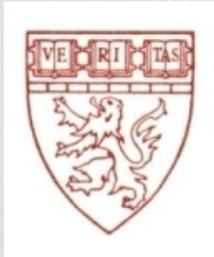




College of Human Medicine
MICHIGAN STATE UNIVERSITY

Endometriosis: A Fundamental Example for Women's Health Discovery

NICHD Council Meeting
June 11, 2019



Stacey Missmer, Sc.D.

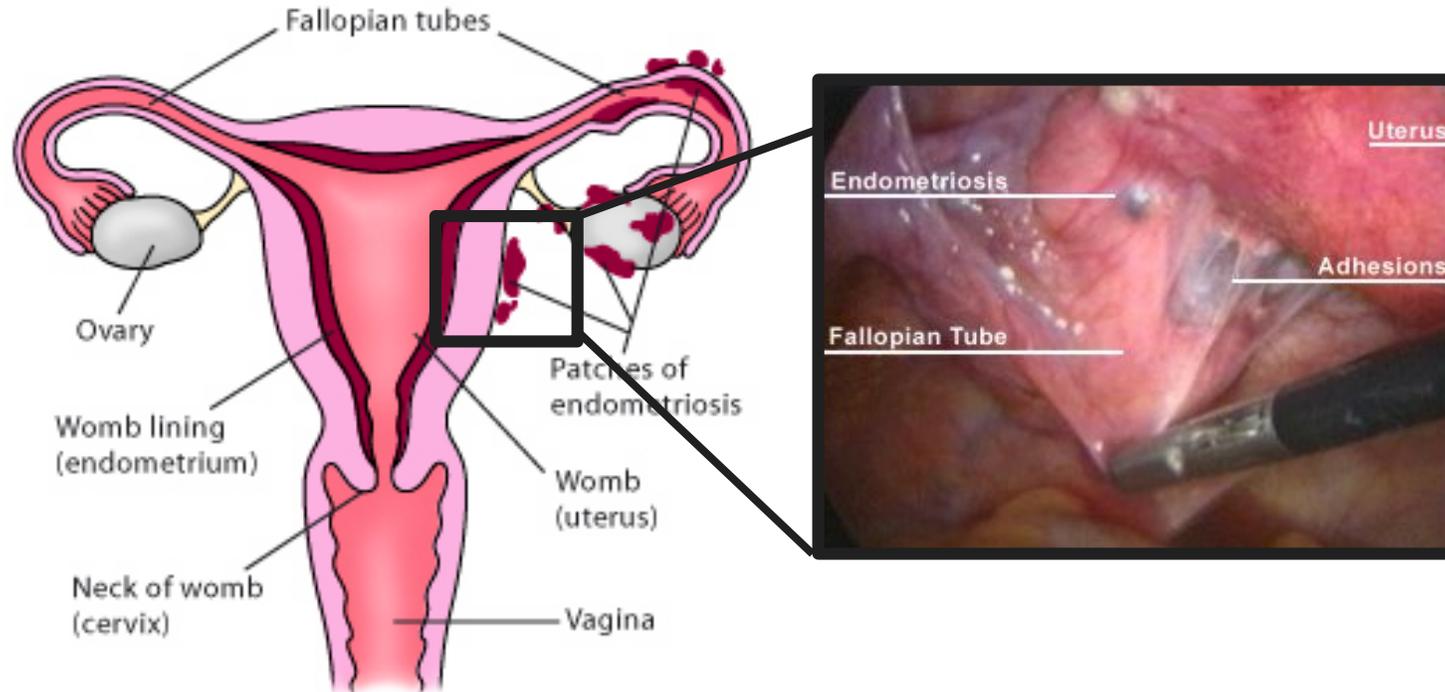
Michigan State University College of Human Medicine
Harvard T.H. Chan School of Public Health
Harvard Medical School



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What is endometriosis?



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

Major Health Issue

1 in 10 women have endometriosis during their reproductive years

35–50% of women with pelvic pain or infertility

190 Million women worldwide

U.S. costs for diagnosis, treatment, and quality of life / work productivity = **\$69 Billion**

Similar to Crohn's, Rheumatoid Arthritis, and **Diabetes Mellitus**

Higher risk of ovarian cancer, autoimmune disease, CVD

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

World Bank. *Population Projection Tables*

Simoens S, et al. *Hum Reprod* 2012

Missmer SA. *Int J Epidemiol* 2009

Kvaskoff M, et al. *Hum Reprod Update* 2015

Symptoms

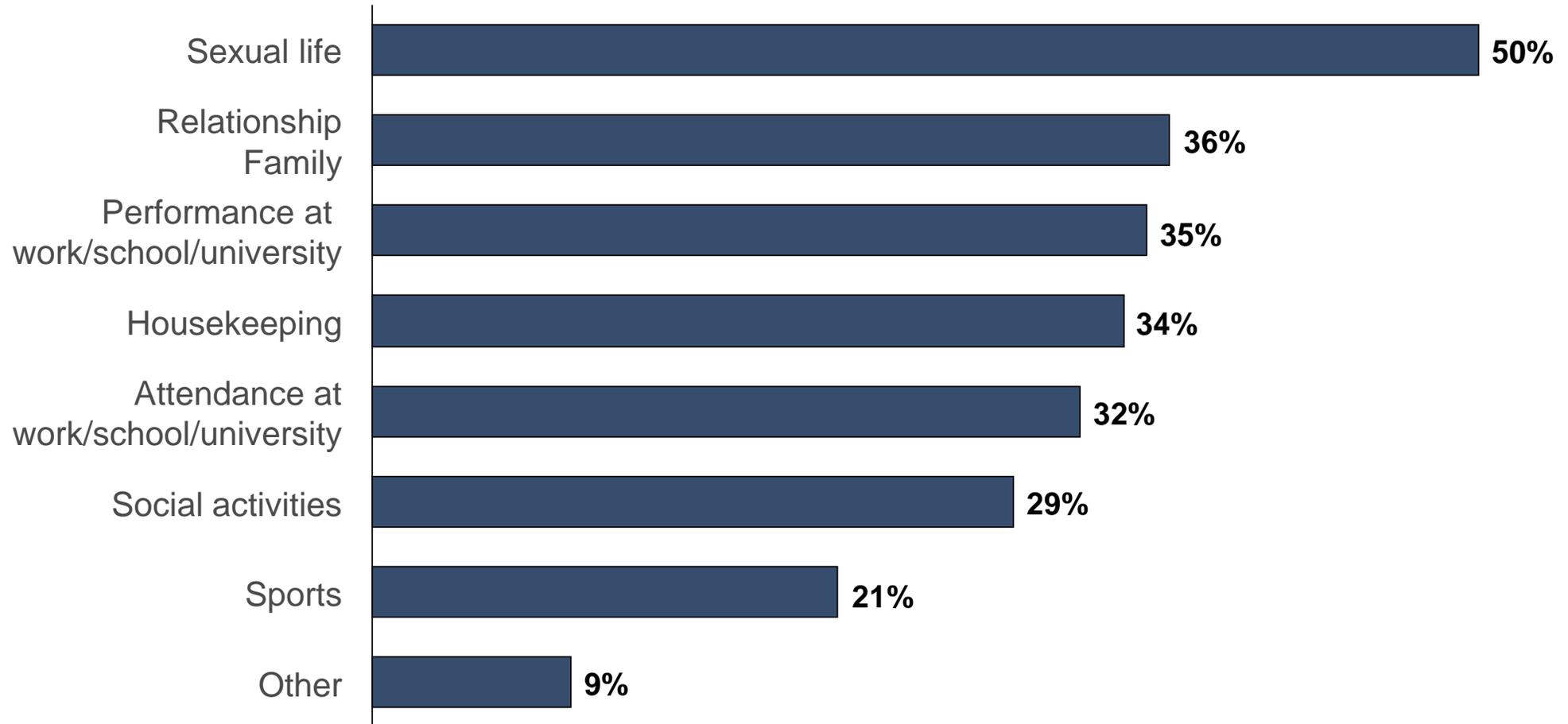
- Severe menstrual cramping (dysmenorrhea)
- Pelvic pain not associated with menses
- Painful intercourse (dyspareunia)
- Painful urination (dysuria)
- Painful defecation (dyschezia)

- U.S. Interview Survey (n = 31,617)
 - Mean number of “bed” days = 18 / year

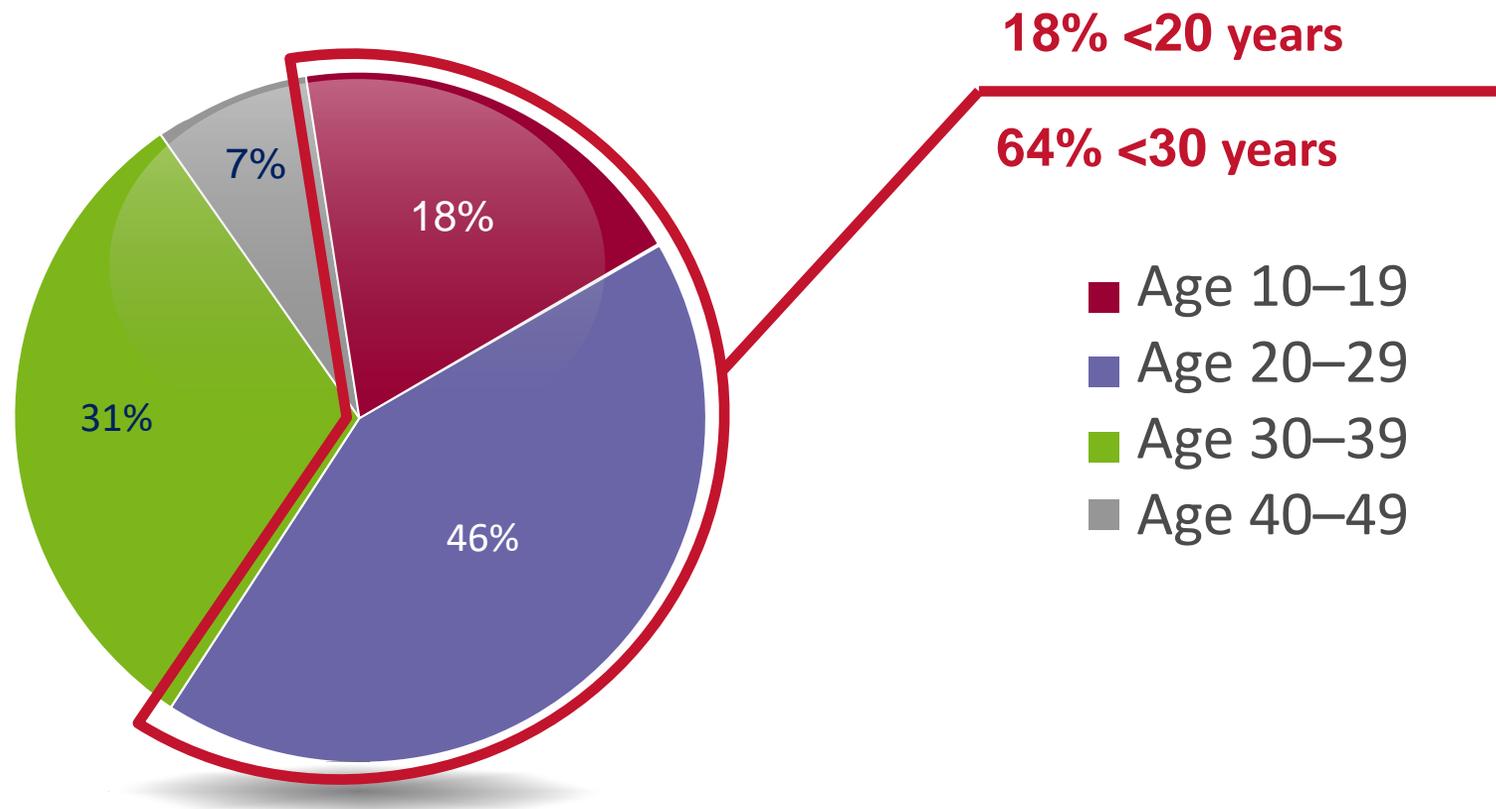


GSWH - QOL Impact

Activities negatively impacted by symptoms (n=2,753 women in eight countries)



Age at first consultation for symptoms



Impact of Pain

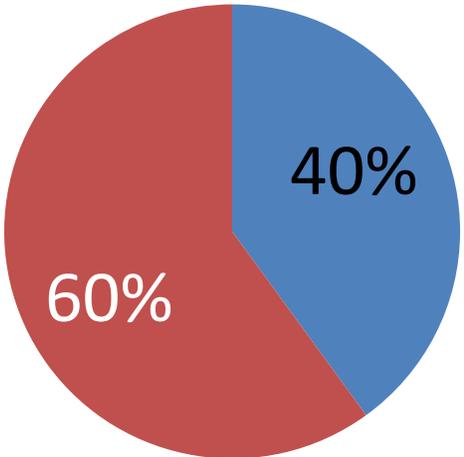


The Women's Health Study

From Adolescence to Adulthood

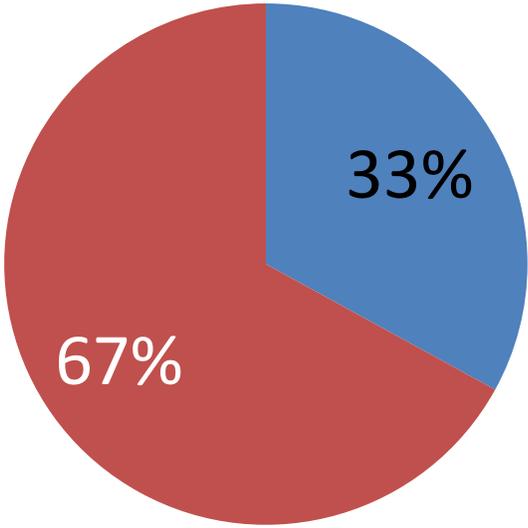
Adults

- No/mild pain interfering with work/school
- Moderate/severe pain interfering with work/school



Adolescents

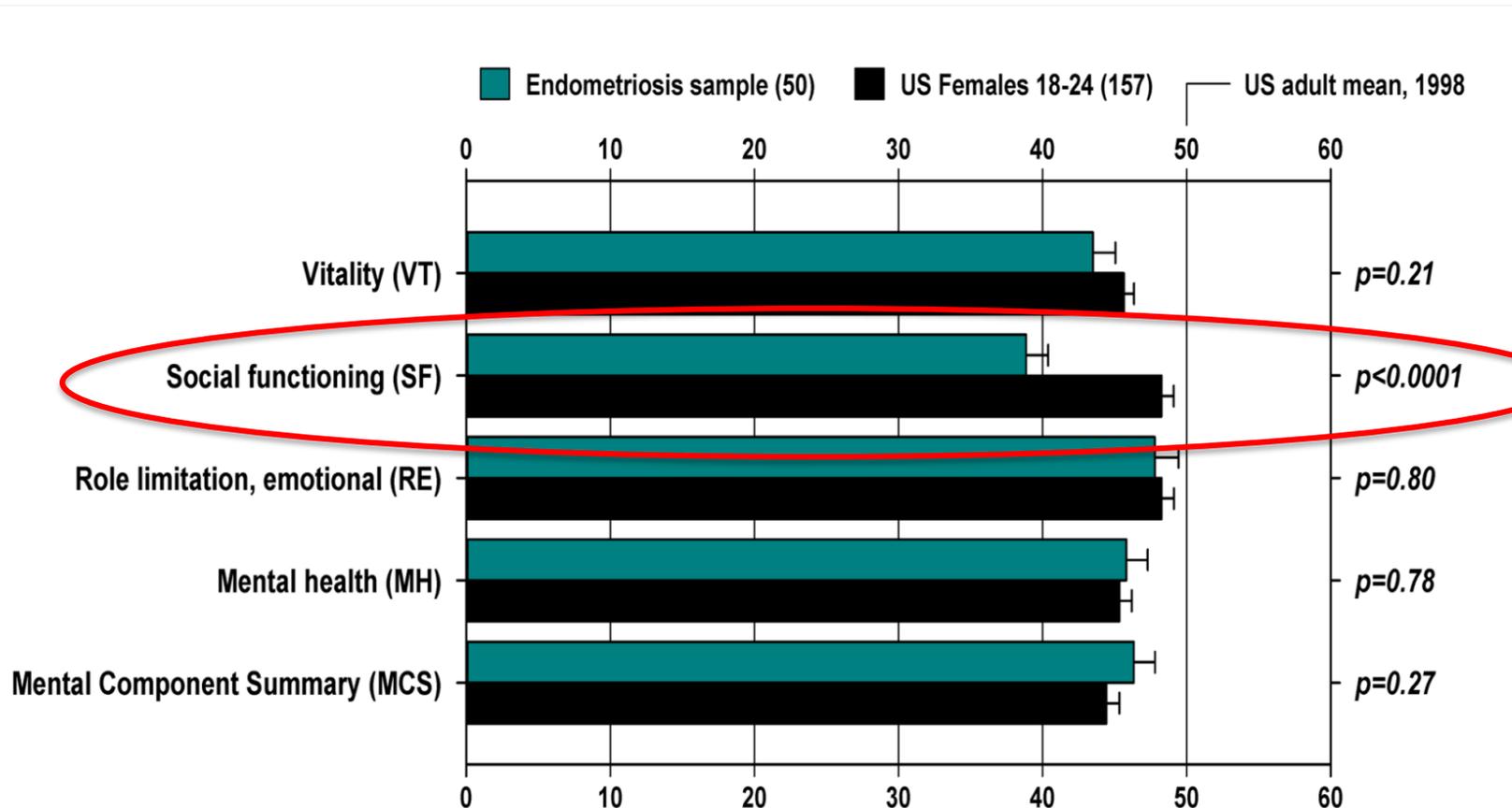
- No/mild pain interfering with work/school
- Moderate/severe pain interfering with work/school



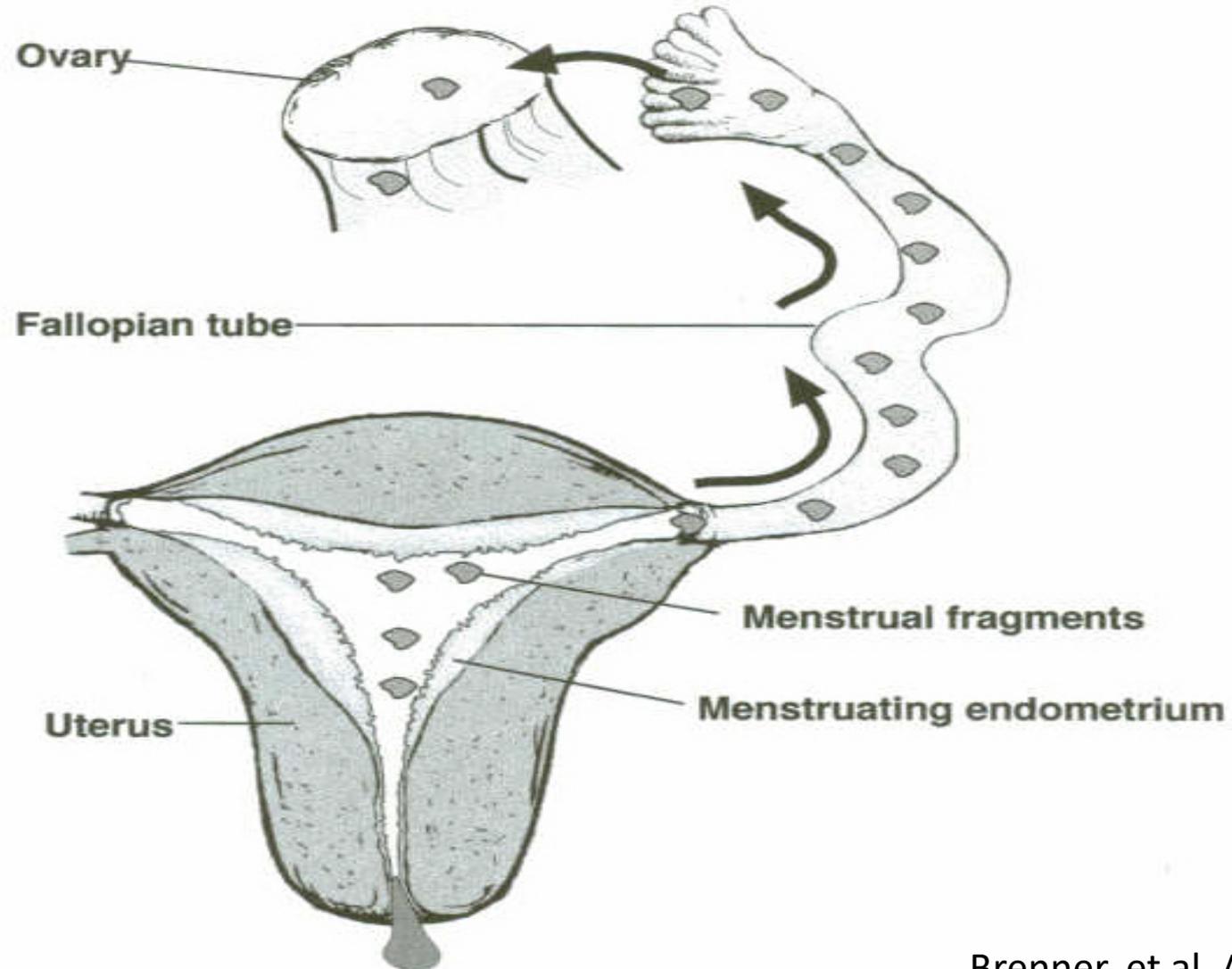
Adolescent QOL



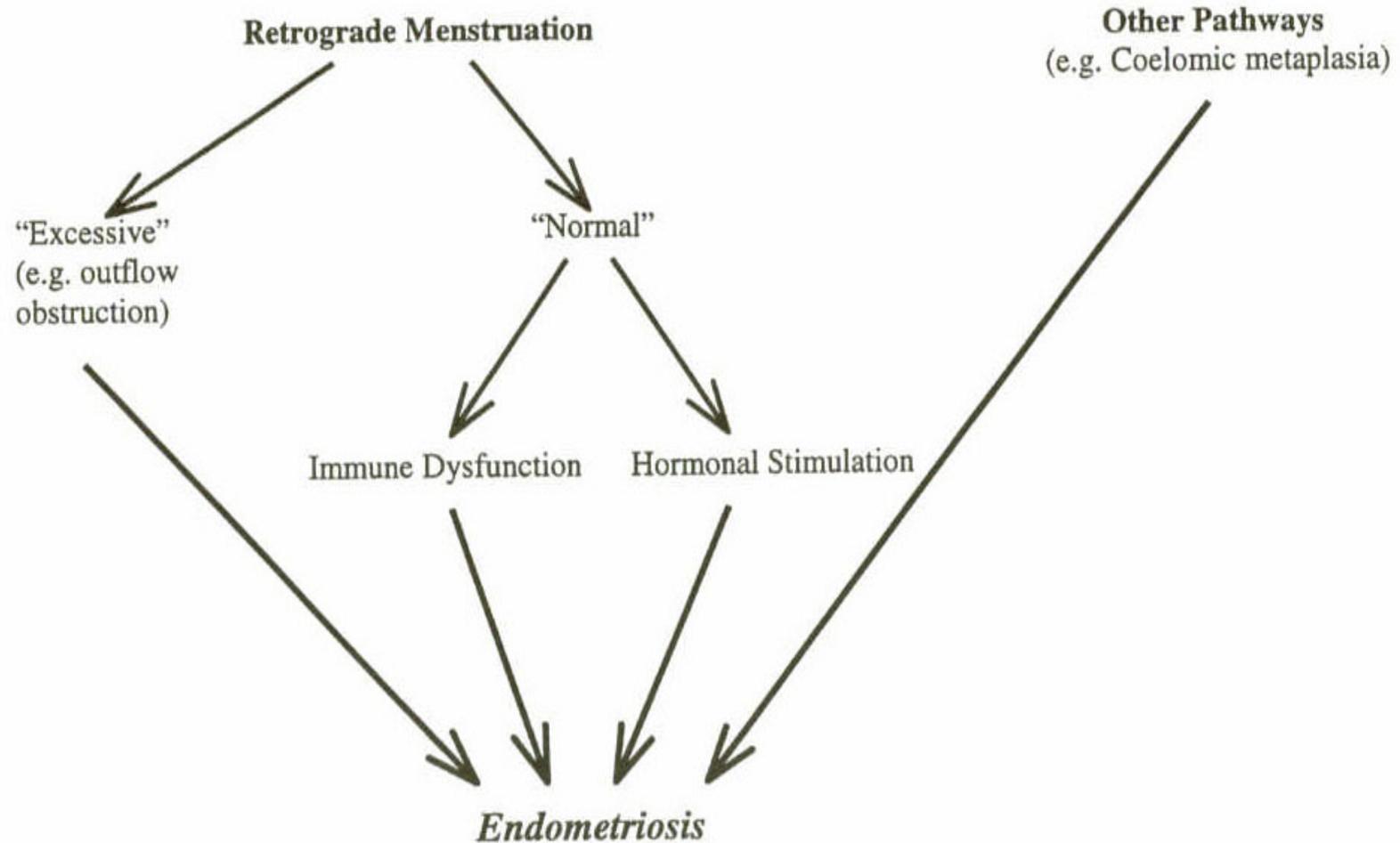
SF-36: Girls with endometriosis did not differ on mental health domains, except for Social Functioning which was significantly lower than the norm



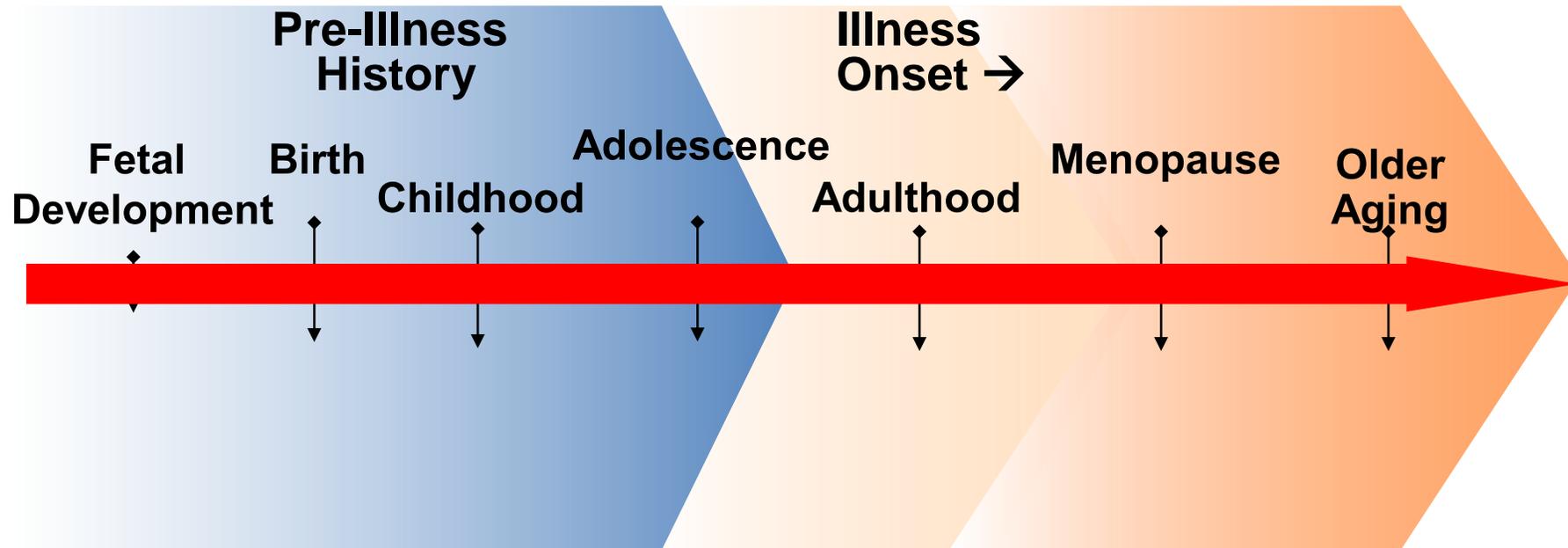
Retrograde Menstruation – Sampson 1927



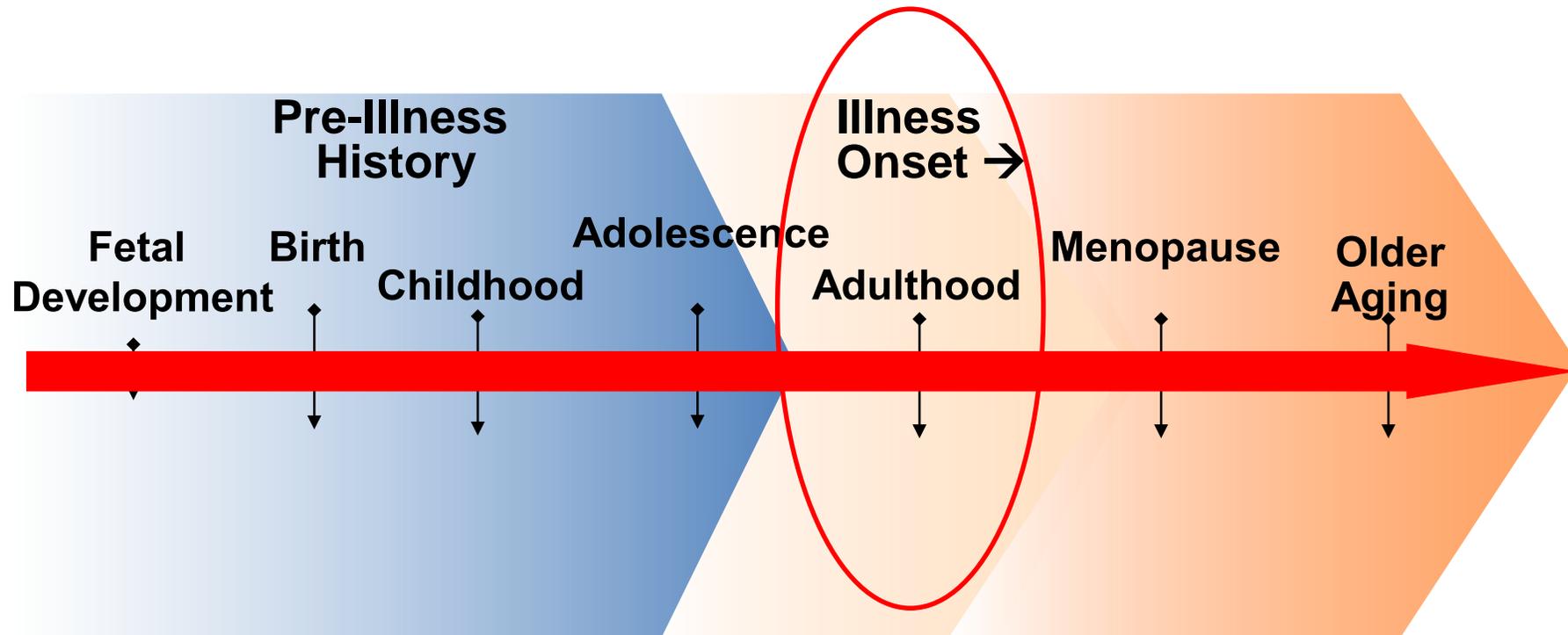
Pathogenic Hypotheses



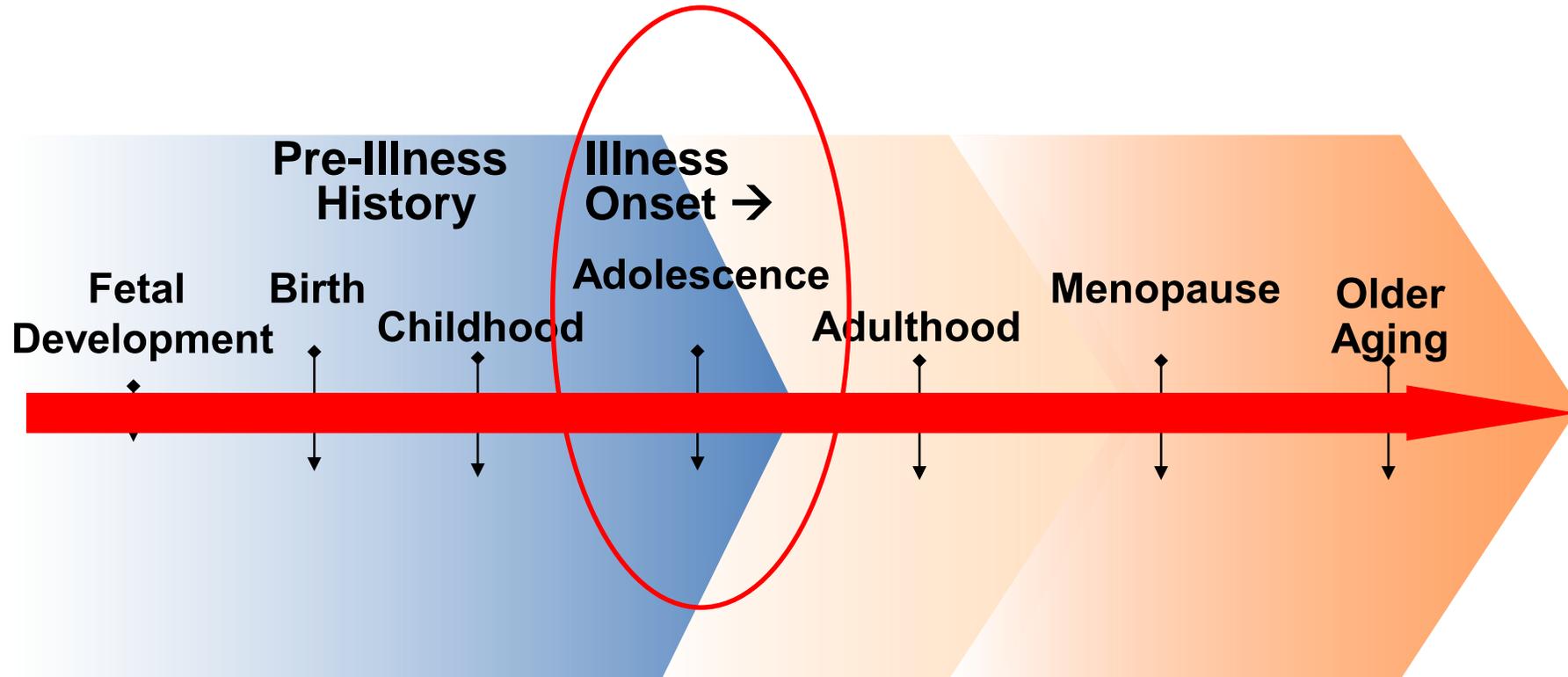
Health Across the Lifespan



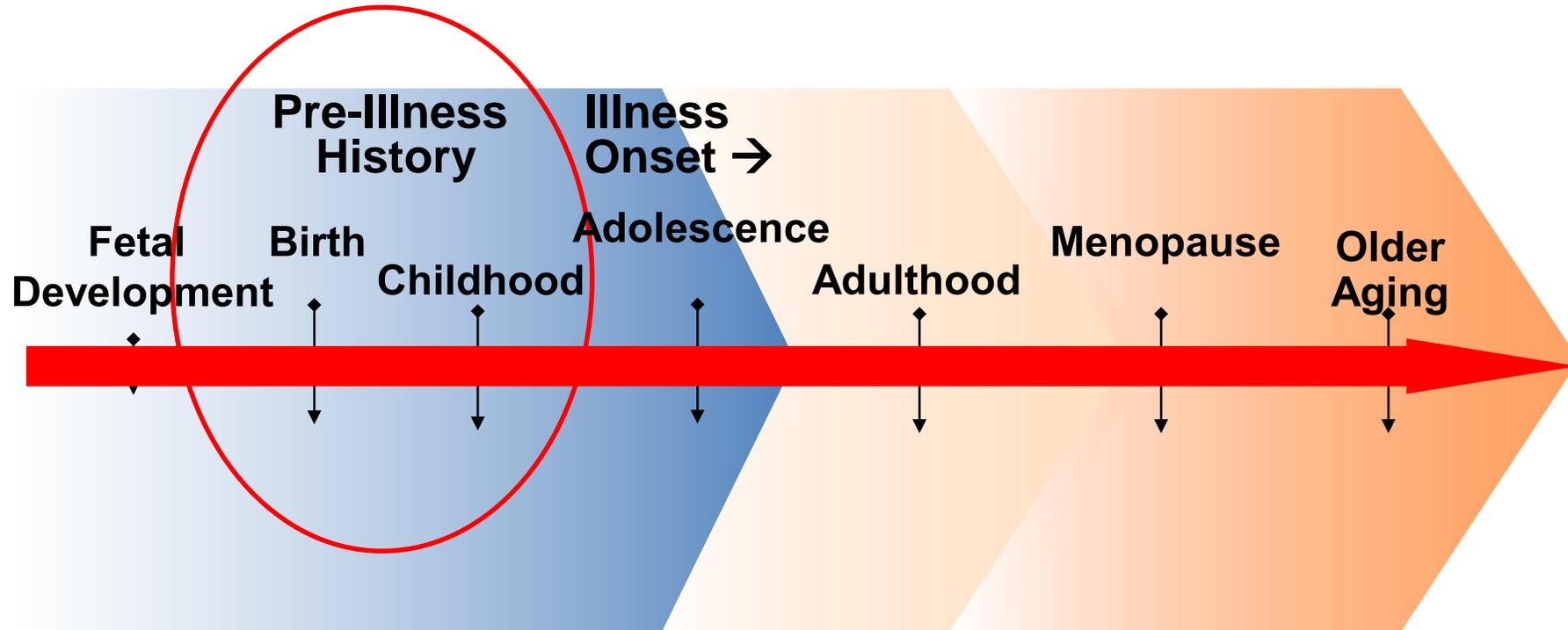
Health Across the Lifespan



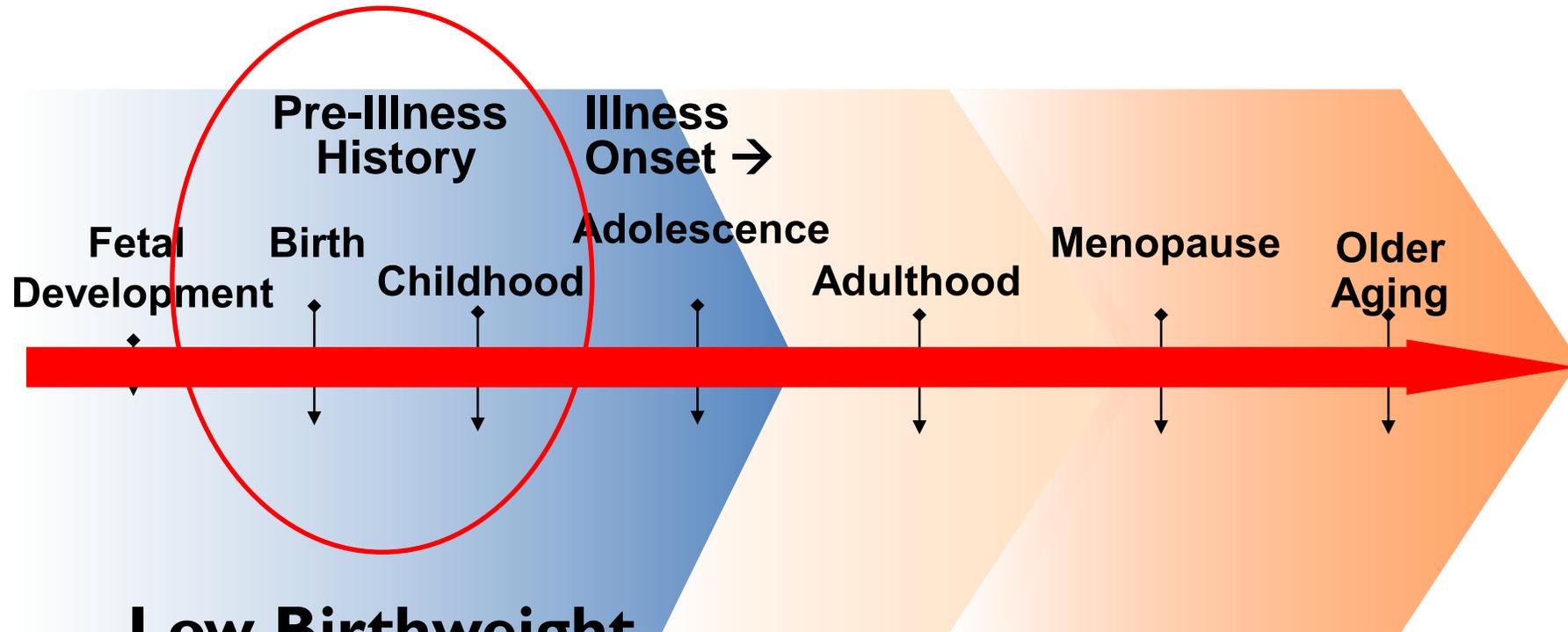
Health Across the Lifespan



Health Across the Lifespan



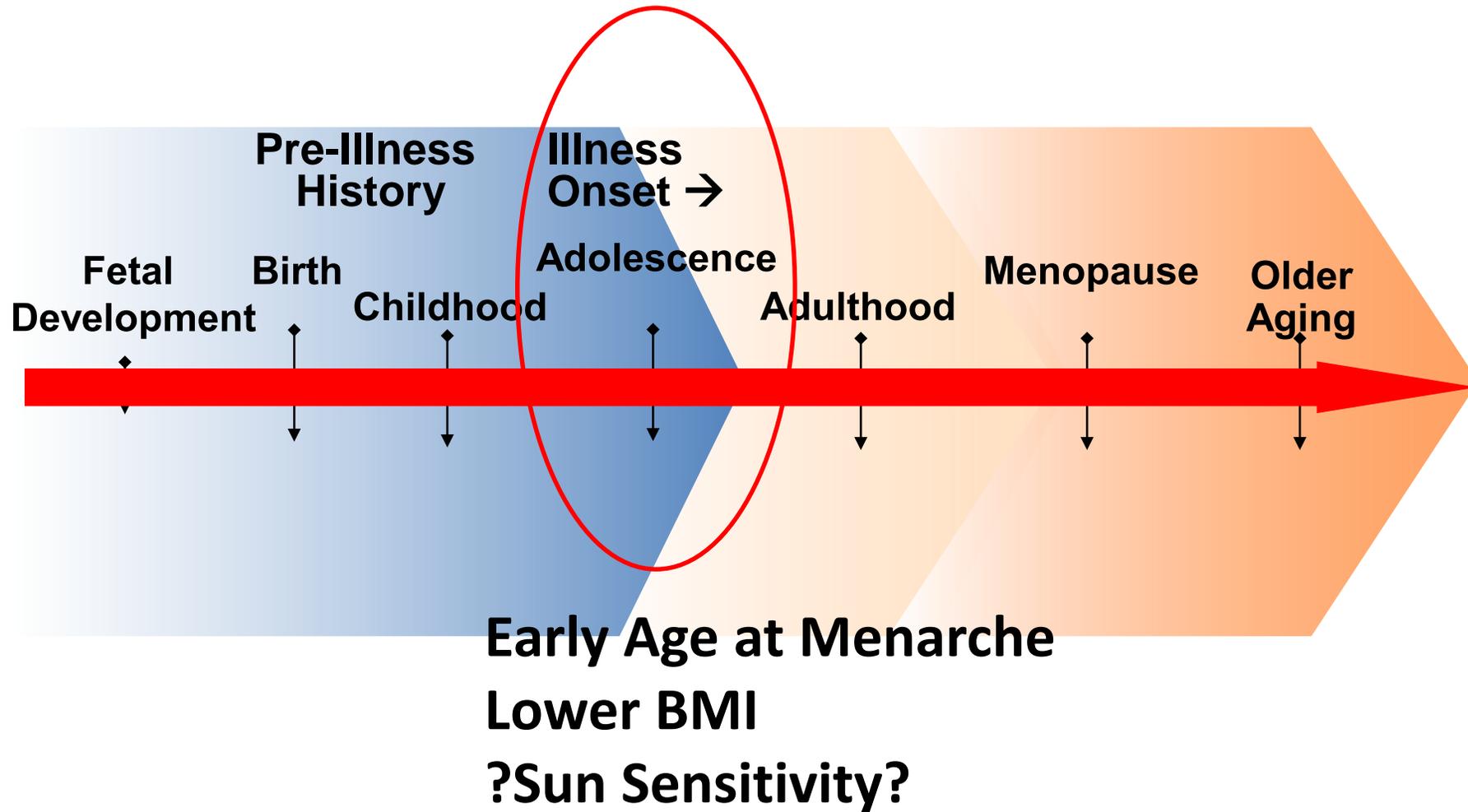
Health Across the Lifespan



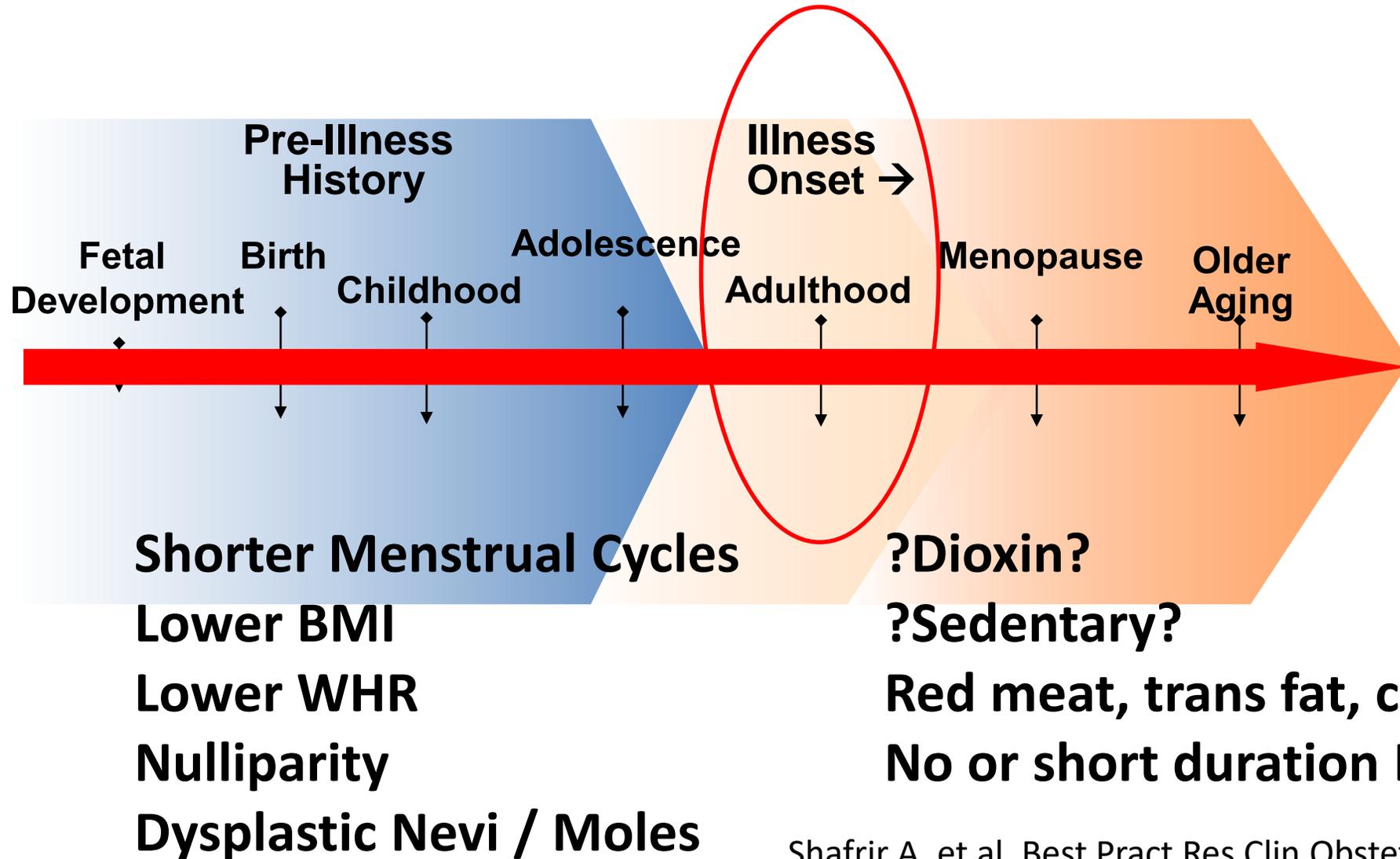
**Low Birthweight
DES**

?Premature Delivery?

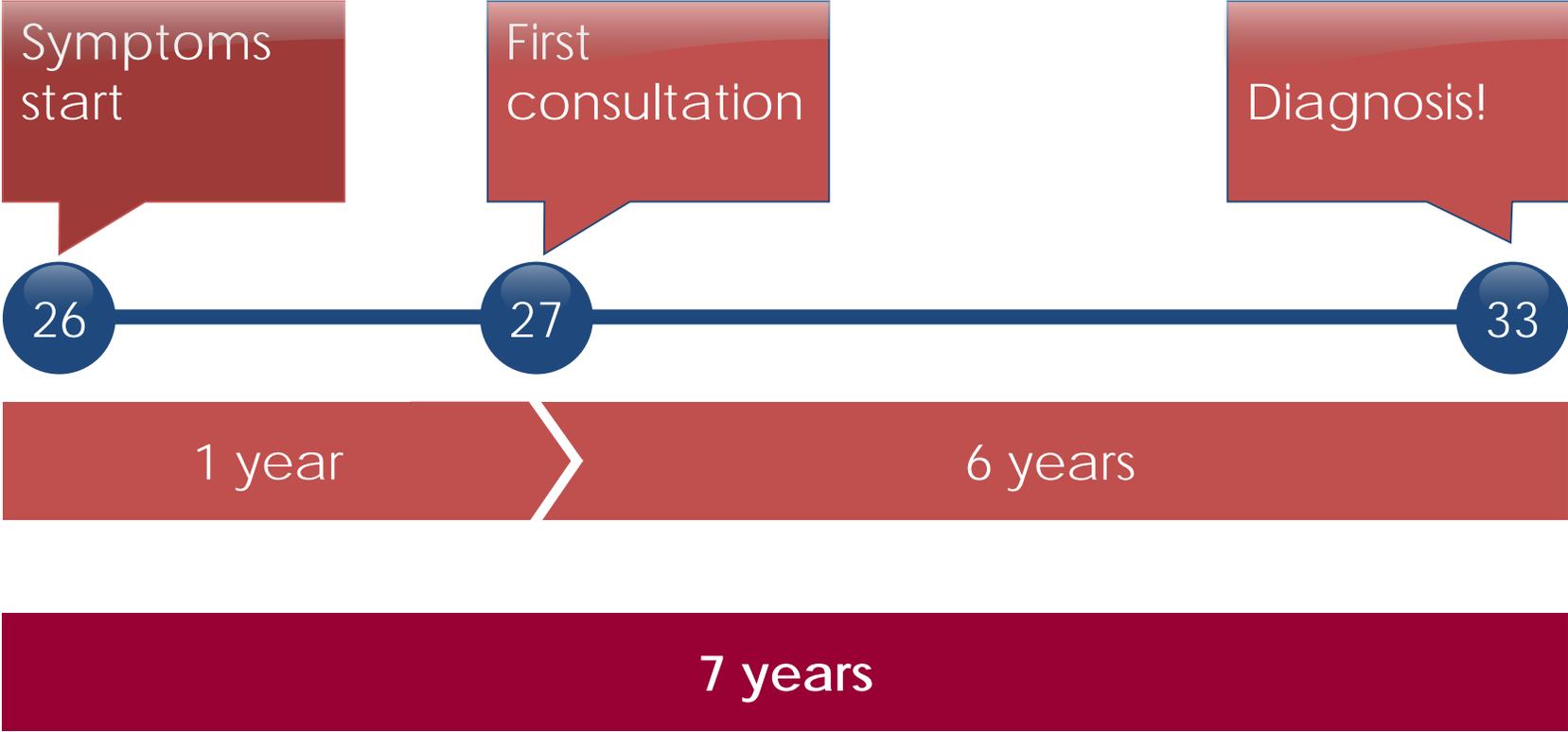
Health Across the Lifespan



Health Across the Lifespan



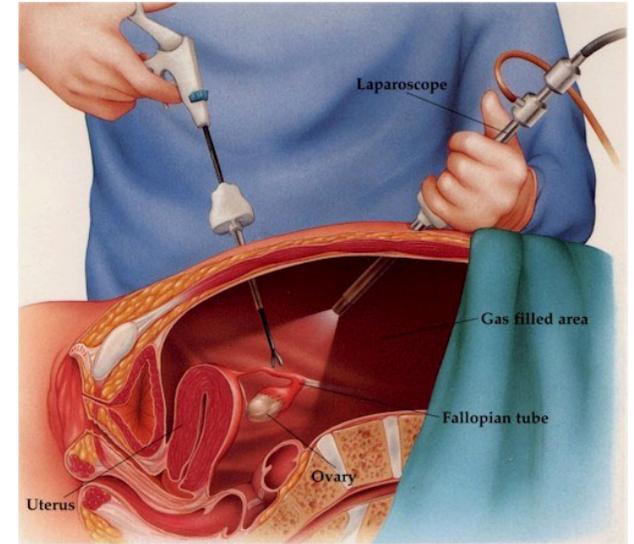
Global Study of Women's Health: Endometriosis average diagnostic delay



Average of 8 clinicians before Gyn specialist referral

Major Clinical Obstacles

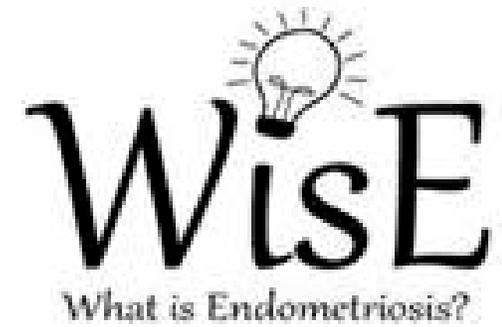
- Currently, diagnosis requires surgery
- Imaging only effective for large and deep infiltrating lesions
- No blood, urine, or other biomarkers
- Many PCPs unaware of disease
- Reluctance to perform surgery without severe disease
- Symptoms are nonspecific or associated with other disorders
 - May be mistakenly dismissed as “normal” menstrual pain
 - Family and friends’ attitudes towards menstrual pain
 - Embarrassment specific to pelvic pain
- Survey of N = 7,025 women
 - 65% misdiagnosed
 - 46% saw ≥ 5 MDs to get correct diagnosis



Ohio Reproductive Medicine

Ballard K, et al. Fertil Steril 2006
May KE, et al. Hum Reprod Update 2010
Mihalyi A, et al. Hum Reprod 2010

What is endometriosis?



Endo appearance (red, yellow, clear, white, brown, blue/black)

– Continuum or distinct disease?

Superficial Peritoneal (SPE), Deep, Endometrioma

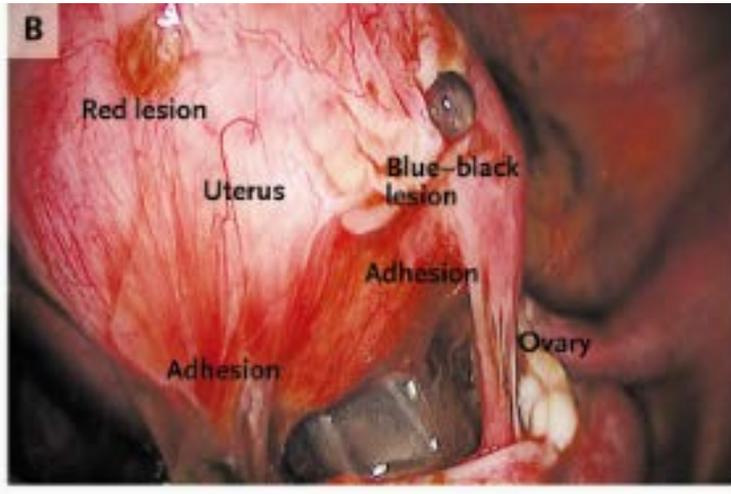
Propensity for scarring/adhesion

Infertility risk

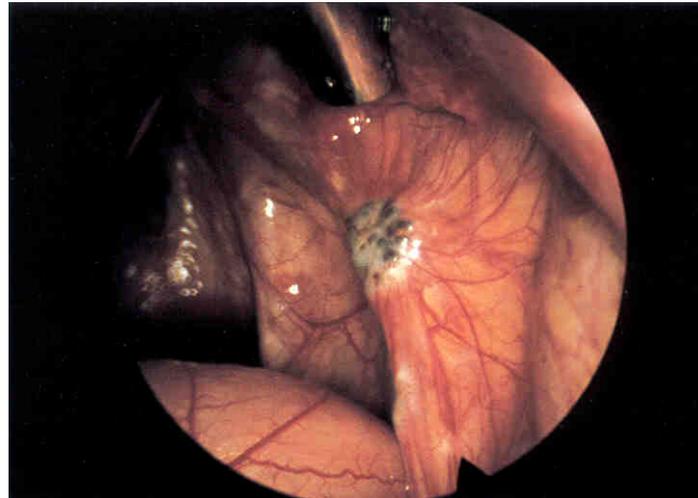
Molecular / somatic phenotypes?

Appearance at surgery

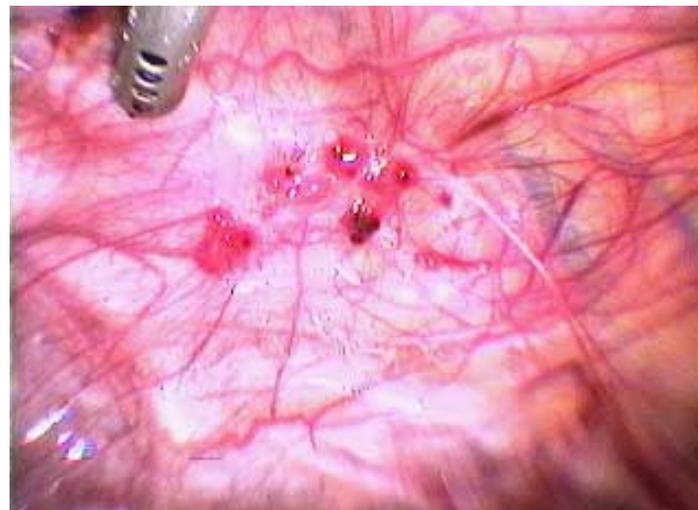
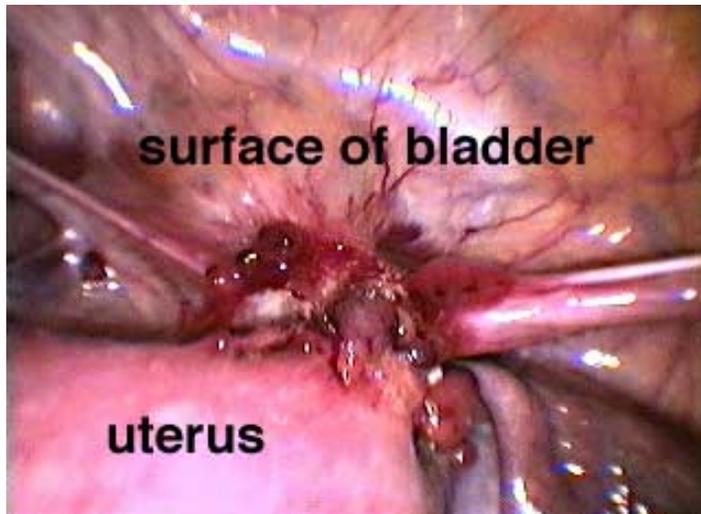
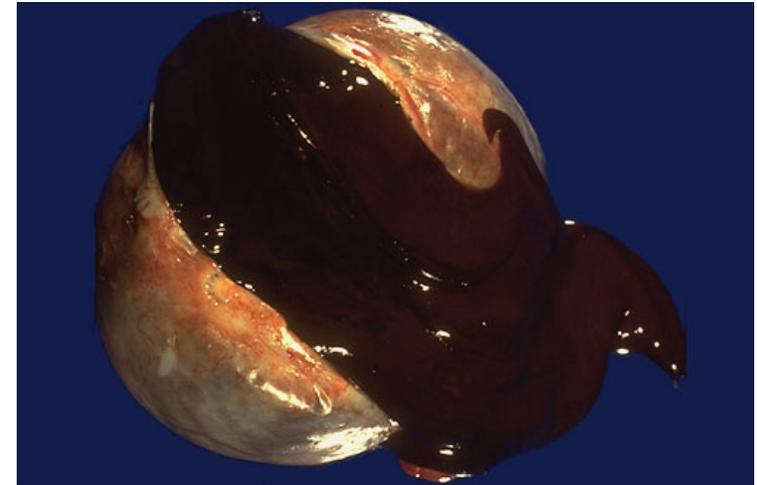
Adhesions



“Powder-burn” Lesion



“Chocolate” Ovarian Cyst



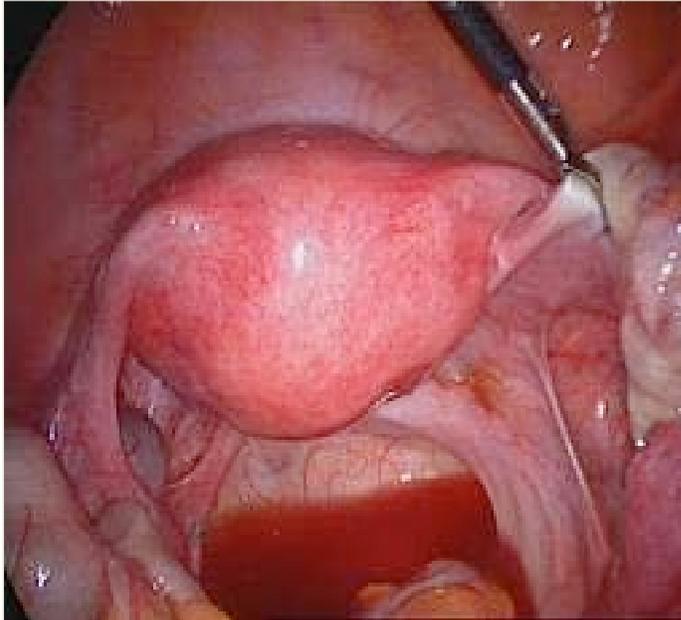
St. Charles Endometriosis Program

Martin D, 1997

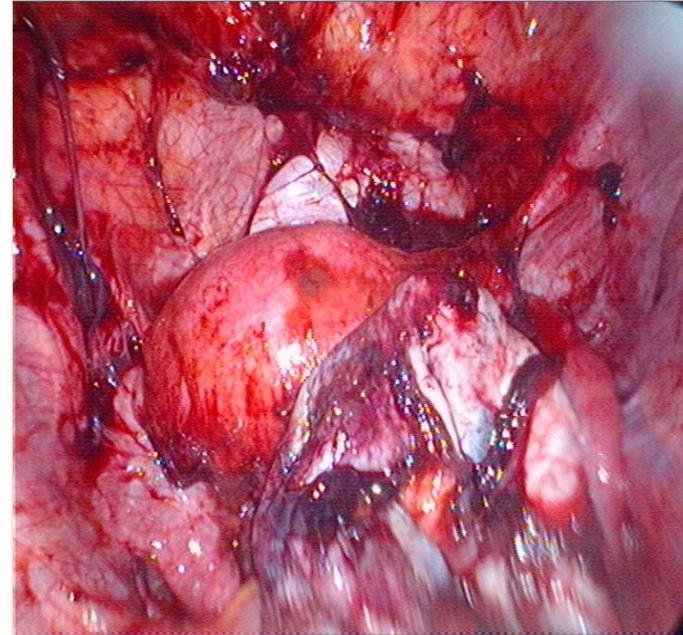
Giudice LC, NEJM 2010

rASRM Staging

Stage I

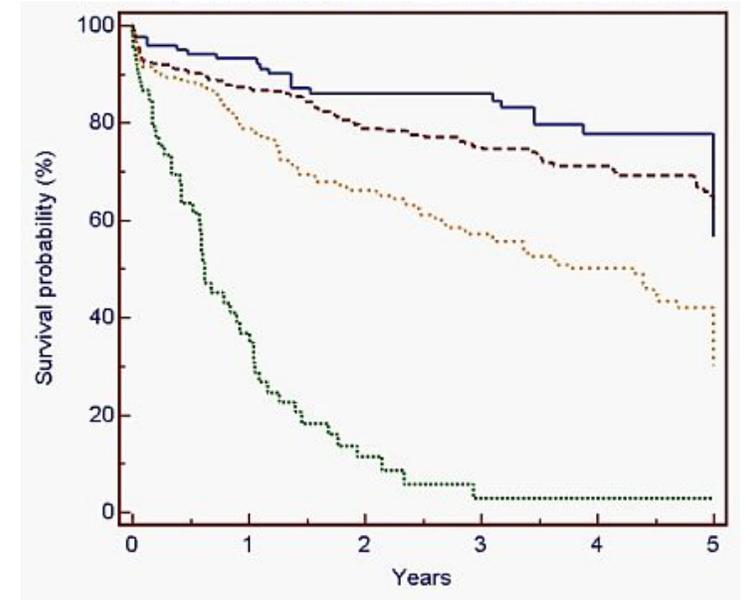
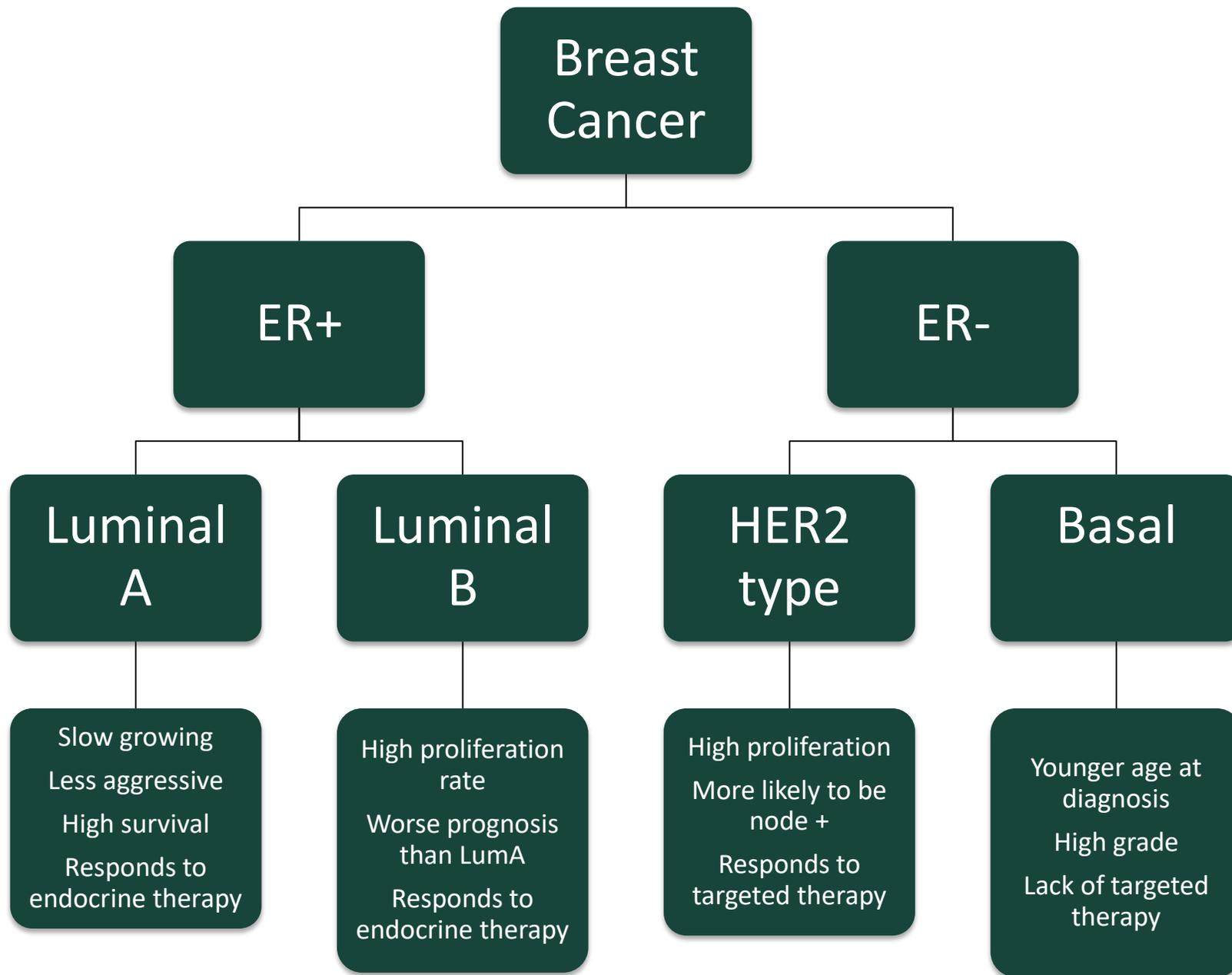


Stage IV



Surgically visualized disease:

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



Adapted from Dr. Rulla Tamimi, Harvard University

Treatment Options

Over-the-counter pain medication / opioids

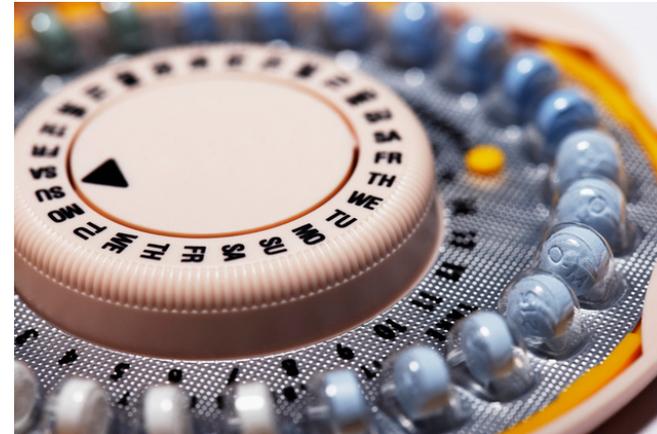
Oral contraceptives

GnRH Agonists

Surgical excision / ablation

Hysterectomy

Oophorectomy



Current therapeutic options are limited

Primarily hormonal pathways with impactful side effects

Limited geographic and economic access to expert surgeons

Informative Subtypes Discovery

Obvious Heterogeneity of

- Lesions
- Symptoms
- Co-Morbidities
- Treatment response

What peripheral and tissue markers and characteristics define them?

Do they have different risk factors? Pathophysiology?

Can we maximize treatment response through personalized medicine?

Do they have different long-term health outcomes?

WERF ePHect

**Endometriosis Phenome and
Biobanking Harmonization Project**



WERF ePHect

Endometriosis Phenome
and Biobanking Harmonisation Project



STANDARDIZED DATA AND SAMPLE COLLECTION TOOLS

- Surgical
- Clinical
- Fluids
- Tissue

World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: I. Surgical phenotype data collection in endometriosis research

Christian M. Becker, M.D.,^{1,2,3,4} Marc R. Laufer, M.D.,^{2,4,5} Pamela Stratton, M.D.,¹ Lone Hummelshøj,⁶ Stacy A. Maiman, Sc.D.,^{1,4,5} Krina T. Zondervan, D.Phil.,^{1,4,5} and G. David Adamson, M.D.,^{3,4} for the WERF ePHect Working Group

¹ Nuffield Department of Obstetrics and Gynaecology and ² Endometriosis Centre, Centre for Reproductive Health, University of Oxford, Oxford, United Kingdom; ³ Division of Gynecology, Department of Surgery, Boston Children's Hospital and Harvard Medical School; ⁴ Department of Obstetrics, Gynecology, and Biobanking, Brigham Young University, Salt Lake City, Utah; ⁵ Harvard Medical School, Boston, Massachusetts; ⁶ Kennedy Krieger Institute, Pittsburgh, Pennsylvania

Received April 23, 2014; revised August 12, 2014; accepted September 22, 2014. The complete alphabetical list of authors is available in the online version of this article. Correspondence: Christian M. Becker, M.D., Nuffield Department of Obstetrics and Gynaecology, University of Oxford, Oxford, United Kingdom. E-mail: christian.becker@oxford.ac.uk

World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: III. Fluid biospecimen collection, processing, and storage in endometriosis research

Nilufer Rahmiloglu, Ph.D.,^{1,2} Amelie Fassbender, Ph.D.,^{1,2} Allison F. Vitonis, S.M.,^{1,2,3} Shelley S. Tivovger, Ph.D.,^{1,2} Lone Hummelshøj,⁴ Thomas M. D'Hooghe, M.D., Ph.D.,^{1,2} G. David Adamson, M.D.,^{1,2,3} and Stacy A. Maiman, Sc.D.,^{1,2,3,4} for the WERF ePHect Working Group

¹ Wellcome Trust Centre for Human Genetics, University of Oxford, Oxford, United Kingdom; ² Organ System, Department of Development and Regeneration, Katholieke Universiteit Leuven, Leuven, Belgium; ³ Department of Obstetrics and Gynecology, University of Oxford, Oxford, United Kingdom; ⁴ Department of Obstetrics and Gynecology, University of Oxford, Oxford, United Kingdom

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Key Words: endometriosis; fluid; biospecimen; collection; processing; storage; endometriosis research

Abstract: The WERF ePHect Working Group is a consortium of researchers from 12 countries who are working to harmonize data and sample collection in endometriosis research. This project is the third in a series of projects that will be published in the next few months. The first project, 'Surgical phenotype data collection in endometriosis research', was published in the journal *Human Reproduction* in August 2014. The second project, 'Clinical and covariate phenotype data collection in endometriosis research', was published in the journal *Human Reproduction* in September 2014. This project, 'Fluid biospecimen collection, processing, and storage in endometriosis research', is the third in the series. The project aims to develop a standardized protocol for the collection, processing, and storage of fluid biospecimens in endometriosis research. The protocol will be published in the journal *Human Reproduction* in the next few months. The project is supported by the Wellcome Trust, the Nuffield Department of Obstetrics and Gynaecology, the Organ System, the Department of Development and Regeneration, the Katholieke Universiteit Leuven, and the University of Oxford.

World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: II. Clinical and covariate phenotype data collection in endometriosis research

Allison F. Vitonis, S.M.,^{1,2,3} Katy Vincent, M.B.B.S., D.Phil.,¹ Nilufer Rahmiloglu, Ph.D.,^{1,2} Amelie Fassbender, Ph.D.,^{1,2} Germaine M. Buck Louis, Ph.D.,¹ Lone Hummelshøj,⁴ Krina T. Zondervan, D.Phil.,^{1,2,3} Pamela Stratton, M.D., G. David Adamson, M.D.,^{1,2,3} and Stacy A. Maiman, Sc.D.,^{1,2,3,4} for the WERF ePHect Working Group

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World Endometriosis Research Foundation Endometriosis Phenome and Biobanking Harmonisation Project: IV. Tissue collection, processing, and storage in endometriosis research

Amelie Fassbender, Ph.D.,^{1,2} Nilufer Rahmiloglu, Ph.D.,^{1,2} Allison F. Vitonis, S.M.,^{1,2,3} Shelley S. Tivovger, Ph.D.,^{1,2} Lone Hummelshøj,⁴ Thomas M. D'Hooghe, M.D., Ph.D.,^{1,2} G. David Adamson, M.D.,^{1,2,3} and Stacy A. Maiman, Sc.D.,^{1,2,3,4} for the WERF ePHect Working Group

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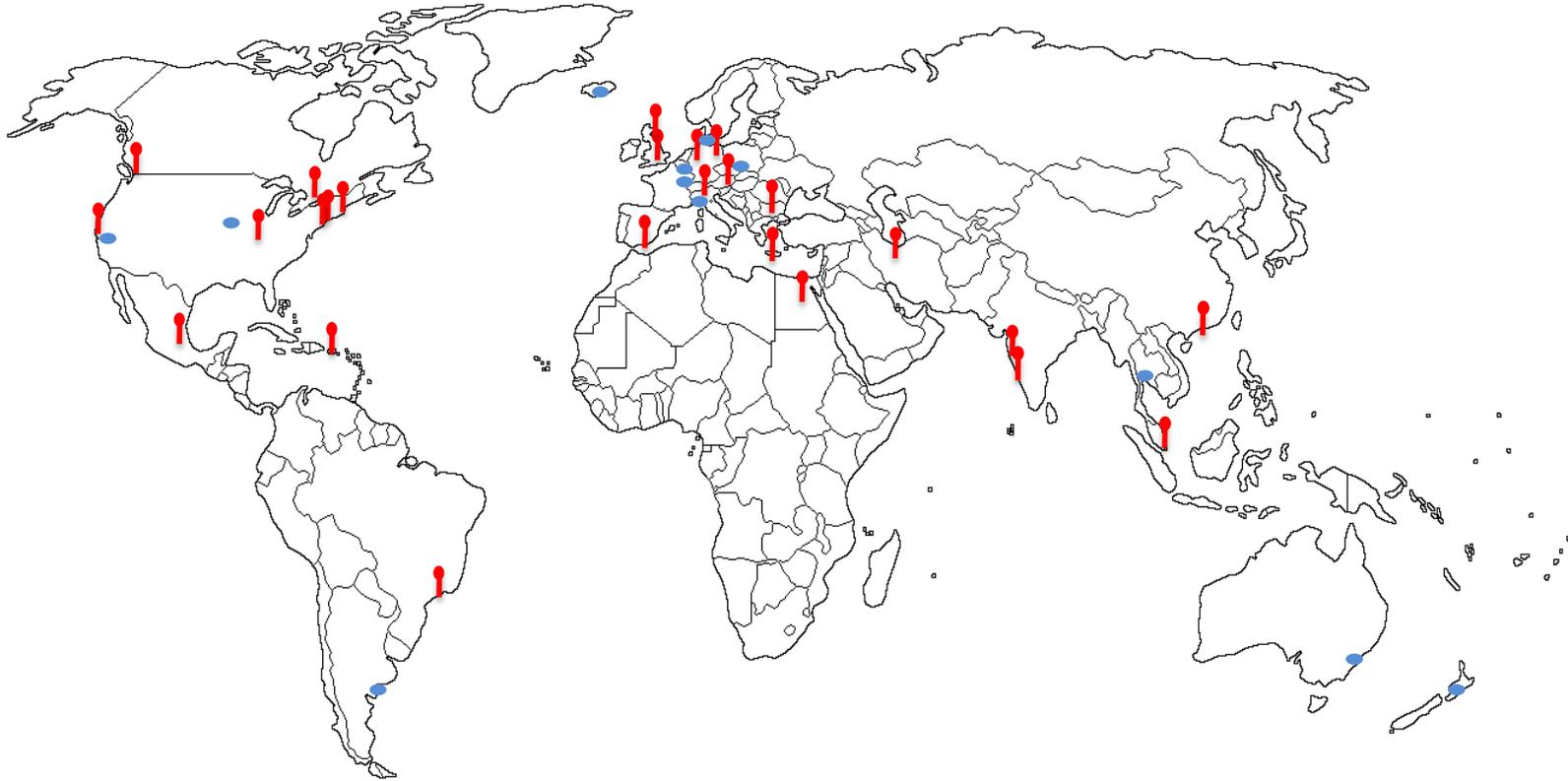
Key Words: endometriosis; tissue; collection; processing; storage; endometriosis research

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CENTERS USING TOOLS

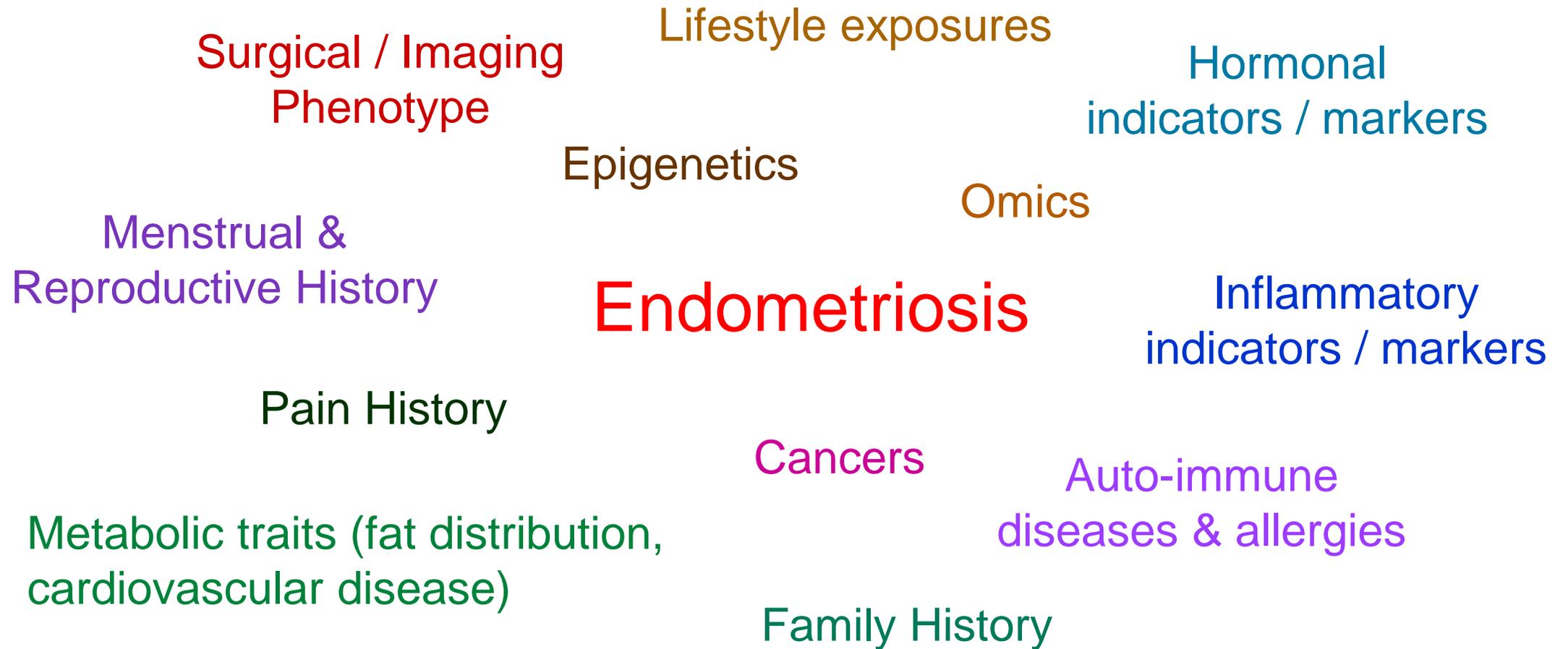


WERF ePHect
Endometriosis Phenome
and Biobanking Harmonisation Project



25 centers in 17 countries

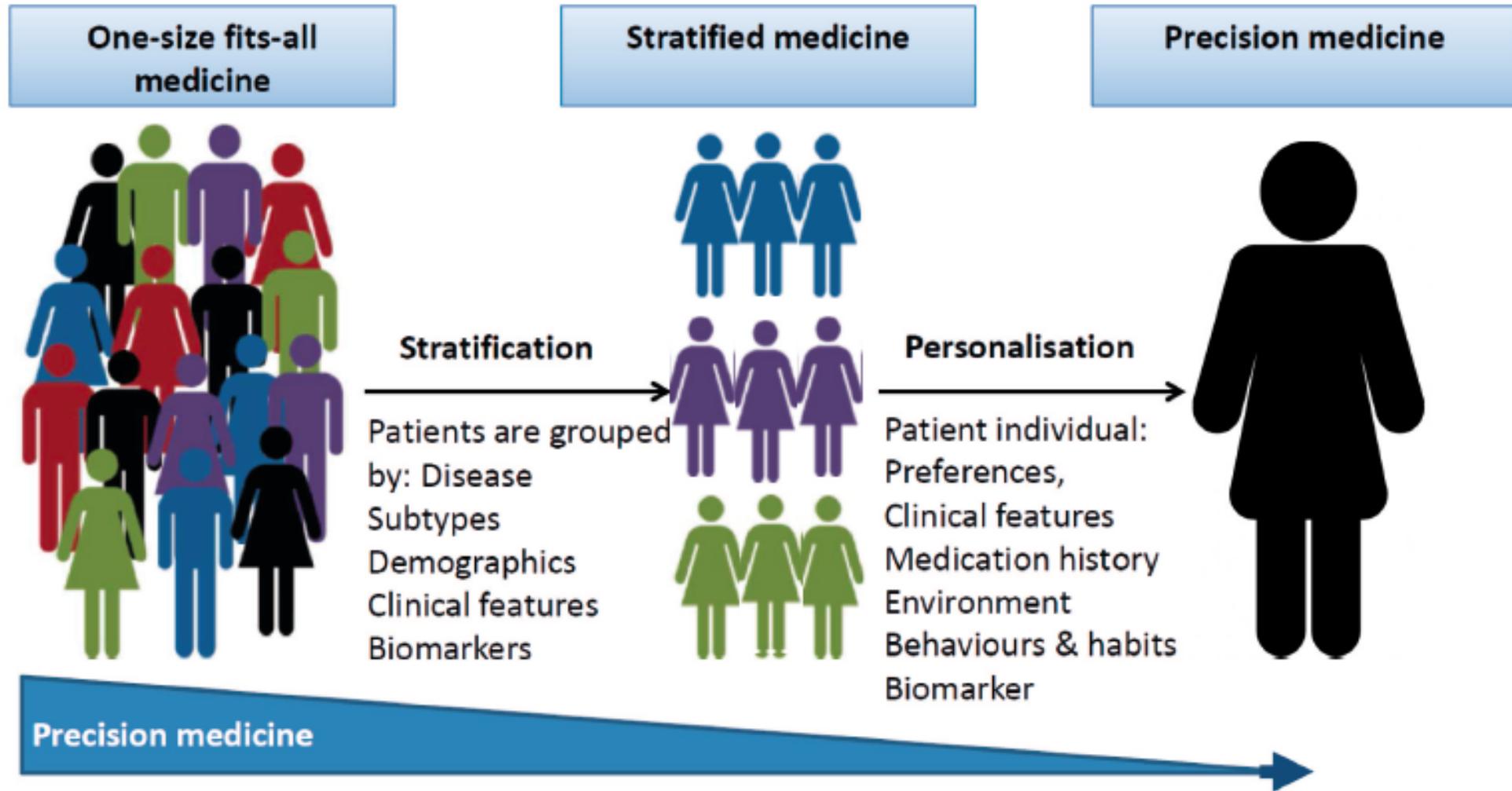
12 emerging centers in 9 additional countries



The Future for Endometriosis Discovery

- 2003 - 15 years since discovery of Triple Negative Breast Cancer
 - informative subtypes advanced **risk understanding**, drive **personalized treatment** and **save lives**
- WILL be true for endometriosis

Vision: Stratified and Precision Medicine



Vision: Rapid Accurate Diagnosis

- Ideally in hands of first line health care practitioners
- Define magnitude of undiagnosed women / true prevalence
- Shorten time interval from diagnosis to begin effective treatment
- May successfully modify infertility or co-morbidity risk
- A biomarker may elucidate physiologic pathways that will catalyze novel treatment development or prevention potential
- Utilize the millions of samples and decades of data poised for discovery

What is endometriosis?



- Prevalent, impactful disease affecting millions of women
- Identifying critical windows of etiologic physiology may allow prevention and cure
- Informative subtypes that predict risk, treatment selection, and prognosis must be defined
- Large, collaborative, diverse studies with **multidisciplinary** teams will drive forward
- Fundamental questions for encouraged investigators

Thank you!

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College of
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Boston Center for Endometriosis



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SCHOOL OF PUBLIC HEALTH



Nurses'
Health Study



The Women's
Health Study

From Adolescence to Adulthood



EndometriosisCaRe



O X F O R D
Care & Research



WERFePHect

Endometriosis Phenome
and Biobanking Harmonisation Project



N°	Research Priority
1	Can a cure be developed for endometriosis?
2	What causes endometriosis?
3	What are the most effective ways of educating healthcare professionals throughout the healthcare system resulting in reduced time to diagnosis and improved treatment and care of women with endometriosis?
4	Is it possible to develop a non-invasive screening tool to aid the diagnosis of endometriosis?
5	What are the most effective ways of maximising and/or maintaining fertility in women with confirmed or suspected endometriosis?
6	How can the diagnosis of endometriosis be improved?
7	What is the most effective way of managing the emotional and/or psychological and/or fatigue impact of living with endometriosis (including medical, non-medical and self-management methods)?
8	What are the outcomes and/or success rates for surgical or medical treatments which aim to cure or treat endometriosis, rather than manage it?
9	What is the most effective way of stopping endometriosis progressing and/or spreading to other organs (e.g. after surgery)?
10	What are the most effective non-surgical ways of managing endometriosis-related pain and/or symptoms (medical/non-medical)?

WCE2017 survey results

N°	Research Priority
1	Is it possible to develop a non-invasive screening tool to aid diagnosis of endometriosis?
2	What causes endometriosis?
3	How can endometriosis be prevented?
4	What are the most effective non-surgical ways of managing endometriosis-related pain and/or symptoms (medical/non-medical)?
5	Is endometriosis a single disease or are there different disease subtypes which represent different, but related, pathological entities?
6	How can the diagnosis of endometriosis be improved?
7	How can we prevent endometriosis in women and/or young girls with a family history of the disease?
8	What is the natural history of endometriosis (e.g. how, and how quickly, does it progress and spread)?
9	Is there a link between endometriosis and auto-immune diseases, and endometriosis and/ or inflammatory disorders (e.g. MS, Lupus, RA, osteoarthritis, asthma, eczema and thyroid) and if so why?
10	What can be done to stop endometriosis from recurring (e.g. after treatment)?