

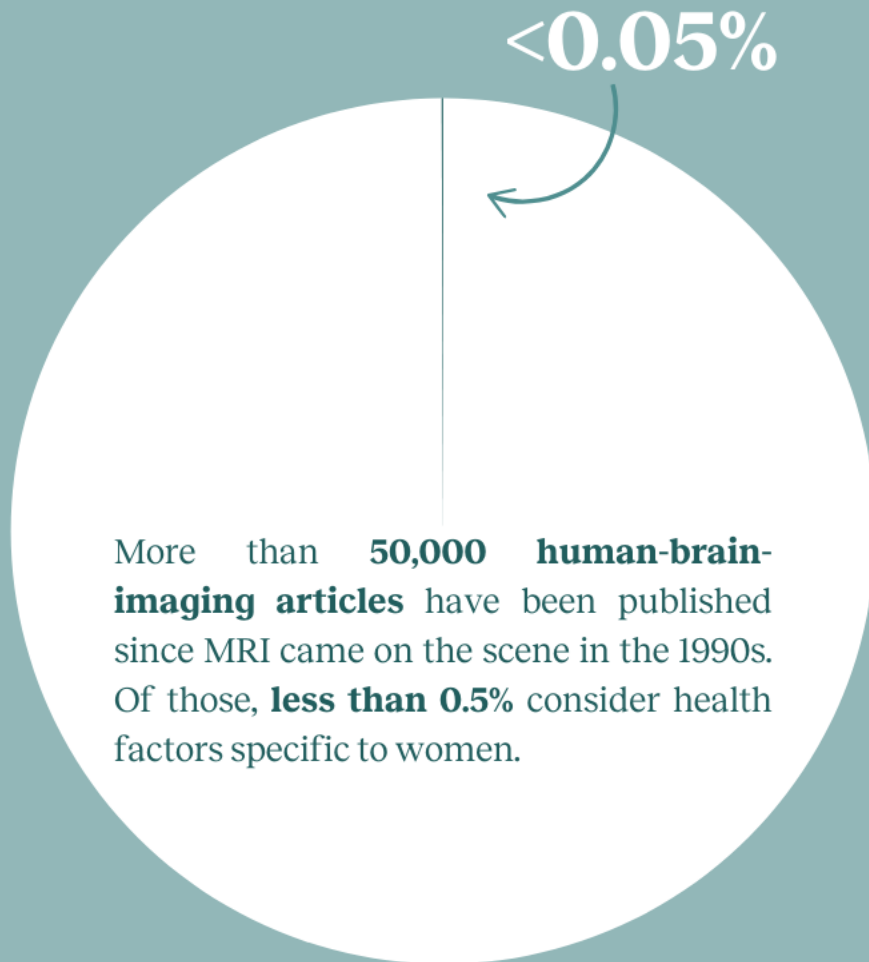
Sex & Gender in Alzheimer's Disease: The Evidence, the Gaps, and the Global Opportunity

Rachel Buckley, PhD

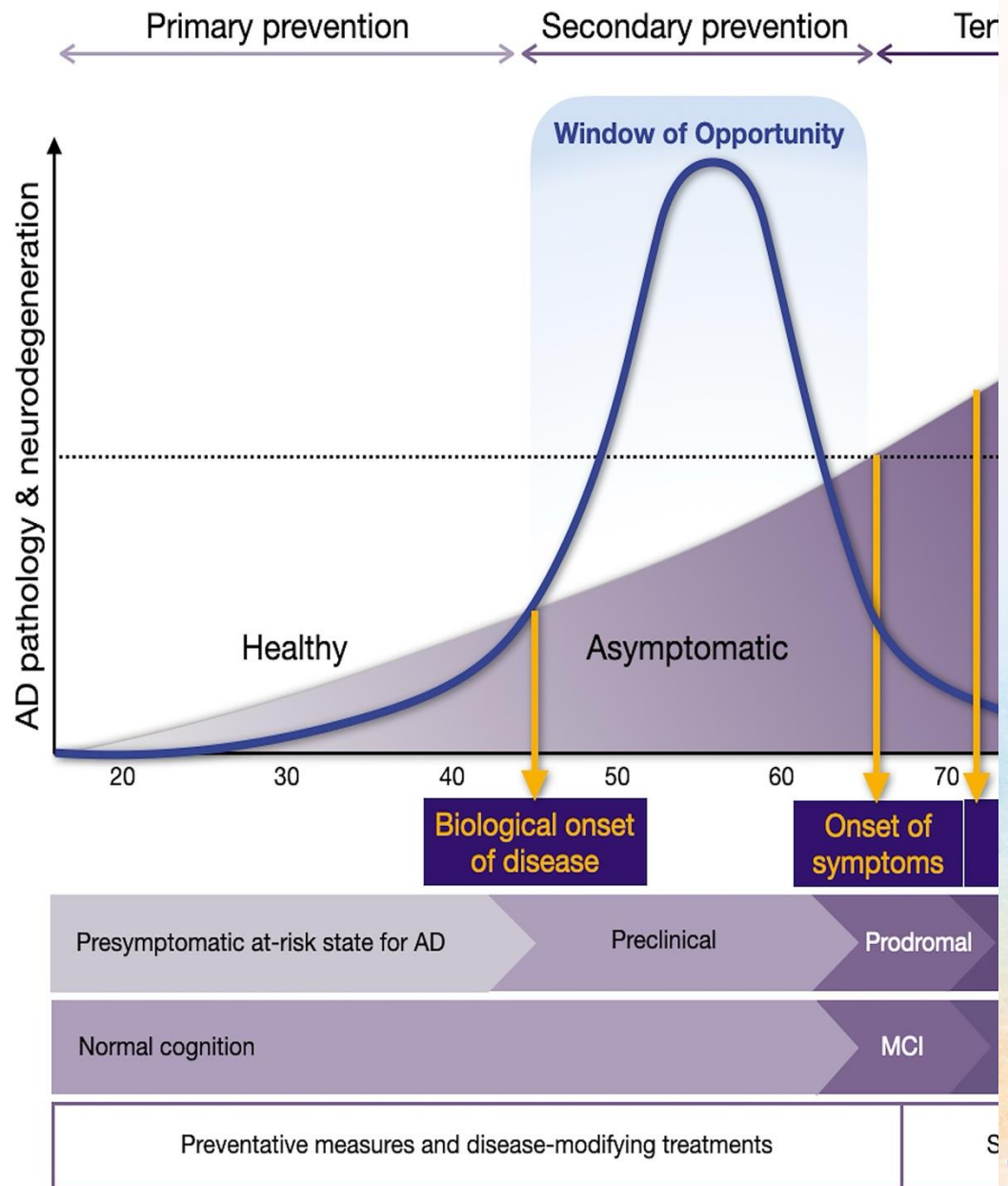
Associate Professor, Department of Neurology, Mass General Brigham/Harvard Medical School

The Moment We're In





Advancing
women's health
will require
“a global shift in
science culture.”



Key Facts and Figures: The SWAN Study



The Study of Women's Health Across the Nation followed over 3,300 midlife women across 7 US sites for 25 years.



↑ SYMPTOMS

- Vasomotor Symptoms:** Up to 80% experience hot flashes and night sweats
- Sleep Issues:** Shorter sleep duration, poorer sleep quality
- Depression & Anxiety:** Higher rates, especially perimenopause
- Vaginal & Sexual Changes:** Vaginal dryness, sexual pain

+ HEALTH IMPACTS

- Cardiovascular Risk:** Higher triglycerides, higher body fat, lower HDL
- Bone Health:** Bone loss accelerates, earlier fractures in Asian & white women
- BMI Increases:** +6-7% increase in body mass index over the transition

🕒 AGING & PHYSICAL FUNCTION

- Declining Lean Mass:** Particularly in Black women
- Lower Intercourse Frequency:** Especially in Black women
- Perceived Stress Linked to:** Symptom severity, lingering cognitive slowdown

💡 CONTEXTUAL INSIGHTS

- Hormones:** Estradiol (& FSH) rise around the final menstrual period
- Race/Ethnicity:** Different age at menopause, hormone patterns
- Smoking:** Associated with earlier menopause transition



And beyond...

40

50

60

70

80

90



Menopause

Hormone therapy use

Surgical intervention

Women respond differently to anti-amyloid therapeutics

43

12





Recommendations



- Report
 - **Sex-stratified outcomes**
 - **Adverse events and drug tolerability** by sex
 - **Reproductive characteristics** of all participants
- Re-examine existing clinical trial data
- Quantify sex differences using a full interaction model
- Power trials for the examination of sex as a primary end point
- Ensure that the participation mirrors the prevalence of the disease of interest
- Enhance diversity in teams of research, policy, and practice



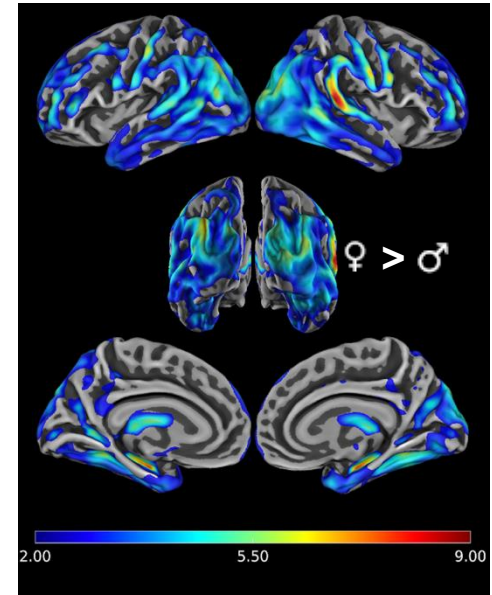
What We Know

Genes & Hormones

- Menopause transition as a critical nexus in AD
- Hormone therapy
- Therapeutic discoveries on the X chromosome
- Longevity and the XX

Gender Matters

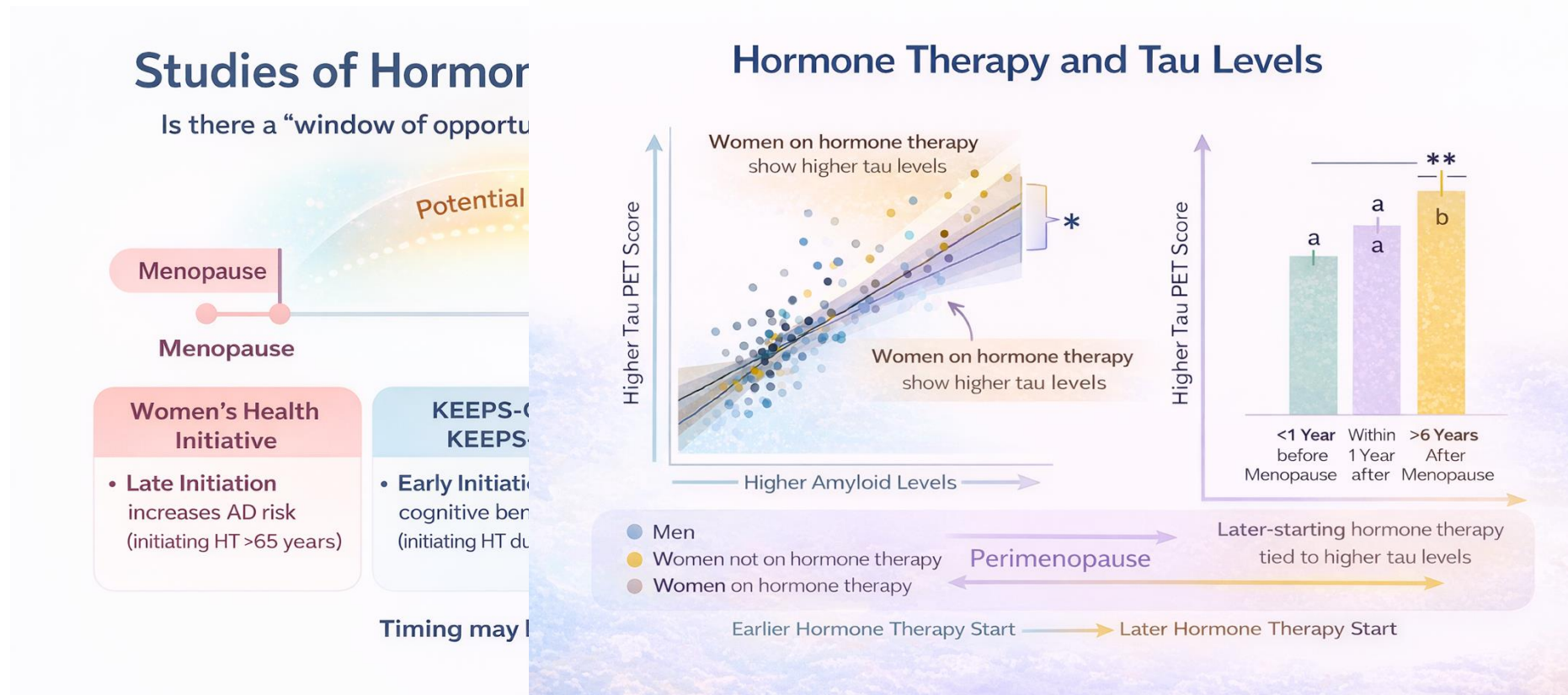
- Women are primary caregivers of patients with AD
- Disparities:
 - Education
 - Occupational attainment
 - Social determinants of health
- Intersectionality (race, SES, global region)



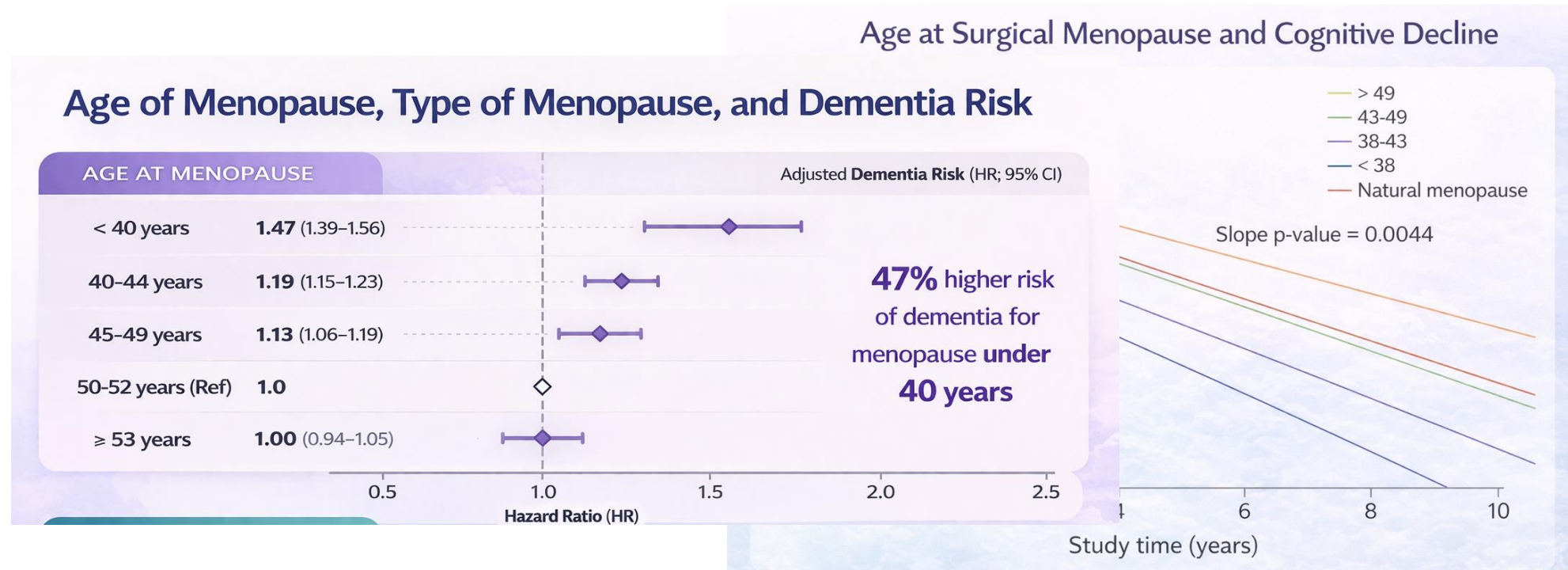
Biomarker Insights

- Tau levels: ♀ > ♂
 - Particularly in:
 - *APOE4* carriers
 - $A\beta+$
 - Faster rates of cognitive decline

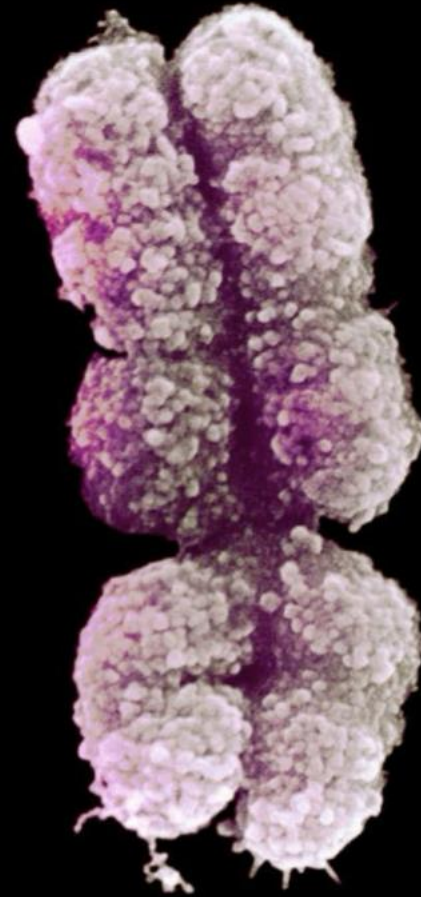
Hormone Therapy Moderates AD Risk



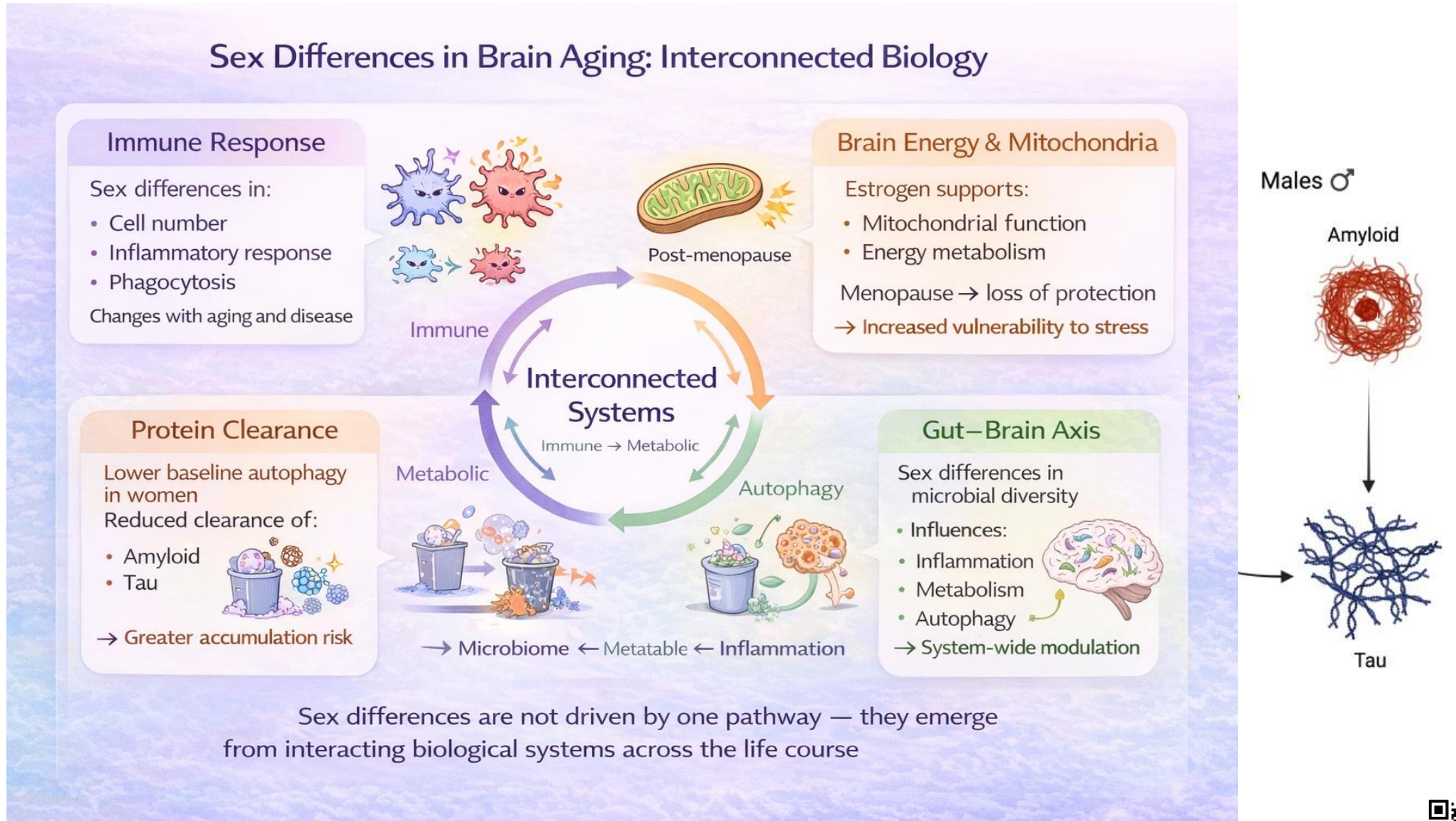
Age at Menopause Impacts AD Risk



The XX Confers Both Protection and Vulnerability



Differential Contributors to Women's Brain Health



What We Don't Know

Biological Pathways

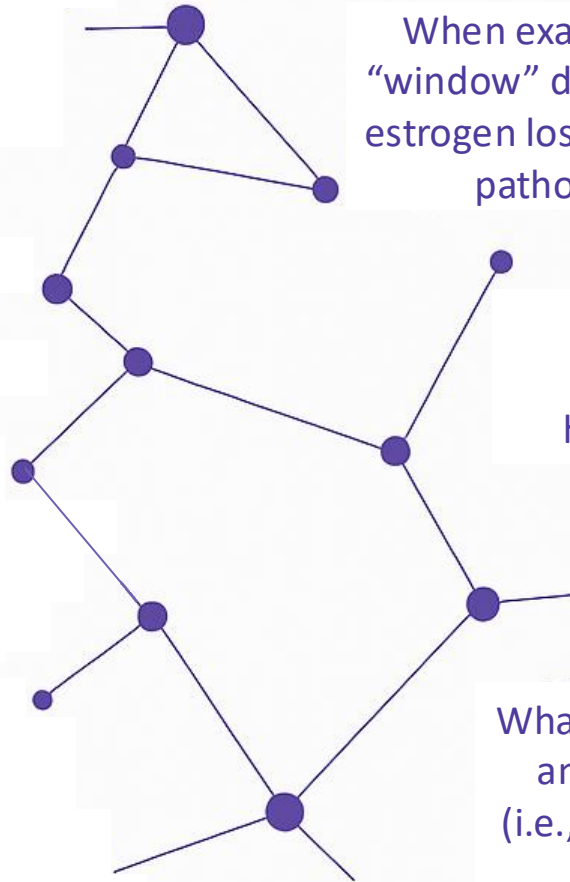
What biological pathways link the menopause transition to AD trajectories?

What are the gendered pathways that influence AD risk across cultures

How and why do sex chromosomes influence AD risk and resilience?

Can we identify sex-specific biological signatures of AD risk?

How does gender affirming care throughout life impact AD risk?



Hormones & Reproductive Transitions

When exactly is the “window” during which estrogen loss affects AD pathology?

How does surgical outcome (bilateral oophorectomy, hysterectomy) impact AD risk?

Do menopause symptoms, (i.e., vasomotor symptoms, sleep disruptions) influence later-life cognitive decline?

What is the role of gender identity and its associated risk factors (i.e., chronic stress, stigma) on AD risk?

Should AD prevention strategies be sex-specific?

What are the long-term effects of different menopausal hormone therapy formulations, doses, durations?

Do anti-amyloid therapies work differently by sex? Are adverse treatment outcomes sex-specific?

Treatment & Prevention-Gaps

Should AD prevention strategies be sex-specific?

Do modifiable risk factors differ substantially by sex to impact AD prevention strategies?

Do we anticipate sex differences in other AD therapeutics i.e., anti-tau?

What are the gendered pathways that influence AD risk across cultures

Does underdiagnosis of AD in women impact our estimates of AD risk?

Gaps in our data capture and analytic designs

- Deeply characterized studies of menopause (i.e., SWAN, WHI)
- Deeply phenotyped studies of aging and Alzheimer's disease (i.e., ADNI)

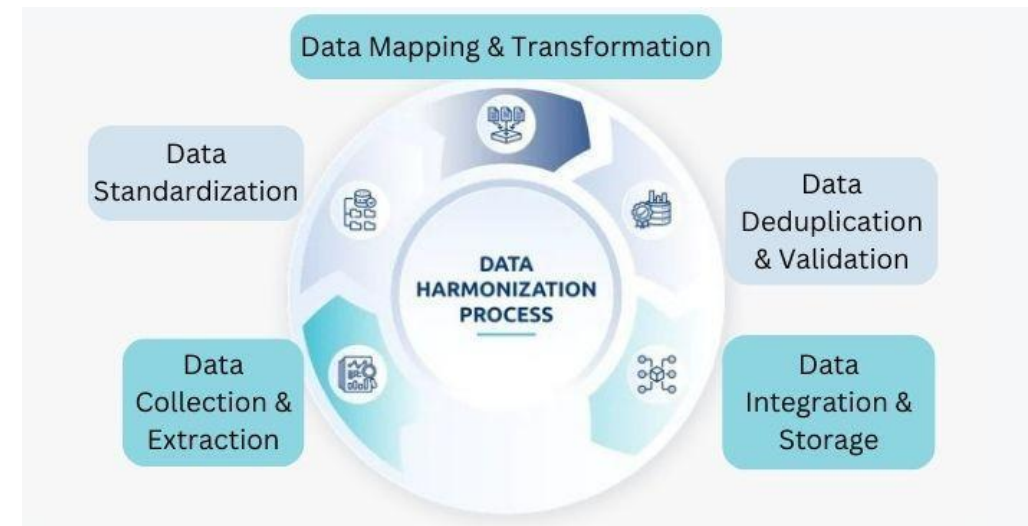
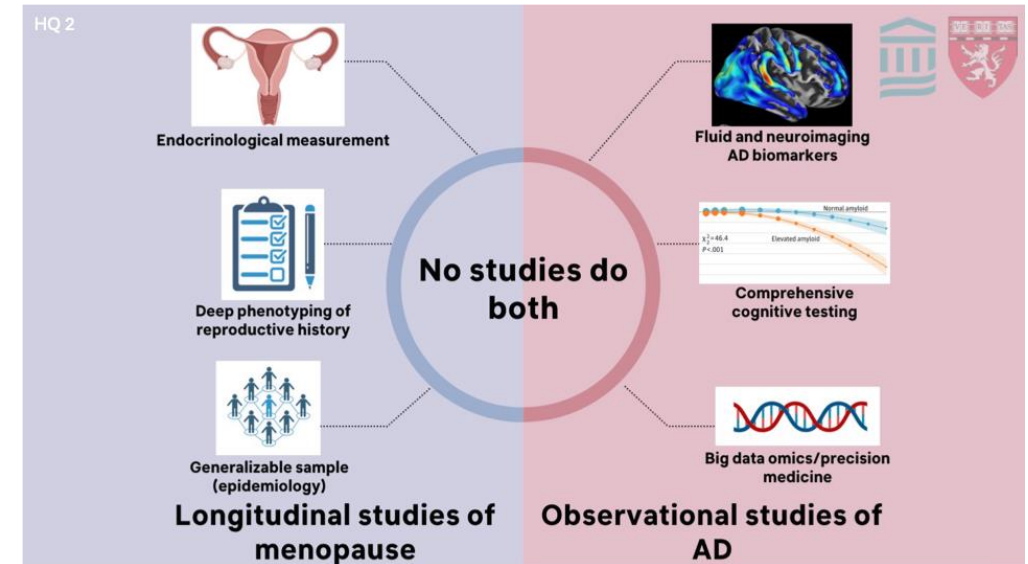
NO STUDIES DO BOTH

No standard measures

No global framework for menopause and hormone therapy data

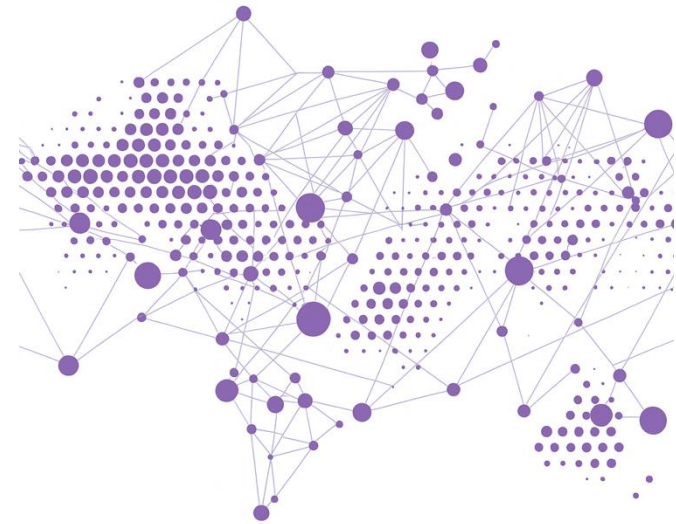
No harmonized analytic pipelines

No consideration of gender



What's emerging: A New Global Opportunity

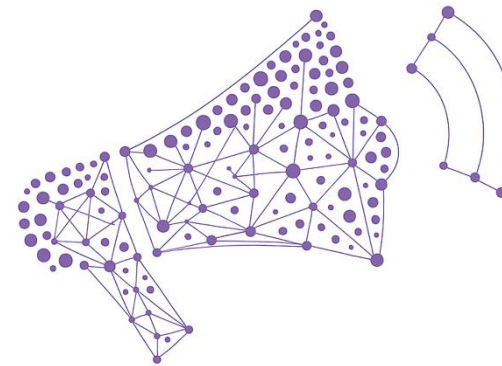
COORDINATED
GLOBAL
INVESTMENT



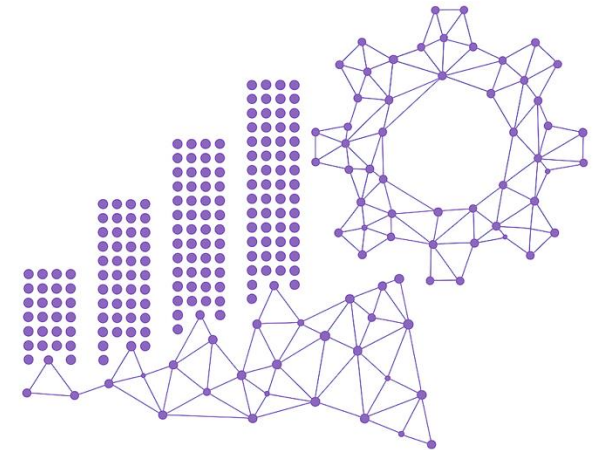
POLICY MOVING IN
TANDEM WITH SCIENCE



SCIENCE
COMMUNICATION
AS A
SCIENTIFIC
IMPERATIVE

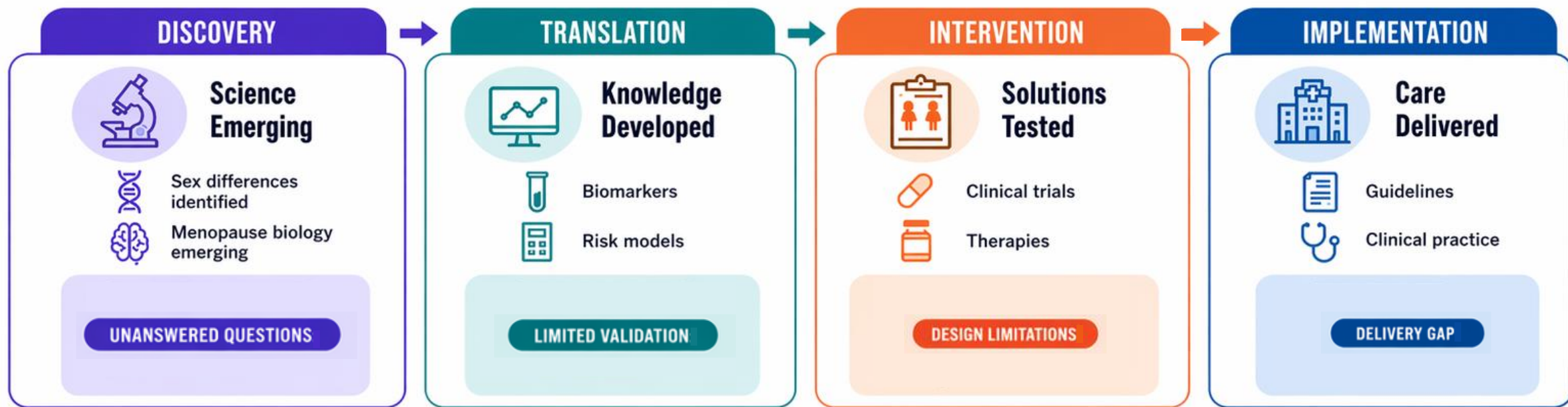


TRANSFORMING
OUR DATA
STANDARDS



FROM DISCOVERY TO IMPACT

ALIGNING WOMEN'S BRAIN HEALTH



POLICY & SYSTEM LAYER

Policy and science are advancing — but not yet aligned.



DISCOVERY

SABV policy exists, funding momentum



Not coordinated



TRANSLATION

Data initiatives, emerging standards



Not standardized



INTERVENTION

Trial inclusion, regulatory awareness



Not targeted



IMPLEMENTATION

Access policies, public health programs



Not implemented



The opportunity isn't starting over.
It's aligning what already exists.

Why Partnerships Matter

No single organization can transform women's brain health.

But together, we can.



leap^w

 wellcomeleap.org

 @wellcomeleap

 wellcome-leap

A \$50M program in women's health

care

Cutting Alzheimer's Risk
through Endocrinology



The Coalition for Women's Brain Health officially launched during the 2025 WAM Forum, hosted by Maria Shriver



Coalition for Women's Brain Health

Mission Statement

The Coalition for Women's Brain Health (CWBH) is a group of organizations and individuals promoting women's brain health and addressing the disproportionate burden of neurological disease on women through a focus on research, advocacy, and collaboration.

Our Vision

To ensure women have access to cognitive health resources & to empower women to actively impact their own cognitive well-being. We will achieve this by advancing women's brain health through research & evidence generation; implementation projects (e.g., toolkits, care delivery models); and advanced treatment options.

Three "Pillars" of Interest

Our efforts to address our goals stated above are organized into the following three priority areas:

1

Research on Sex Differences

Current or future research focused on sex differences related to women's brain health.

2

Patient and Caregiver Burden and Support

Caregiving responsibilities and the entities that impact caregiving burden & support.

3

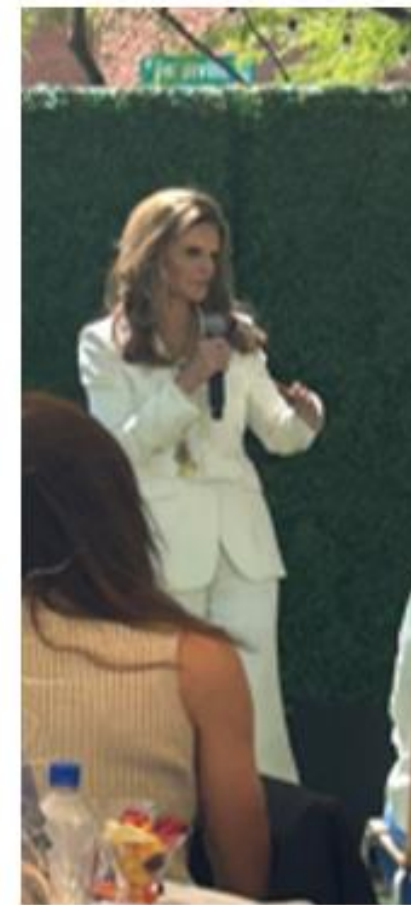
Access to Care and Care Delivery Models

Care delivery models addressing women's brain health and women's ability to seek brain-related care compared to men.



www.coalitionforwomensbrainhealth.org

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ANN S. BOWERS WOMEN'S BRAIN HEALTH INITIATIVE



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Berkeley National Lab



Rachel Buckley, Ph.D.
Harvard-Mass Gen



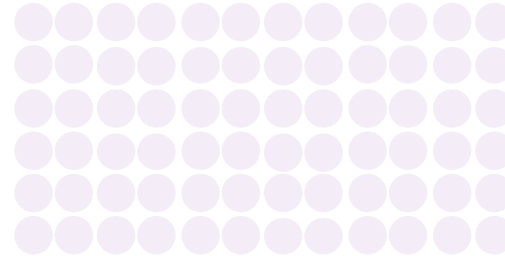
Kaitlin Casaletto, Ph.D.
UC San Francisco



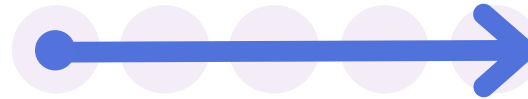
Judy Pa, Ph.D.
UC San Diego



Go Broad – Data from Lots of Women

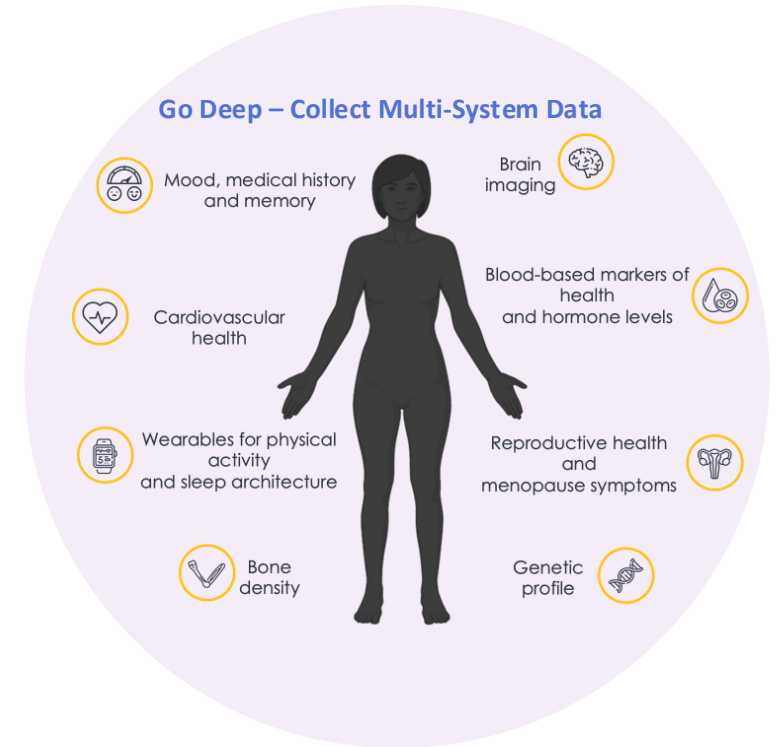


Go Long – Track Changes Longitudinally



Premenopause

Postmenopause



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targeting breakthrough research

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