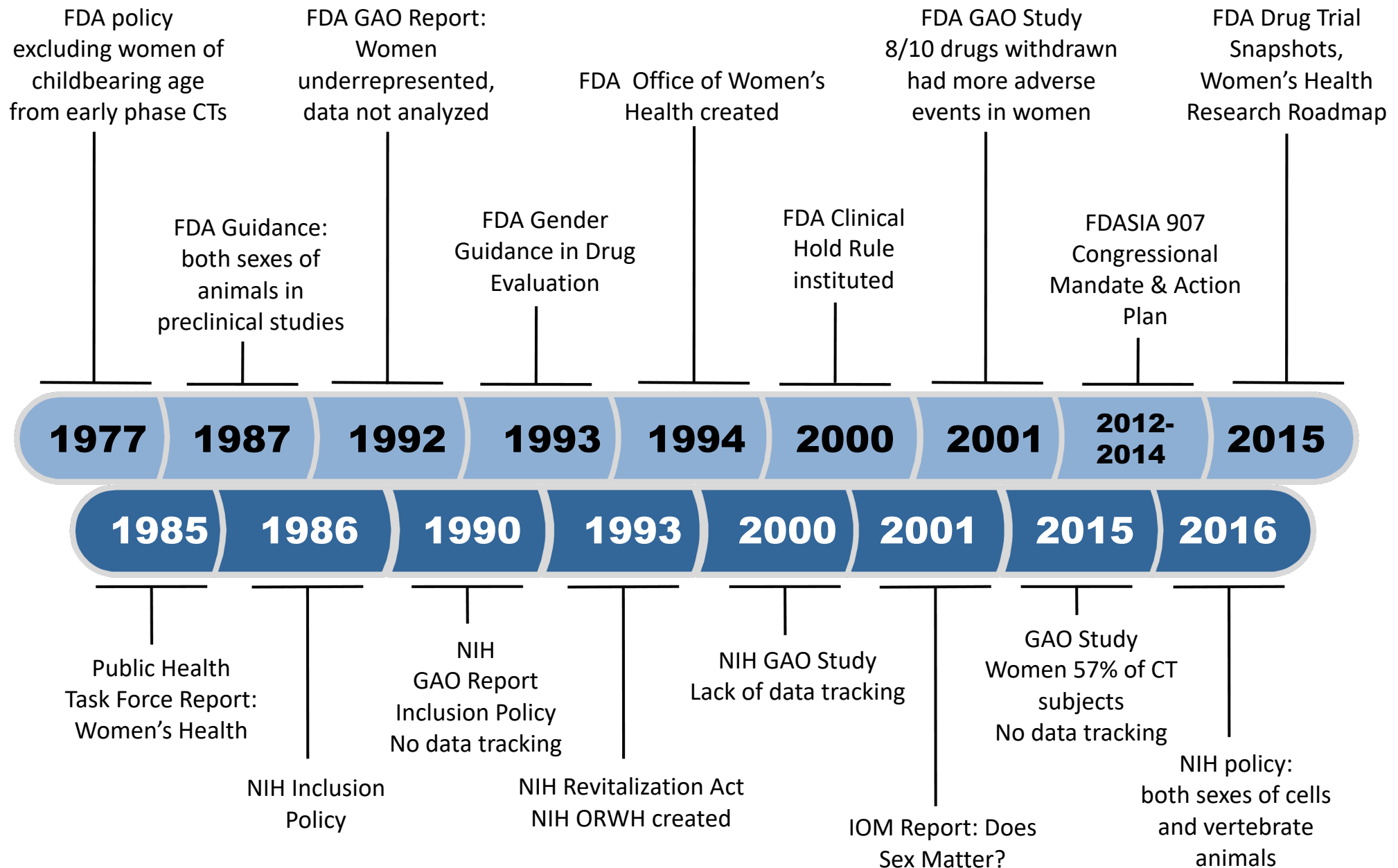


THE BIASED RESEARCH PIPELINE

Source: Jenkins M. TTUHSC Laura W. Bush Institute for Women's Health
J Women's Health 2016 Feb 1; 25(2): 181–187.



Health Policies Which Enable Understudy and Underreporting of Sex and Gender Differences





1977
FDA Policy:
No women of
childbearing age
in early phase
clinical trials



1985
NIH Inclusion
Policy

FDA Policy: No Women of Childbearing Age in Early Phase Clinical Trials



1977

- FDA recommended that **premenopausal women capable of becoming pregnant** be **excluded** from early phases of drug trials.
- “Capable of becoming pregnant” included women using reliable methods of contraception, women whose male partners had had vasectomies or used condoms, and women who were "single."
- Pertained only to early phases of drug development, but in practice the **participation of women in all phases were affected.**

NIH Inclusion Policy

- Consider the inclusion of women in the study populations for all clinical research efforts.
- General differences should be noted and evaluated.
- If women are not to be included, a **clear rationale** should be provided for their exclusion.



1985



1993
FDA
Guidance:
Gender
Differences
in Drug
Evaluation



1990
GAO Study:
NIH

GAO Study: NIH

- NIH policy on inclusion of women in clinical trials **was not well communicated or understood** within NIH or research community.
- Was **applied inconsistently** among institutes, and was applied only to extramural research
- There was “no readily accessible source of data on the demographics of NIH study populations,” so it was **impossible to determine whether NIH was enforcing its own recommendations.**



1990



1993

FDA Guidance: Gender Differences in Drug Evaluation

- Encourages inclusion of women in phase I and II studies
- **Expects inclusion of women** in efficacy studies
- **Expects analysis of data** in regard to race, age, gender**



1998
FDA
Demographic
Rule



1993
NIH
Revitalization Act
Office of Research on
Women's Health Created

NIH: Revitalization Act ORWH Created



1993

- Women & minorities to be included in clinical research
- Ensure that valid scientific analysis **could be** performed in determining whether differences existed between women and minorities in relation to other study subjects
- Include both sexes in adequate numbers to ensure data **could be** analyzed for an effect of gender on safety and efficacy of proposed intervention or drug.



1998

FDA Demographic Rule

REQUIRES sponsors to:

- **Tabulate** the trial population by age group, sex, and race in Investigational New Drug (IND) applications
- **Analyze safety and efficacy** by age group, sex, race, and other variables as appropriate in New Drug Applications (NDA)



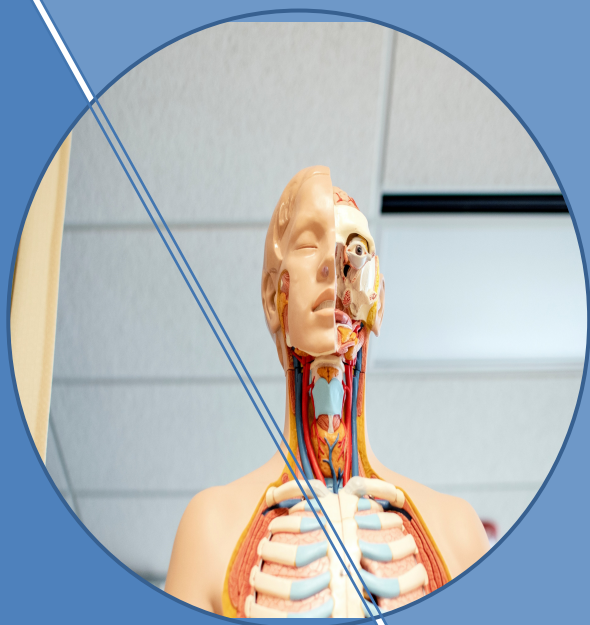
2000

Final Rule: FDA
(*Clinical Hold*):
NIH



2000

GAO Study: NIH



2000

GAO Study: NIH

- Women are in clinical trials at rates proportional to their numbers in general population, however...
- NIH **lacked protocols to enforce** the mandate to perform and report valid scientific analysis of sex differences in late stage (Phase III) clinical trials
- NIH **lacked adequate data tracking** of women and minorities enrolled in trials
- This lack of compliance **could significantly impact the ability to apply sex differences** research to clinical management and outcomes



2000

FDA Final Rule Clinical Hold

Permits the Agency to place a **clinical hold** on an investigational new drug application *if men or women with reproductive potential are excluded from participation only because of the risk or potential risk of reproductive or developmental toxicity* associated with use of the investigational drug



2015 NIH GAO Audit



NIH to balance sex in cell
and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

2016 NIH Sex as a Biological Variable Policy

2015 NIH GAO Study

57% of 2014 NIH-funded CT subjects were women

Does not track whether study includes plans for analysis by sex

Lacks summary data to identify potential sex differences

Limits assurance that NIH is supporting research that can **inform medical practice for both women and men**



2015

2016 NIH SABV Policy

COMMENT



NIH to balance sex in cell and animal studies

Janine A. Clayton and Francis S. Collins unveil policies to ensure that preclinical research funded by the US National Institutes of Health considers females and males.

282 | NATURE | VOL 509 | 15 MAY 2014

- **Consideration of sex may be** critical to the interpretation, validation, and generalizability of research findings.
- Appropriate analysis and transparent reporting of data by sex **may therefore** enhance the rigor and applicability of preclinical biomedical research.
- NIH **expects that sex as a biological variable** will be factored into research designs, analyses, and reporting in vertebrate animal and human studies.
- Strong justification from the scientific literature, preliminary data, or other relevant considerations must be provided for applications proposing to study only one sex.
- Investigators **are strongly encouraged** to discuss these issues with NIH program staff prior to submission of applications.


**NIH
2021**

**Sex as a Biological Variable:
A 5-Year Progress Report and Call to Action**
ME Arnegard et al JWH 2021

“The NIH is engaged in ongoing efforts to develop resources to help investigators consider SABV in their research.”



21st Century Research Crisis: Pregnant Women and Lactating Women



21st Century Cures Act (Sec 2041) Research Specific to Pregnant Women and Lactating Women (PRGLAC) Task Force *Phase 1 2017-2018*

PRGLAC Task Force Recommendations

PRGLAC Report: page 34 and Appendix page 368 describes finding of an audit of drug labeling regarding safety and efficacy in pregnant and lactating women

The lack of human data is striking.

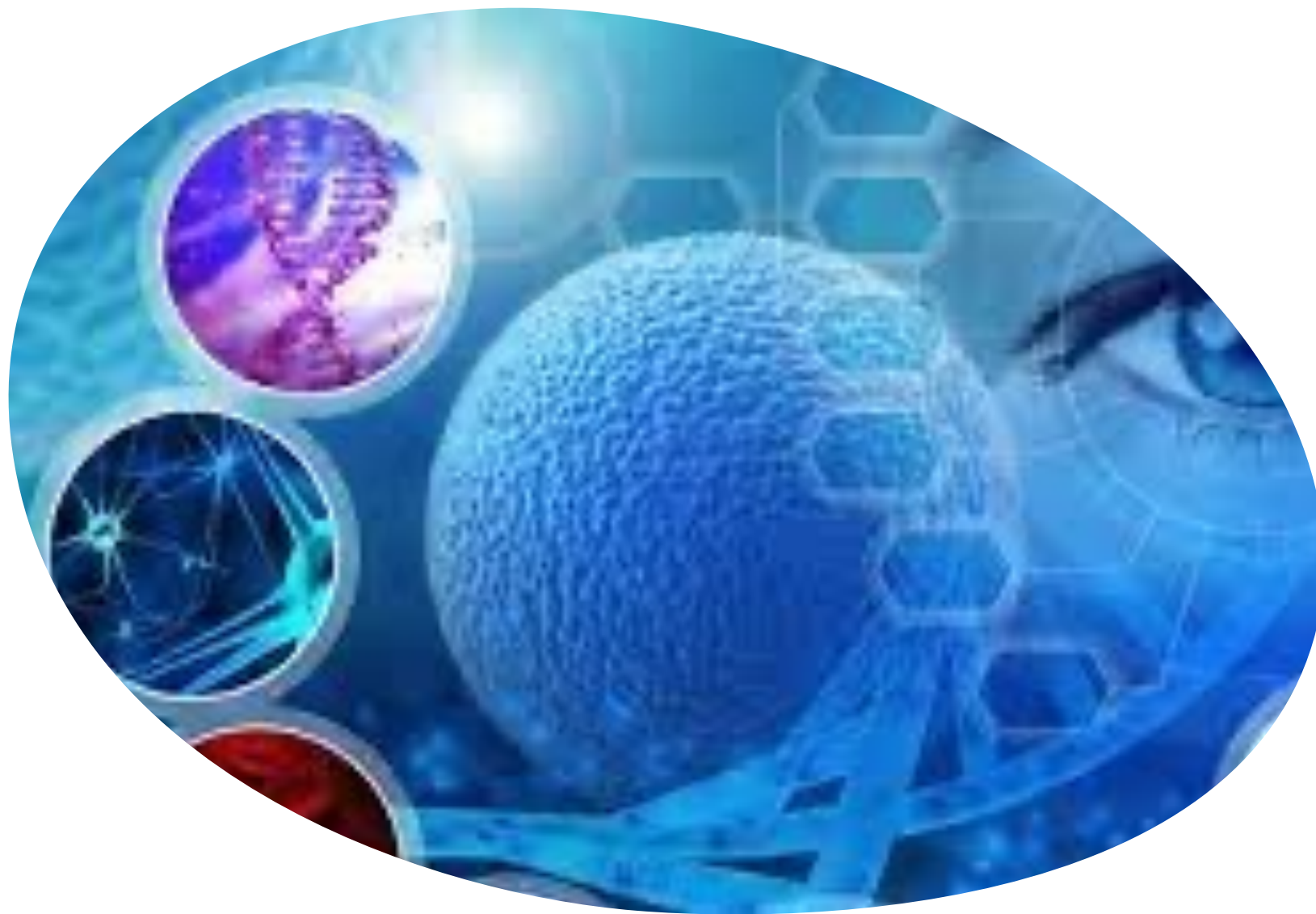
<https://www.nichd.nih.gov/about/advisory/PRGLAC/recommendations>.

PRGLAC: PLLR Labeling Audit

FDA staff identified a total of 575 prescription drug and biological product labeling changes (including labeling for new products) approved in PLLR format between June 30, 2015-September 30, 2017.

- 129 (22.4%) included human data about pregnancy
- 86 (15.0%) included human data about lactation
- 50 products (8.7%) included human data about both pregnancy and lactation
- 414 products (72%) had neither human data about pregnancy nor human data about lactation.

https://www.nichd.nih.gov/sites/default/files/2018-09/PRGLAC_Report.pdf



**We continue to
protect women
from research
instead of
with research**
(quoted by many)



NIH ORWH Cannot Advance The Health Of Women Alone

Achieving true progress requires change across many organizations and institutions

Points of Engagement:

Integrating Sex and Gender into Research, Education, and Clinical Care

Examples: Not All-Inclusive

Accrediting & Certification:

LCME, ACGME, NBME

Curriculum Gatekeepers

Deans of Curriculum, Block Leaders, Educational Policy Committee

Curriculum Integration Committee

Core Faculty Group Leading the Curriculum Integration

Emerging Technologies

Smart Phone and Tablet Apps

Faculty Champions

Grass-roots engagement of Basic and Clinical Faculty to Pioneer Efforts and Engage Others

Institutional Leadership

President, Deans, Assoc/Asst Deans, Chairs

Leading Sex & Gender Academic Health Centers

Mayo Clinic, UCSF, UCLA, TTUHSC, Univ of Wisc, Yale

Gender Medicine-Focused Organizations & Initiatives

SWHR, SGWHC, IGN, NAMS, OSSD, LWBIWH

Government Organizations

DHHS OWH, FDA, NIH ORWH, HRSA, CDC, NSF

Medical Database/Search Engine

PubMed, Ovid, Up-to-Date, Medscape, MD Consult

Journals & Other Scientific Publications:

Peer Reviewers, Editors, and Publishers

Media

Monographs, Reviews, Commentaries

Specialty Organizations

AAFM, ABIM, ACP, ACOG, APGO, AMSA (many more)

Social Media

Blogs, Twitter, Facebook, LinkedIn

Webinars & Online CME

Medscape, Web MD, NIH ORWH, LWBIWH CME



MORE WOMEN PARTICIPATING IN RESEARCH BUT WITHOUT MARKED PROGRESS IN OUTCOMES AND CLINICALLY MEANINGFUL KNOWLEDGE OF SEX AND GENDER DIFFERENCES

FDA and NIH health policies include language such as **might, may, could, should** which (as we have and will hear from the presentations today) result in research design and reporting by sex and gender optional...and as the data shows...far too many researchers have opted out.

This causes inequity in the application of scientific discovery across research and clinical care environments.

Call to Action

- Advocate for appropriate use of sex and gender terminology within your sphere of influence.
- NIH and FDA
 - Health policies need to include specific language which mandates research design, analysis, and reporting by sex and gender.
 - Periodic reporting by NIH and FDA of objective progress in advancing the health of women.
- NIH
 - adopt a definition of “chronic debilitating diseases in women”
 - allow tracking of funding by codifying this variable within applicable databases
- Crucial environments which require strategic and continuous engagement and advocacy
 - Congress
 - Pharmaceutical Industry



THANK YOU

mjenkins@greenvillemed.sc.edu

@MJenkinsMD