CONCEPT CLEARANCE:
Reissuance of *The Intersection of Sex and Gender Influences on Health and Disease Research*

ACRWH: April 6, 2022

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Associate Director,
Basic and Translational Research Programs
OUTLINE

1. Rationale and goals for research at the intersection of sex and gender influences on health and disease

2. R01 OD-19-029: The Intersection of Sex and Gender Influences on Health and Disease (R01 Clinical Trial Optional) Progress report and lessons learned

3. Considerations for concept reissuance
Rationale for a research initiative at the intersection of sex and gender

The ORWH program would be the only NIH-wide funding opportunity that focuses broadly on the health of women. It would:

• Encourage new research on the differential effects of sex and gender and their intersection on women’s health

• Increase collaborative partnerships across NIH institutes, Centers and Offices to support disease - agnostic topics to advance women’s health

• Provide an opportunity to conduct transdisciplinary research that is ordinarily beyond the scope of one NIH IC or Center

• To satisfy evolving public health needs and legislative mandates as identified in the 21st Century Cures Act, and the 2019-2023 Trans-NIH Strategic Plan for Women’s Health Research
New initiative builds on current ORWH programs to advance the integration of sex and gender considerations.

Sex and Gender

FOA

SEX & GENDER SUPPLEMENTS

U3 SUPPLEMENTS

SCORE PROGRAM

BIRCWH

Other Co-Funding

SABV Policy

Sex & Gender
FOA applications must address:

- Sex- and gender-related variables
- The intersection of sex and gender in health and disease
- The 2019-2023 Trans-NIH Strategic Plan for Women's Health Research Goal #1

RFA-OD-19-029: The Intersection of Sex and Gender on Health and Disease
Sex and Gender R01 applications address the Trans-NIH Strategic Plan for Women’s Health Research

**Goal 1 Objectives:**

1. Discover biological differences between females and males.
2. Investigate the influence of sex and gender on disease prevention, presentation, management, and outcomes.
3. Identify the immediate, mid-, and long-term effects of exposures on health and disease outcomes.
4. Promote research that explores the influence of sex and gender on the connection between the mind and body, and its impact on health and disease.
5. Expand research on female-specific conditions and diseases including reproductive stages, and maternal, and gynecologic health.

Additional FOA Considerations:
- Health Disparities
- Life Course/Lifespan
- IC-specific Priorities
- SARS-CoV-2 virus or COVID-19
**Sex and Gender R01:**
Overview (FY’20-23)

RFA-OD-19-029 Program:
NIH Investment
(2020 + 2021) - $9 Million
Overall Success rate - 17%

**Applications reviewed:**

- **2020:** 46
- **2021:** 48
- **2022:** 46

**Grants funded:**

- **2020:** 9
- **2021:** 8
- **2022:** TBD
**Sex and Gender R01:**

Eleven NIH ICs partnered with ORWH to accept applications focused on the intersection of sex and gender influences in disease.
Sex and Gender R01: Applications and Awards by Career Stage of PI

Program* success rate = 17%
NI/ESI success rate = 30%
% NI/ESI awards = 47%

*FY 2020 and FY 21
<table>
<thead>
<tr>
<th>GRANT #</th>
<th>PI</th>
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<tr>
<td>1 R01 AI154541</td>
<td>SCULLY, EILEEN P</td>
<td>Sex, Gender and the Immunopathogenesis of HIV</td>
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<td>1 R01 AI154533</td>
<td>SIMARD, JULIA F</td>
<td>Implicit Bias in the Evidence: An Evaluation of Female-Predominant Disease</td>
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<td>1 R01 AI154539</td>
<td>HOLODICK, NICHOL E</td>
<td>Sex Determines Age-related Changes in the Repertoire and Function of Natural Antibodies Protective against Streptococcus pneumoniae with Increasing Age</td>
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<td>1 R01 DA052016</td>
<td>FLENTJE, ANNESIA</td>
<td>Substance use and DNA methylation at the intersection of sex and gender</td>
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<td>1 R01 AI154518</td>
<td>BOSQUE, ALBERTO</td>
<td>Hormonal control of HIV latency</td>
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<tr>
<td>1 R01 AI154535</td>
<td>PISARSKA, MARGARETA</td>
<td>The impact of sex and gender on disease progression, from developmental origins</td>
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<tr>
<td>1 R01 ES032163</td>
<td>FLAWS, JODI A</td>
<td>Gender and sex differences in phthalate-induced toxicity in the reproductive system</td>
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<td>1 R01 ES03225</td>
<td>SHAVIT, JORDAN A</td>
<td>Dissection of the mechanisms underlying sex-influenced cardiovascular disease</td>
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<td>1 R01 AG074392-01</td>
<td>KIRKLAND CALDWELL JESSICA</td>
<td>Interactions of Sex and Gender Factors in Risk for Alzheimers Disease: Links Between Stress, Neural Activity, Inflammation, and Memory</td>
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<td>1 R01 AI164504-01</td>
<td>JEFFERIES CAROLINE</td>
<td>Sex and gender differences in lupus - intersection between immunometabolism, epigenetic remodeling and cardiac involvement</td>
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<td>1 R01 DA054617-01</td>
<td>TOMKO RACHEL LYNN</td>
<td>Gender and Sex Hormone Influences on Cannabis Use Disorder Remission</td>
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<tr>
<td>1 R01 DE029963-01A1</td>
<td>RUSSELL STEFANIE L</td>
<td>Pathways to Oral Health Among Low-income Pregnant Urban Women</td>
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<td>1 R01 HG011405-01A1</td>
<td>DAVIS LEA K</td>
<td>Elucidating the phenome-wide impact of sex and gender on disease</td>
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<td>1 R01 HG011393-01A1</td>
<td>DEMEO DAWN L</td>
<td>Networks Tools to Understand Sex- and Gender-Specific Drivers of Disease</td>
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<td>1 R01 HL159760-01</td>
<td>MAJITHIA AMIT</td>
<td>Credentialing novel cardiovascular disease genes in women by sex-specific genomic investigation of insulin resistance</td>
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<tr>
<td>1 R01 HL159764-01</td>
<td>SILVEYRA PATRICIA</td>
<td>Gonadal hormones as mediators of sex and gender influences in asthma</td>
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<tr>
<td>1 R01 NR020309-01</td>
<td>YBARRA MICHELE L</td>
<td>Harnessing the power of technology to develop a population-based HIV prevention program for trans girls</td>
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**SPOTLIGHT: Sex and Gender RO1 awardee FY 2021**

**Gonadal hormones as mediators of sex and gender influences in asthma 1 R01 HL159764-01**

**The Study:** The first to characterize estrogen-mediated mechanisms of inflammation in asthma phenotypes in the male and female lung, contributing to the characterization of sex- and gender specific factors accounting for inter-individual differences, as well as the effects of feminizing hormone therapy in lung pathobiology.

**Innovation:** The use of the four-core genotype mouse as well as human cells exposed to in an asthma paradigm generating inflammatory responses.

**Significance:** Potential to provide mechanistic and pre-clinical data that could improve current clinical practices for cisgender and transgender women.

* Patricia Silveyra, Ph.D*.
Associate Professor, Indiana University at Bloomington
The *Sex and Gender R01* program has successfully met its objectives to date:

- To stimulate research that incorporates and/or enhances understanding of the influence of sex and gender **and** its intersectionality in health outcomes across a broad array of scientific disciplines.

- To include one or more **sex-based variables**, including but not limited to: evaluation of sex as a biological variable; sex-based comparisons on conditions in females and males; biologically based variables such as hormones, physical features, anatomy, or biomarkers.

- To include one or more **gender-based variables**, including but not limited to: assessment of psychosocial variables relevant to health conditions; measures of socially constructed roles, experiences, identities, or behaviors of girls, women, boys, men, or gender diverse people.
RFA-OD-19-029 *Sex and Gender R01* program provides unexpected dividends to the scientific community to advance women’s health:

- Recruiting new and early-stage investigators into biomedical research investigations on sex and gender
- Identifying a cadre of reviewers with broad expertise in sex and gender and the intersection of sex and gender research
- Stimulating cross-cutting research on understudied populations
- Advancing research on the consideration of sex and gender research and its intersectionality in SARS CoV-2
**Sex and Gender R01 program: Future Directions**

- Reissuance of The Intersection of Sex and Gender Influences on Health and Disease Research - R01 mechanism

- Encourage additional ICs to partner with ORWH

- Expand scientific areas of interest:
  - COVID-19
  - Leverage and curate large sex and gender datasets

- New Investigators Forum
Thank you!
Comments and Feedback?
EXTRA SLIDES
Gonadal hormones as mediators of sex and gender influences in asthma  1 R01 HL159764-01

The Study: The first to characterize estrogen-mediated mechanisms of inflammation in asthma phenotypes in the male and female lung, contributing to the characterization of sex- and gender specific factors accounting for inter-individual differences, as well as the effects of feminizing hormone therapy in lung pathobiology

Innovation: The use of the four-core genotype mouse as well as human cells exposed to in an asthma paradigm generating inflammatory responses.

Significance: Potential to provide mechanistic and pre-clinical data that could improve current clinical practices for cisgender and transgender women
Sex and Gender R01: Applications and Awards by NIH Institute

![Bar chart showing applications and awards by NIH Institute](chart.png)

- **2020 Awards**: 0, 0, 5, 0, 1, 0, 2, 0, 0, 0, 0, 0
- **2020 Applications**: 1, 11, 13, 1, 9, 2, 4, 2, 0, 2, 3
- **2021 Awards**: 0, 0, 5, 1, 1, 0, 1, 0, 2, 2, 0, 1
- **2021 Applications**: 1, 4, 10, 0, 3, 4, 2, 2, 14, 1, 5
- **2022 Applications**: 3, 5, 6, 1, 2, 3, 1, 1, 20, 2, 2
Sex and Gender RO1 program merits renewal

Cutting edge research by New Investigator is uncovering sex, gender, and race influences in clinical care

**Problem** | Over-reliance of the evidence base and potential implicit bias may perpetuate diagnostic delay and poorer management for certain patients

**Project Focus** | Clinicians’ use of mental shortcuts** in diagnostic decision making for conditions that do not have definitive diagnostic tests

- Rules of thumb based on representativeness of given case among “the average” case
- Repeated use introduces errors into evidence base – may lead to confirmation bias in evidence-based medicine

**Testing** |

- Does a patient’s deviation from the “norm” based on the evidence influence the diagnosis?
- In these circumstances, does a patient’s diagnosis vary when all that differs is their sex, gender, and/or race?
- Are there differences in diagnosis of female-predominant diseases in specialty & primary care?
- What’s the clinicians’ perspective regarding differential diagnoses?

**Methods** | Adapts a novel method by combining methods from sociology, experimental design, and behavioral science

*Also an Early Stage Investigator
** Cognitive heuristics
R01-Equivalent Grants, New (Type 1): Competing Applications, Awards, and Success Rates, by Career Stage of Investigator

Established Contact PI

- **Applications**
- **Awards**
- **Success Rate**

Data for this report are available at NIH Data Book - https://report.nih.gov/nihdatabook/report/136
• **ORWH is encouraging application submissions on the influence and intersection of sex and gender factors related to the SARS-CoV-2 virus or COVID-19 disease in alignment with RFA-OD-19-029.**

• **Within the focus of RFA-OD-19-029, research topics of interest could include investigations of sex- and gender-related risk factors associated with COVID-19 disease prevalence, treatment and prevention, including the influence of co-morbid conditions. Studies examining the influence and intersection of sex and gender on COVID-19 related to health-seeking behaviors, access to health care, and health care systems are also within the scope of this funding opportunity.**

• **Applications submitted in response to this FOA are encouraged to consider populations of women that may be at higher risk for adverse COVID-19 outcomes due to: biological, physiological and genetic factors, cultural and socioeconomic factors such as education, sexual orientation, gender expression or identity, effects of poverty, access to care, quality of care, and access to opportunities for inclusion in clinical trials and studies. Of particular interest are NIH-designated health disparity populations, women living in underserved rural or urban settings, pregnant and lactating women, women who are frontline healthcare workers, or women who are incarcerated or with low socioeconomic status.**

• All other aspects of this FOA remain the same.