



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

# Fortifying Opportunities to Advance Female-Specific Chronic Disease Research

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# Disclosures

- President-Elect, World Endometriosis Society
- Trustee, World Endometriosis Research Foundation
- Member, Interdisciplinary Network on Female Pelvic Health, Society for Women's Health Research
- Past Chair, American Society for Reproductive Medicine Endometriosis Special Interest Group
- International Advisor, European Society of Human Reproduction and Embryology Special Interest Group for Endometriosis and Endometrial Disorders
- Member, International Endometriosis Advisory Committee, AbbVie
- Statistical Editor – *Human Reproduction*
- Field Chief Editor – *Frontiers in Reproductive Health*
- Research Grant Recipient – NIH, DoD, AbbVie, Marriott Family Foundations

The views expressed in this presentation are the presenters and do not represent any private or public institution, professional society, or the US federal government.

# Chronic Debilitating Conditions

## Female Specific

- Gyn Cancers
- Menstrual abnormalities
- Fibroids
- **Endometriosis**
- Adenomyosis
- Infertility
- Miscarriage
- PCOS
- Pelvic Floor d/o
- Menopause
- PID

## Female Prevalent

- Depression
- Migraine
- Breast Cancer
- Autoimmune
- Rheumatoid Arthritis
- Multiple Sclerosis
- STIs
- Chronic Fatigue
- Fibromyalgia
- Osteoporosis
- Candidiasis

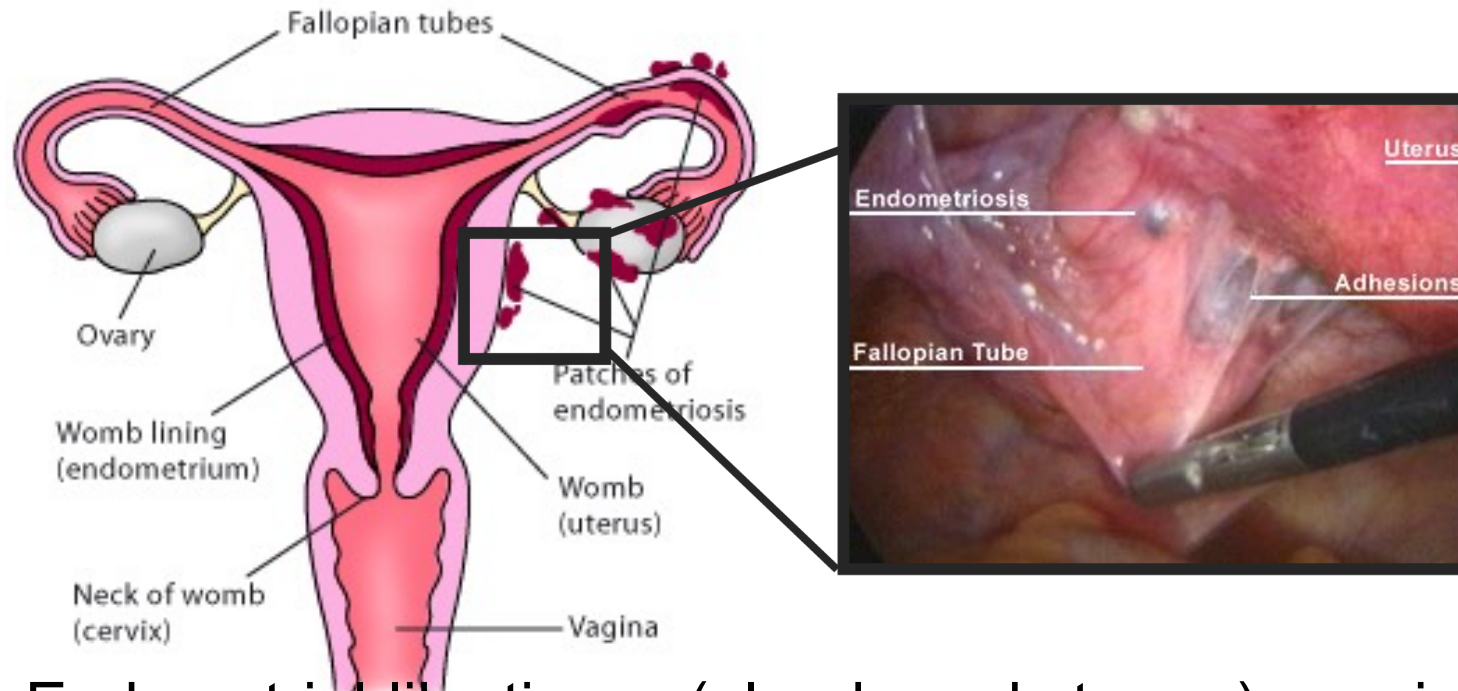
## Poorly Understood in Women

- Violence
- Dementia
- Osteoarthritis
- Endocrine d/o
- Metabolic d/o
- Blood d/o
- Immune d/o
- Recurrent UTIs
- HIV
- Neuropathy
- Incontinence
- Chronic pain

## Morbid in Women

- Heart Disease
- Low back pain
- COPD
- Drug use d/o
- Stroke
- Diabetes
- Obesity
- Influenza
- Pneumonia

# What is Endometriosis?



200 MILLION  
WOMEN WORLDWIDE



Endometrial-like tissue (glands and stroma) growing outside of the uterus  
-- Peritoneal cavity, but also distal sites (e.g. lung, heart, brain)

Estrogen-dependent, progesterone-resistant, inflammatory disorder

Zondervan, Becker, Missmer. *NEJM* 2020

Shafrir A, et al. *Best Pract Res Clin Obstet Gynaecol* 2018

Simoens S, et al. *Hum Reprod* 2012

# Diagnostic Obstacles in Female-Specific Conditions

- Symptoms are nonspecific or associated with other disorders
  - Circuitous path
  - Mistakenly dismissed as “normal” menstrual pain
  - Embarrassment specific to menstruation and pelvic pain



**6.7 YEARS**

*average delay in diagnosis*



**65% Misdiagnosed**

**Median see 5+ MDs before correct diagnosis**

Zondervan, Becker, Missmer. *NEJM* 2020

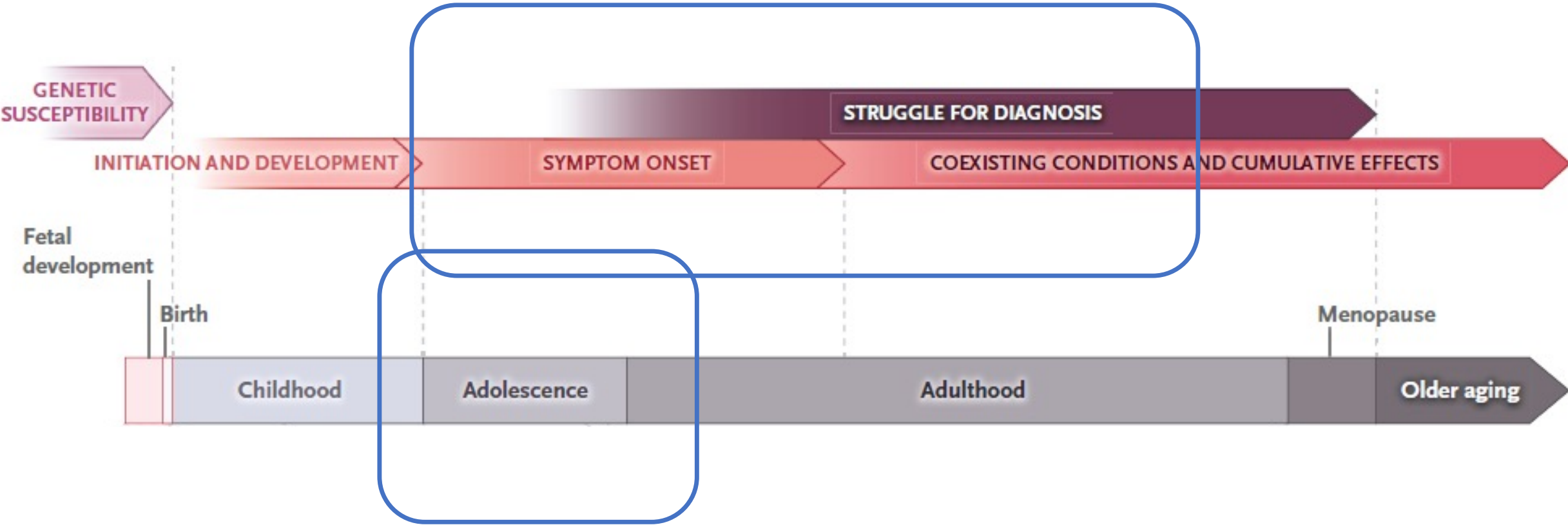
Ballard K, et al. *Fertil Steril* 2006

Nnoaham K, et al. *Fertil Steril* 2011

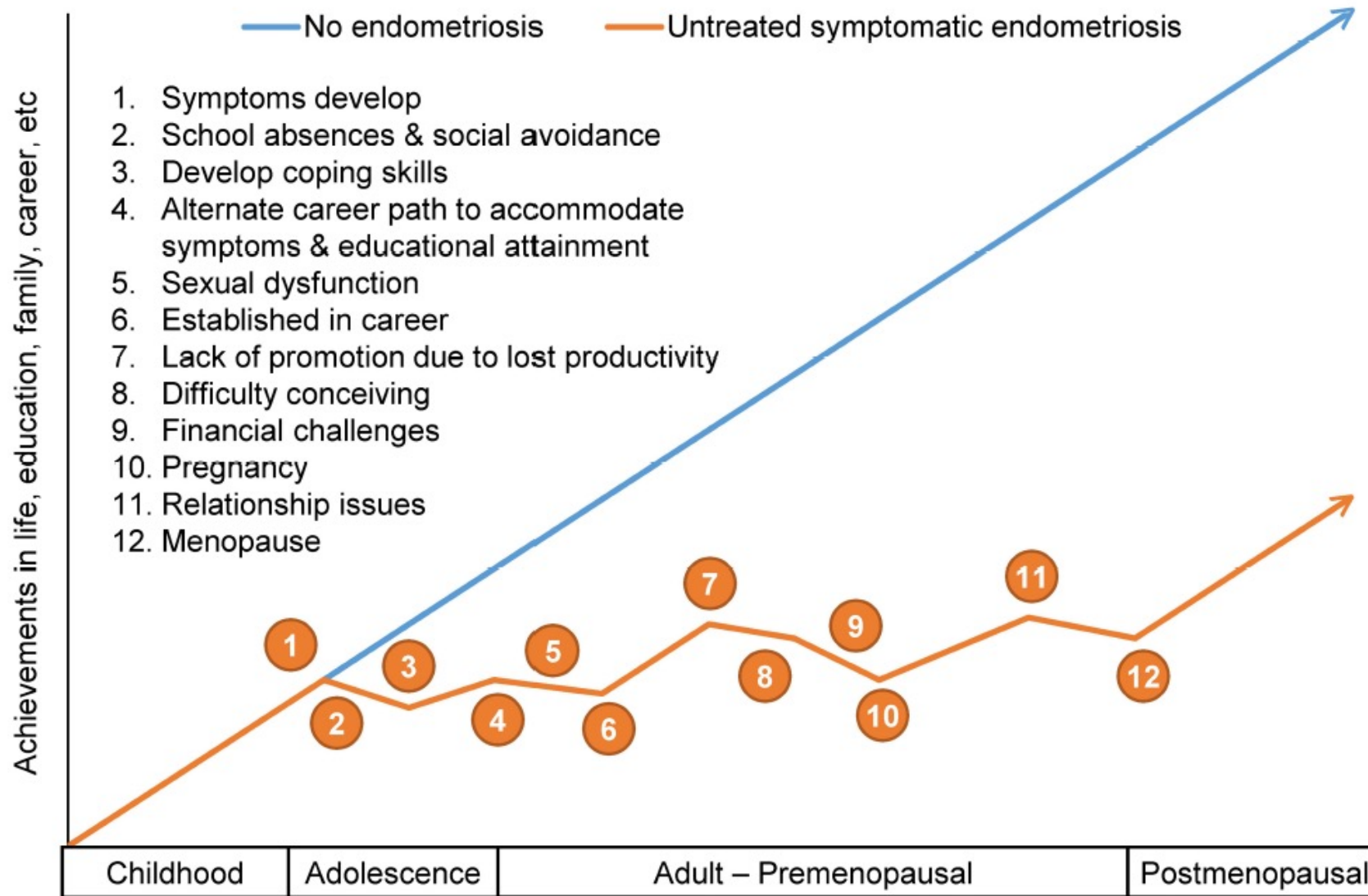
Mihalyi A, et al. *Hum Reprod* 2010

WaterAid – No Shame Campaign 2017

# Treatment Obstacles in Female-Specific Conditions

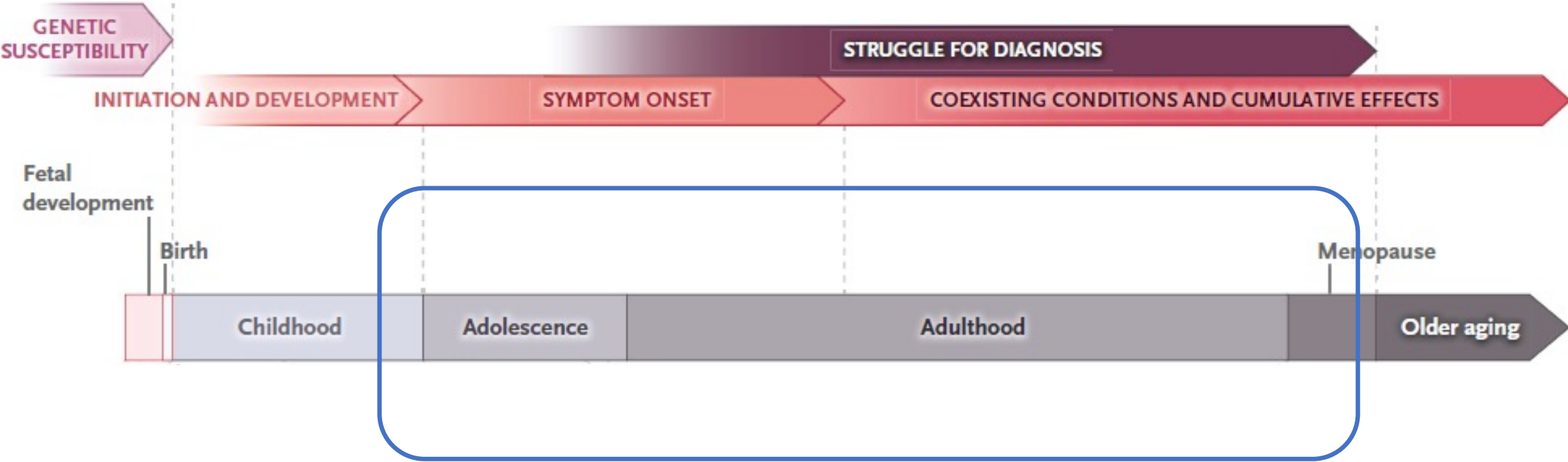


## Life Course Impact of Untreated Symptomatic Endometriosis



**Figure 2** Theoretical effects of endometriosis on life-course trajectory. Life exposures and their influences on a patient's attainments in life, education, family, career, etc. A comparison of untreated or persistently symptomatic endometriosis vs no endometriosis.

# Treatment Obstacles in Female-Specific Conditions





# Treatment Obstacles in Female-Specific Conditions



PERSPECTIVE AND CONTROVERSY

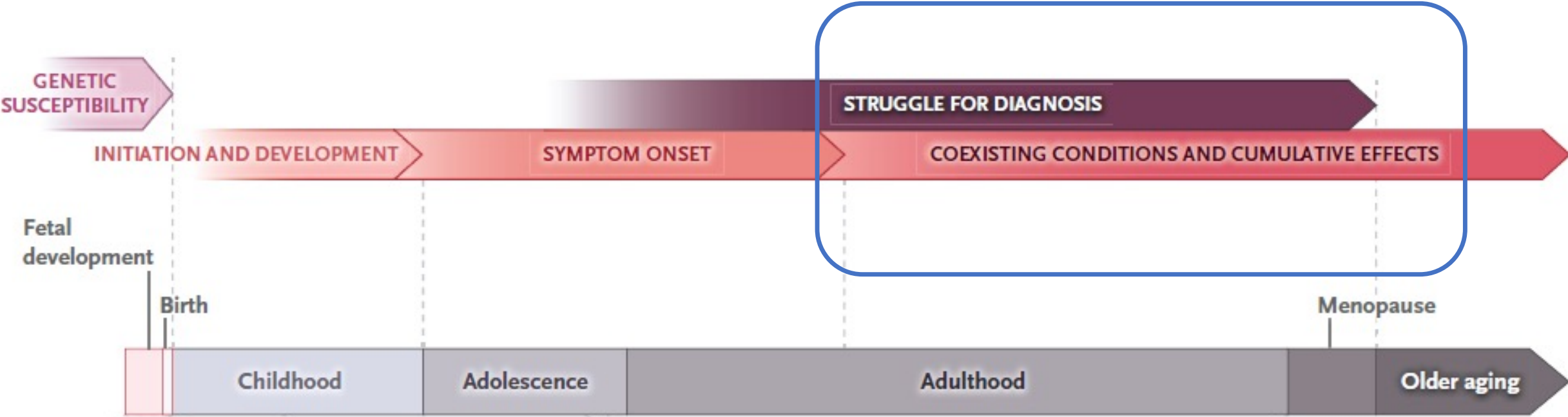
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## Moving Beyond Reflexive and Prophylactic Gynecologic Surgery



Elizabeth A. Stewart, MD; Stacey A. Missmer, ScD; and Walter A. Rocca, MD, MPH

# Treatment Obstacles in Female-Specific Conditions



## Coexisting Conditions and Subsequent Disorders

### Gynecologic

Uterine fibroids, adenomyosis

### Pain

Fibromyalgia, migraine

### Central sensitization

### Gastroenterologic

Irritable bowel syndrome, ulcerative colitis

### Genitourinary

Interstitial cystitis

### Mental health

Depression, anxiety

### Immunologic

Rheumatoid arthritis, systemic lupus erythematosus, multiple sclerosis, allergies, asthma

### Cancer

Ovarian cancer, melanoma, thyroid cancer

### Cardiovascular disease

**Figure 2. Multisystemic Endometriosis Phenome.**

Zondervan, Becker, Missmer. *NEJM* 2020  
Kvaskoff M, et al. *Hum Reprod Update* 2015  
Missmer S. *Int J Epidemiol* 2009

# Research Obstacles in Female-Specific Conditions

Environmental / Behavioral exposures

Requires:

Detailed clinical and phenotypic data

Collected from many women

Tied to critical lifecourse windows

Inflammatory  
indicators / markers

**RARELY** exist in biobanks or in eMR!

Exist in longstanding prospective cohorts

# NCI Cohort Consortium

Home / Research Resources / NCI Cohort Consortium

## Overview

The NCI Cohort Consortium is an extramural-intramural partnership formed by the National Cancer Institute (NCI) to address the need for large-scale collaborations to pool the large quantity of data and biospecimens necessary to conduct a wide range of cancer studies.

[//dccps.cancer.gov](https://dccps.cancer.gov) collaborative network of

## About

Byla

Lead

Mem

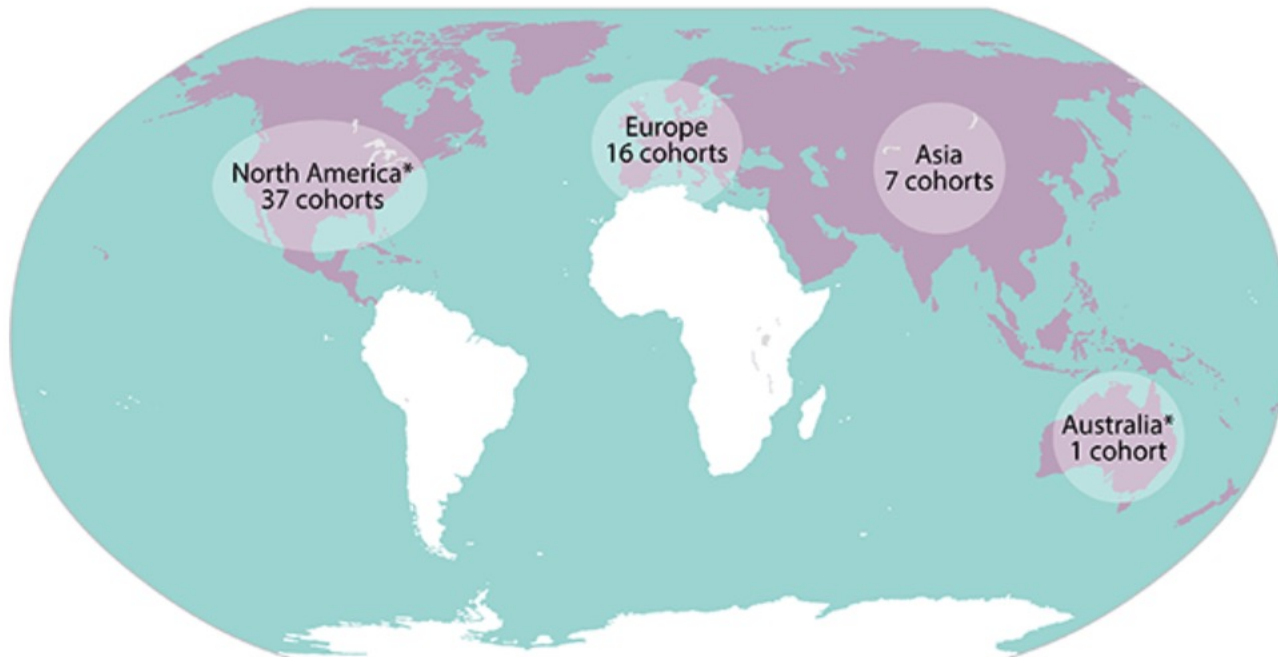
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## Current Members

The NCI Cohort Consortium membership is international in scope. It includes investigators responsible for more than 61 high-quality cohorts who are studying large and diverse populations in more than 15 different countries.

The purple regions on the map below represent the locations of populations that NCI Cohort Consortium members are currently studying.

Map of NCI Cohort Consortium Membership by Continent, 2021



# Research Obstacles in Female-Specific Conditions

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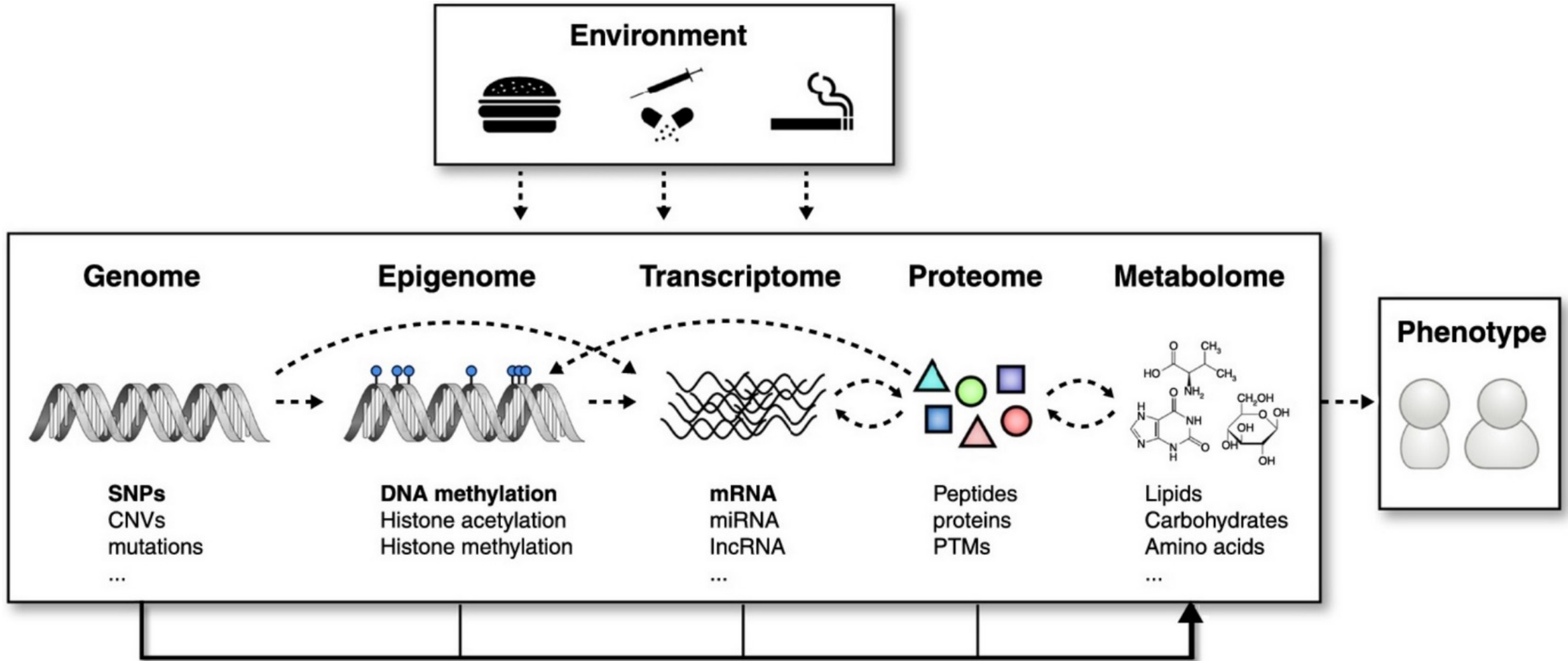
Inflammatory  
indicators / markers

RARELY exist in biobanks or in eMR!

Exist in longstanding prospective cohorts

**BUT Don't have pain or endometriosis data**

# Research Obstacles in Female-Specific Conditions



# Publicly available datasets... No endometrium

- Link genetic results to levels of gene and protein expression
- Examine the environment's impact on this ('epigenetics')
- Target tissue: endometrium and constituting cells

ENCODE at UCSC (2007-2012) - Downloads - Experiment Summary - ChIP-seq

ENCODE Experiment Matrix hg19 2007 - 2012

ROADMAP epigenomics PROJECT

HOME PARTICIPANTS BROWSE DATA PROTOCOLS COMPLETE EXPERIMENTS TOOLS PUBLICATIONS

SEARCH: [ ] GO

OVERVIEW PROJECT DATA MAPPING CENTERS PROTOCOLS & STANDARDS PUBLICATIONS

ABOUT THE ENCODE EXPERIMENT MATRIX

The ENCODE Experiment Matrix is a set of web pages that visually summarize the types of data generated after 2012, see the ENCODE Portal, [encodeproject.org](http://encodeproject.org).

The data summarized here is all hosted at UCSC as browser tracks and downloadable files. Experiment Matrix page provides a more detailed view of the chromatin immunoprecipitation marked with a colored dot. The companion Experiment Summary page lists the number of genome.

An ENCODE experiment is defined as a biochemical assay and follow-on data analyses performed on different views of the data (e.g., enrichment signal graph, peak calls) and is available for download analysis methods. Data for multiple replicates are included in a single experiment.

To display or download ENCODE data, select either the tracks or files option in the search for window (via the UCSC Track Search or File Search tool) that lists the full set of browser track the list of downloadable files.

These pages are best viewed in Firefox, Chrome, or Safari browsers.

Assays

search for: tracks files

Cell Types

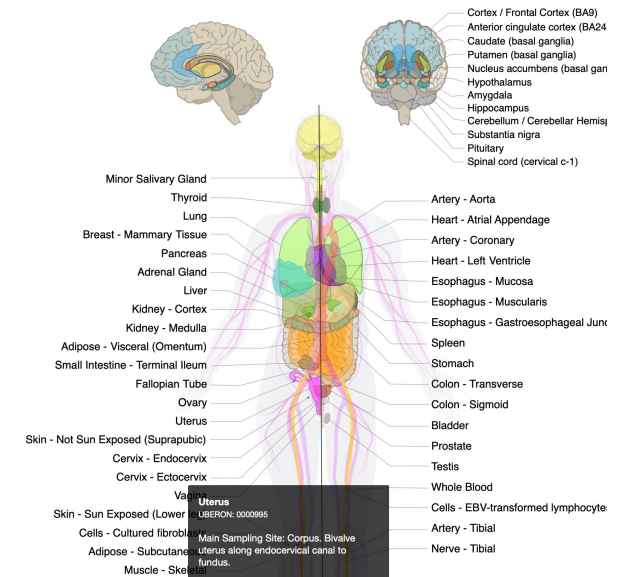
NIH Roadmap Epigenomics Mapping Consortium

The NIH Roadmap Epigenomics Mapping Consortium was launched with the goal of producing a public resource of human epigenomic data to catalyze basic biology and disease-oriented research. The Consortium leverages experimental pipelines built around next-generation sequencing technologies to map DNA methylation, histone modifications, chromatin accessibility and small RNA transcripts in stem cells and primary ex vivo tissues selected to represent the normal counterparts of tissues and organ systems frequently involved in human disease. The Consortium expects to deliver a collection of normal epigenomics that will provide a framework or reference for comparison and integration within a broad range of research. The Consortium also aims to close the gap between data

## GTEX Portal

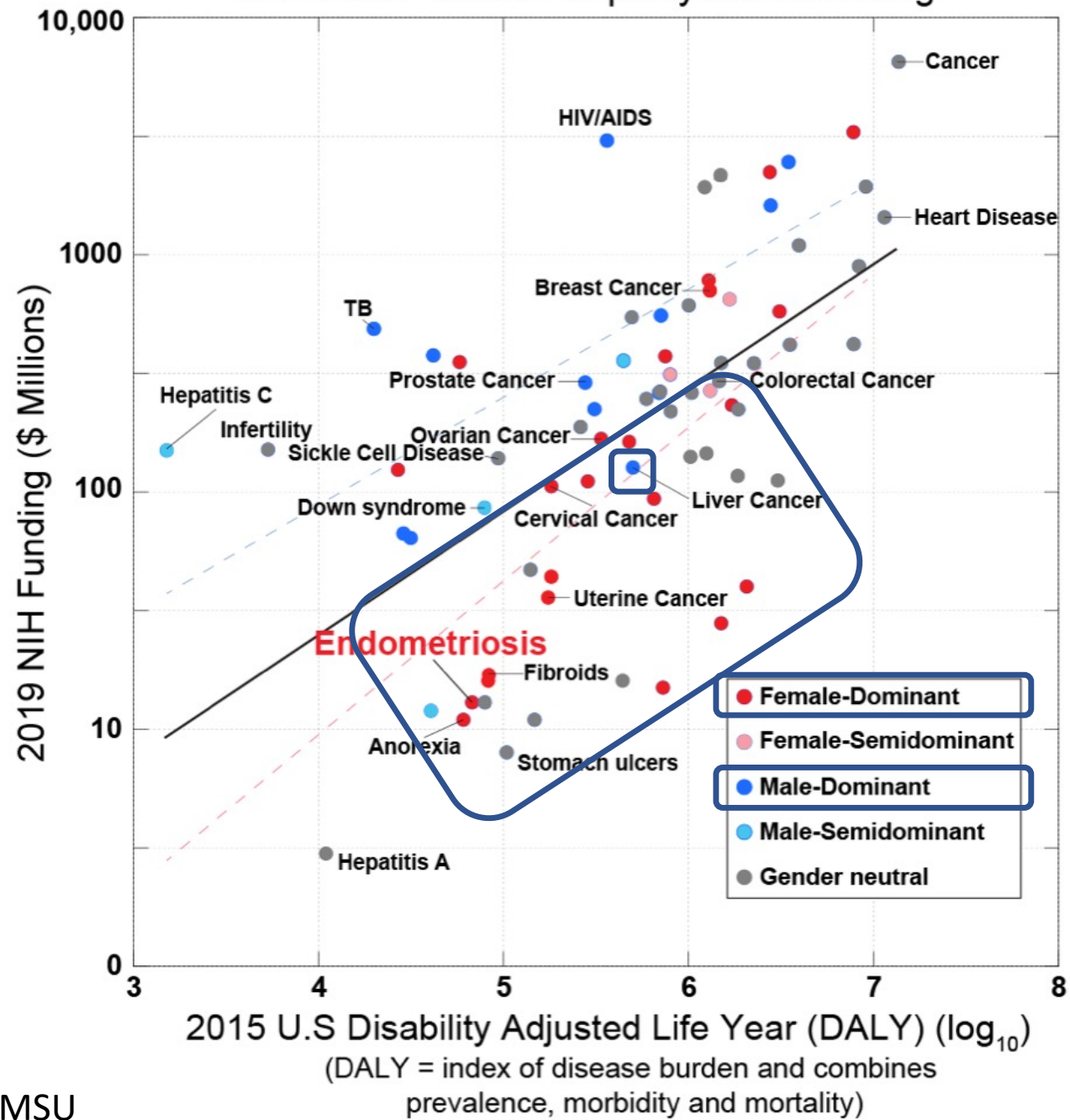
### Tissue Sampling Sites

This page provides a visual representation of the biospecimen source sites (BSSs) for the collection of tissue from postmortem/organ procurement cases for the Genotype-Tissue Expression (GTEx) project. The full documentation on tissue collection procedures can be found on the [GTEx Tissue Harvesting Work Instruction](#).





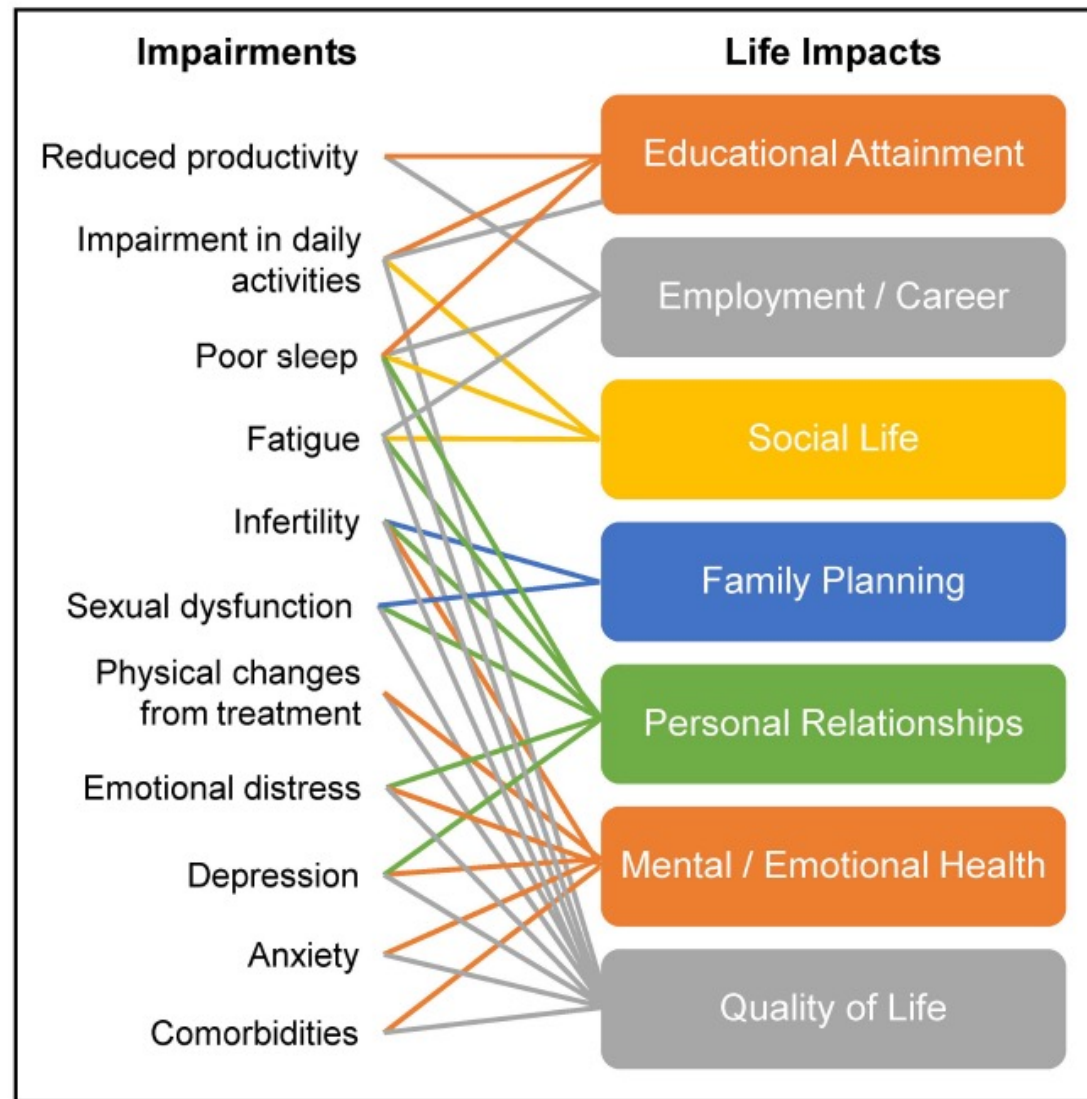
# Mirin 2020. Gender disparity in NIH funding



# Need to Advance Female-specific Chronic Disease Research

- Adding women to a study is not the same as studying women
- Intermittent research in women's health insufficient
- Female-specific (and female-dominant) conditions result in life-long disability
- Recommendations:
  - Establish a National Institute of Women's Health
  - Specifically address female-specific and female-dominant disorders across the lifecycle
  - Collaborate with other institutes whose missions involve exposures or diseases that impact women
    - Build female-specific foundational normative and chronic condition databases
    - Design trials directly related to the disease and symptom experience in women

**Following are extra slides for potential questions**



**Figure 1** Connections between endometriosis-associated impairments and life impacts.

# Impact Factors by Field

- Reproductive Medicine
  - AJOG (Gray) 6.50
  - Fertility and Sterility 6.31
  - Human Reproduction 5.73
  - Ultrasound in ObGyn 5.57
  - Obstetrics and Gynecology (Green) 5.52

# Impact Factors by Field

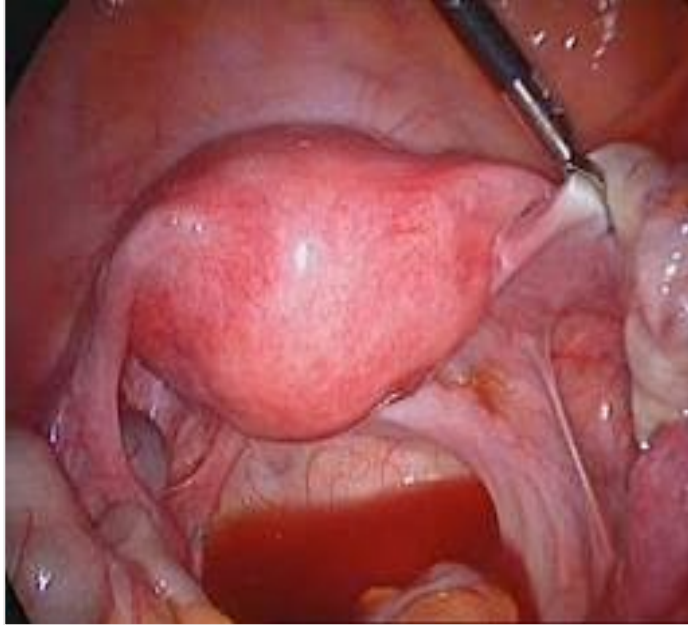
- Cancer (173)
  - Lancet Oncology (4) 33.75
  - Journal of Clinical Oncology (5) 32.96
  - JNCI (12) 11.58
  - Cancer Research 9.73
  - European Journal of Cancer 7.28
  - British Journal of Cancer (45) 5.79

# Impact Factors by Field

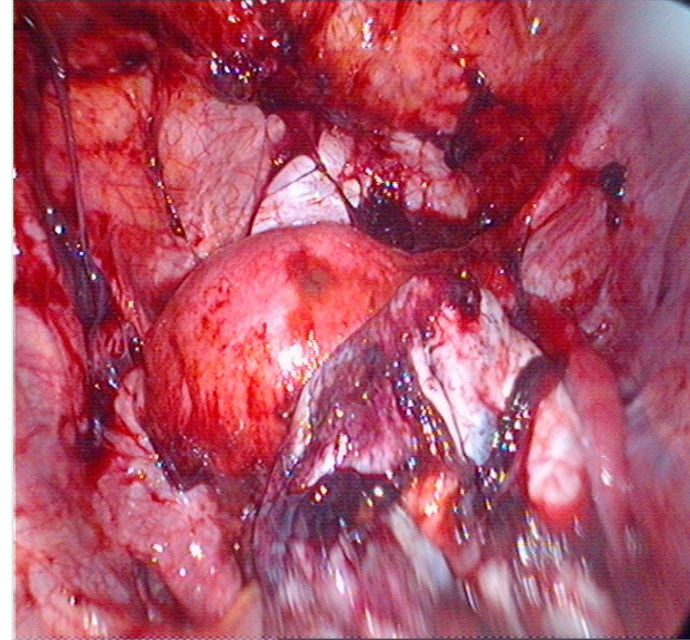
- Cardiology (139)
  - Circulation 23.60
  - European Heart Journal 22.67
  - Circulation Research (5) 14.47
  - Hypertension 6.29
  - J Am Soc Echocardiography (21) 5.51

# Endometriosis rASRM Staging

Stage I



Stage IV



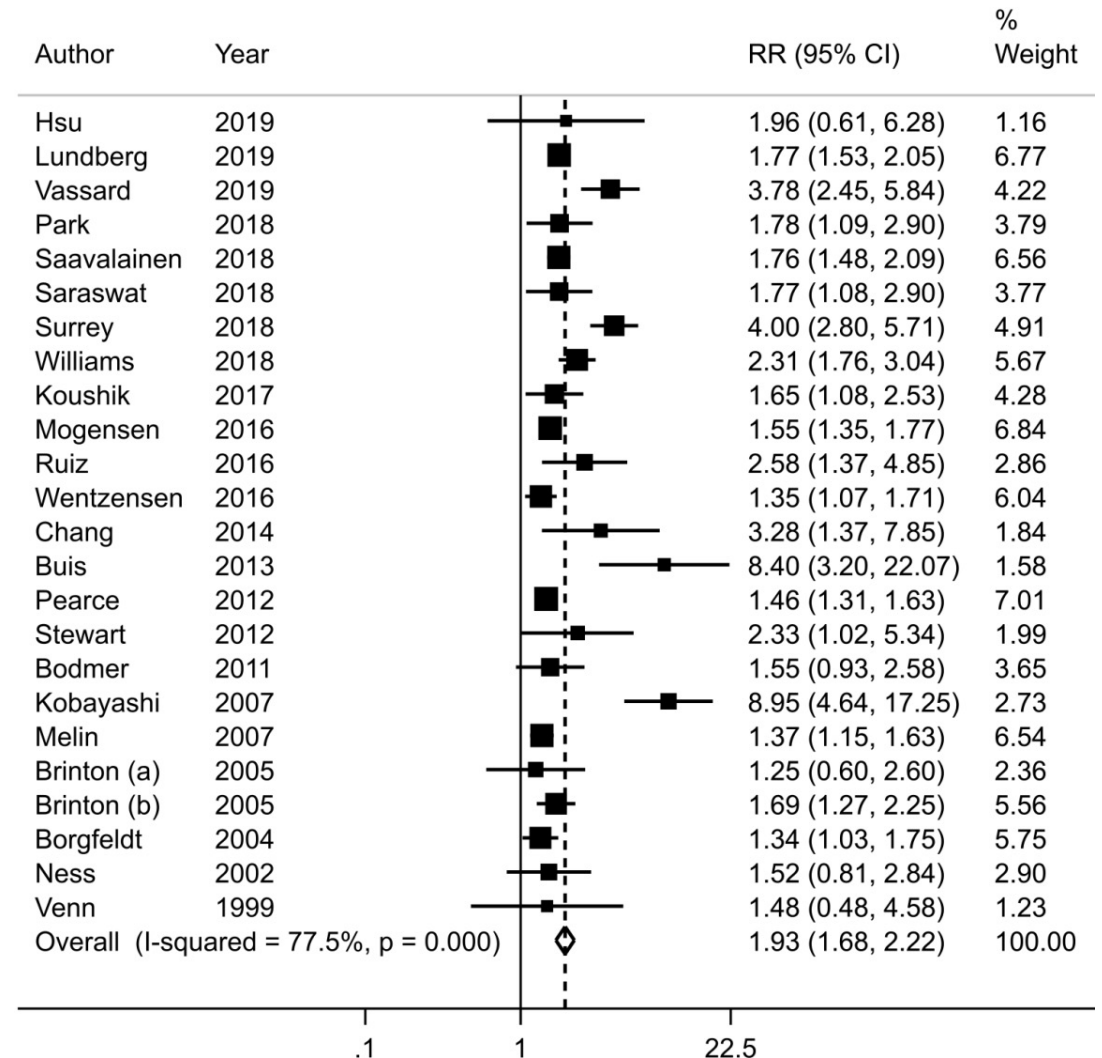
Surgically visualized disease:

- Does NOT correlate with symptoms
- Does not predict treatment response

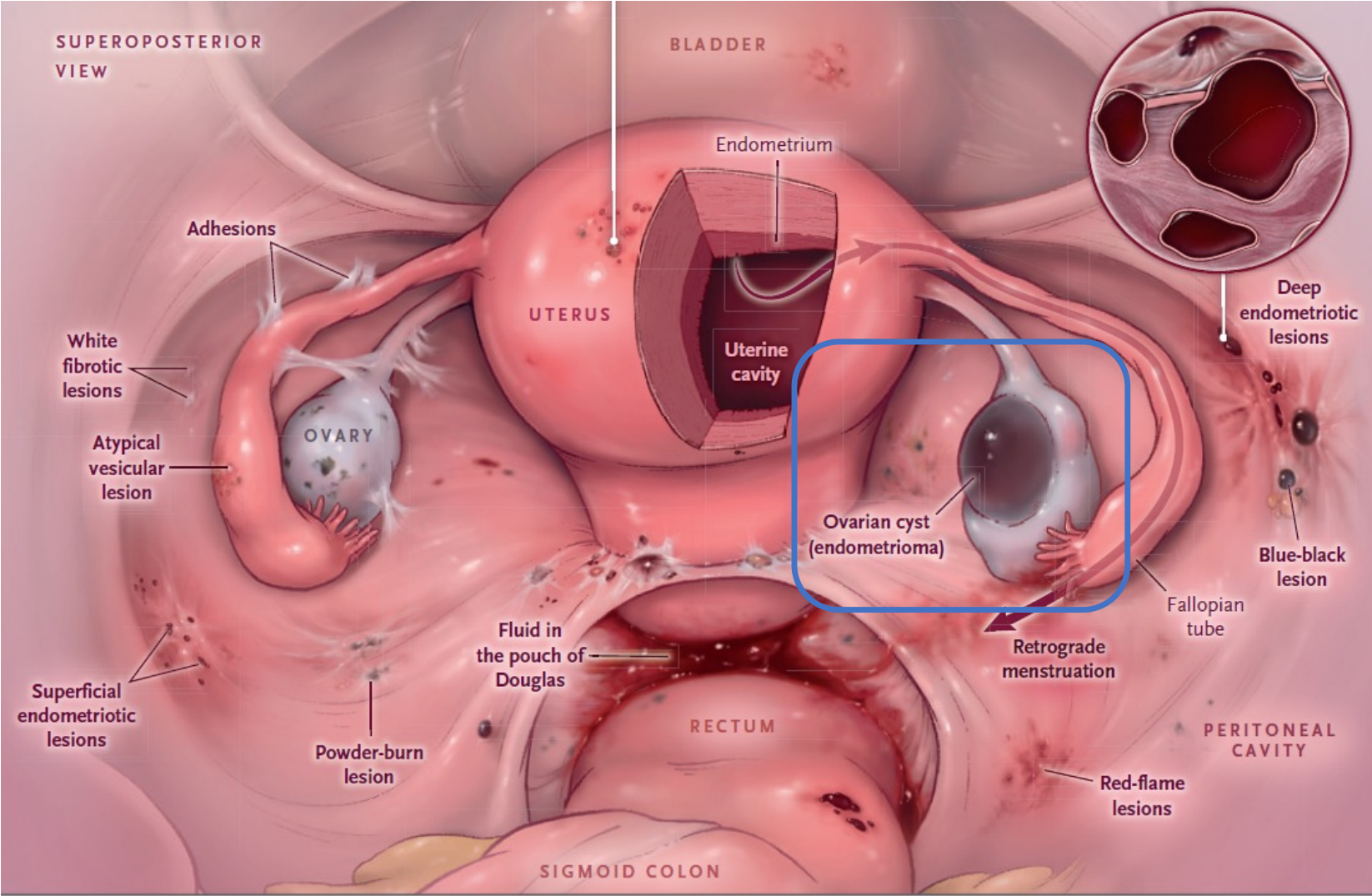


# Endometriosis and Ovarian Cancer Risk

- 24 studies
- All studies: **1.93 (1.68-2.22)**
- High level of heterogeneity:  $I^2=78\%$ ,  $P<0.0001$



# Endometriosis rASRM Staging



# Endometriosis x Ovarian Cancer Subtypes

Cancer Type or Site	Type of Endometriosis								
	Ovarian (n=23,210)			Peritoneal (n=20,187)			Deep (n=2,372)		
	Observed	SIR	95% CI	Observed	SIR	95% CI	Observed	SIR	95% CI
Cervix uteri*	15	0.96	0.54–1.58	9	0.53	0.24–1.00	3	1.80	0.37–5.25
Adenocarcinoma	4	0.91	0.25–2.32	5	1.05	0.34–2.45	1	2.17	0.05–12.1
Invasive squamous cell carcinoma	4	0.55	0.15–1.41	2	0.25	0.03–0.90	2	2.75	0.33–9.93
Other	7	1.80	0.72–3.70	2	0.47	0.06–1.68	0	0.00	0.00–7.69
Corpus uteri*	33	1.12	0.77–1.57	29	1.04	0.70–1.49	1	0.74	0.02–4.12
Endometrioid	27	1.12	0.74–1.62	24	1.06	0.68–1.58	1	0.95	0.02–5.26
Other	6	1.13	0.41–2.46	5	0.96	0.31–2.24	0	0.00	0.00–12.7
Ovary <sup>†</sup>	64	2.56	1.98–3.27	54	1.32	0.99–1.72	3	1.41	0.29–4.10
Serous	20	1.62	0.99–2.49	25	1.21	0.79–1.79	2	2.05	0.25–7.41
Mucinous	5	1.29	0.42–3.01	5	0.80	0.26–1.86	0	0.00	0.00–9.58
Endometrioid	17	4.72	2.75–7.56	12	2.03	1.05–3.54	1	3.35	0.08–18.7
Clear cell	14	10.1	5.50–16.9	6	2.67	0.98–5.81	0	0.00	0.00–28.2
Other	8	2.16	0.93–4.26	6	1.02	0.37–2.21	0	0.00	0.07–10.5
Other female genital organs <sup>‡</sup>	21	1.09	0.68–1.67	12	0.78	0.40–1.36	2	0.89	0.27–8.14
Vulva	7	0.87	0.35–1.78	4	0.61	0.17–1.57	1	2.62	0.07–14.6
Vagina	4	1.92	0.52–4.90	1	0.58	0.01–3.24	0	0.00	0.00–33.6
Other	10	1.11	0.53–2.03	7	0.99	0.40–2.04	1	2.50	0.06–13.9
Not included above <sup>§</sup>									
Cervix uteri, noninvasive neoplasms* <sup>§  </sup>	82	0.75	0.60–0.92	109	0.88	0.72–1.05	12	0.78	0.40–1.36
Borderline tumor of ovary <sup>†§</sup>	20	1.63	1.00–2.52	24	1.25	0.80–1.85	0	0.00	0.00–2.65

- Endometrioma ↑ OvCa risk, clear-cell, endometrioid, serous
- SPE ↑ OvCa risk, endometrioid, clear-cell
- Deep ✗ OvCa risk