THE WOMEN'S HEALTH INITIATIVE

2026 IGNITE Sessions

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Wide-scale validation of epigenetic biomarkers of aging

Which epigenetic clock to use in WHI, and for what outcome?

WHI Investigators Meeting 2026 – IGNITE Sessions

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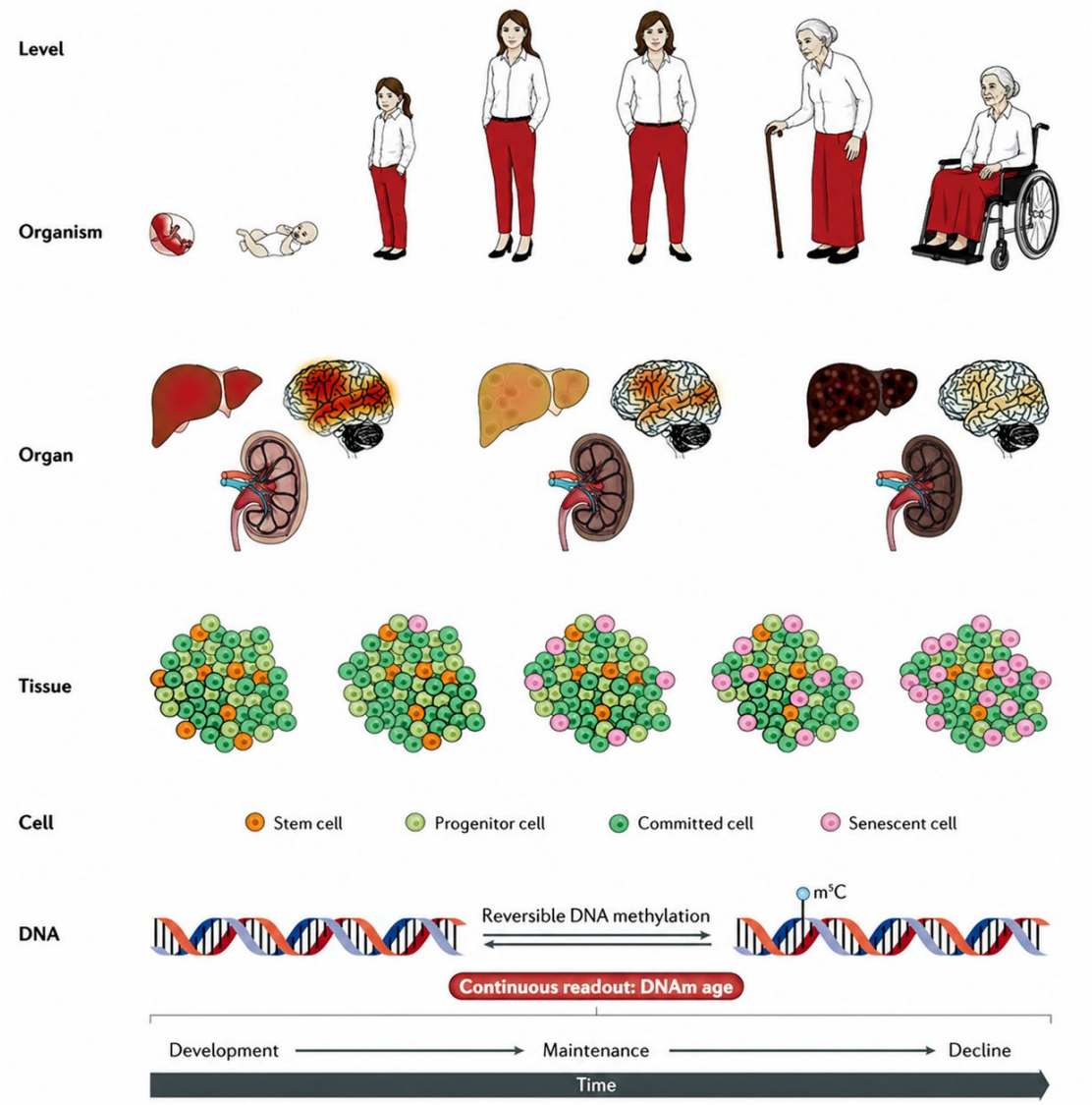
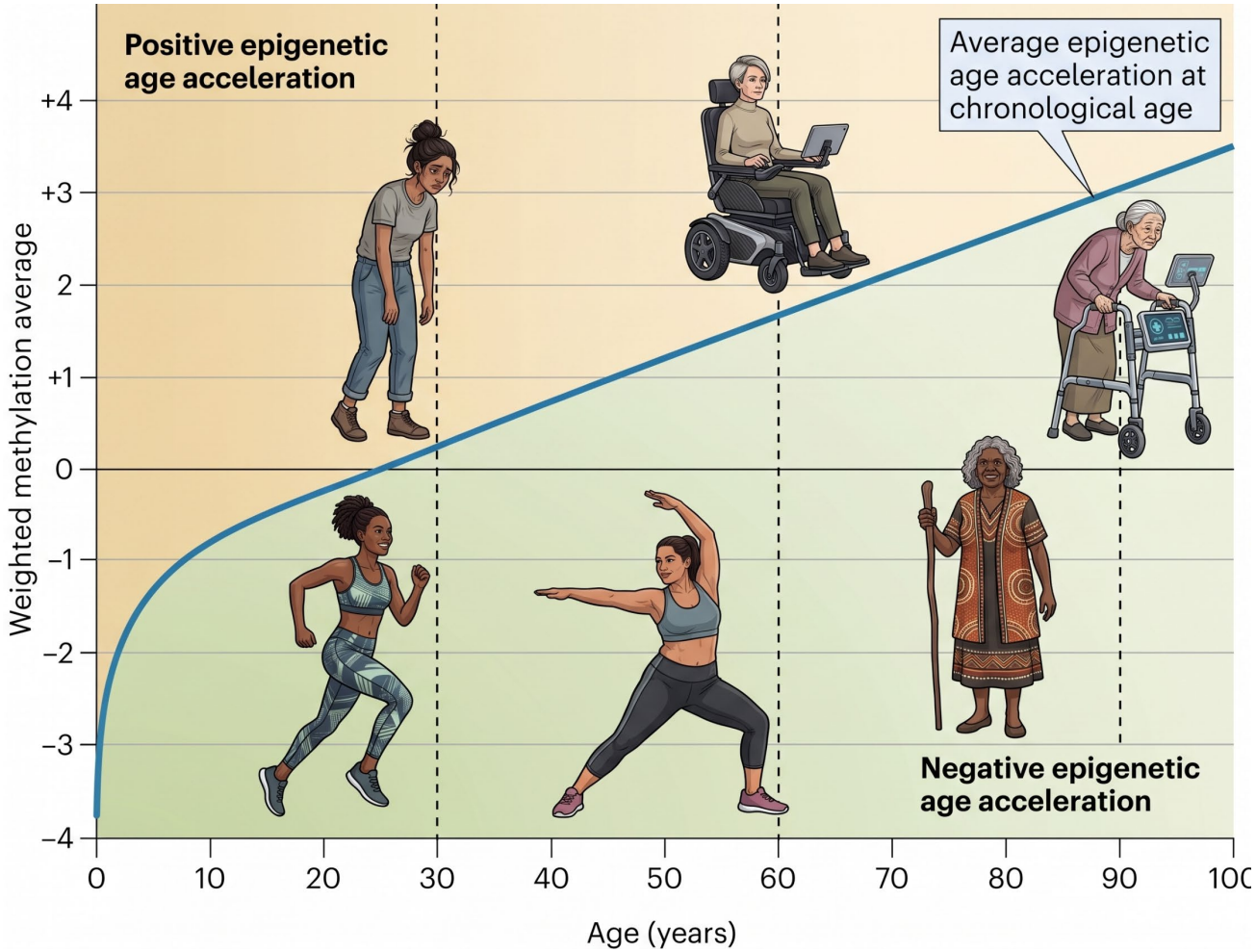
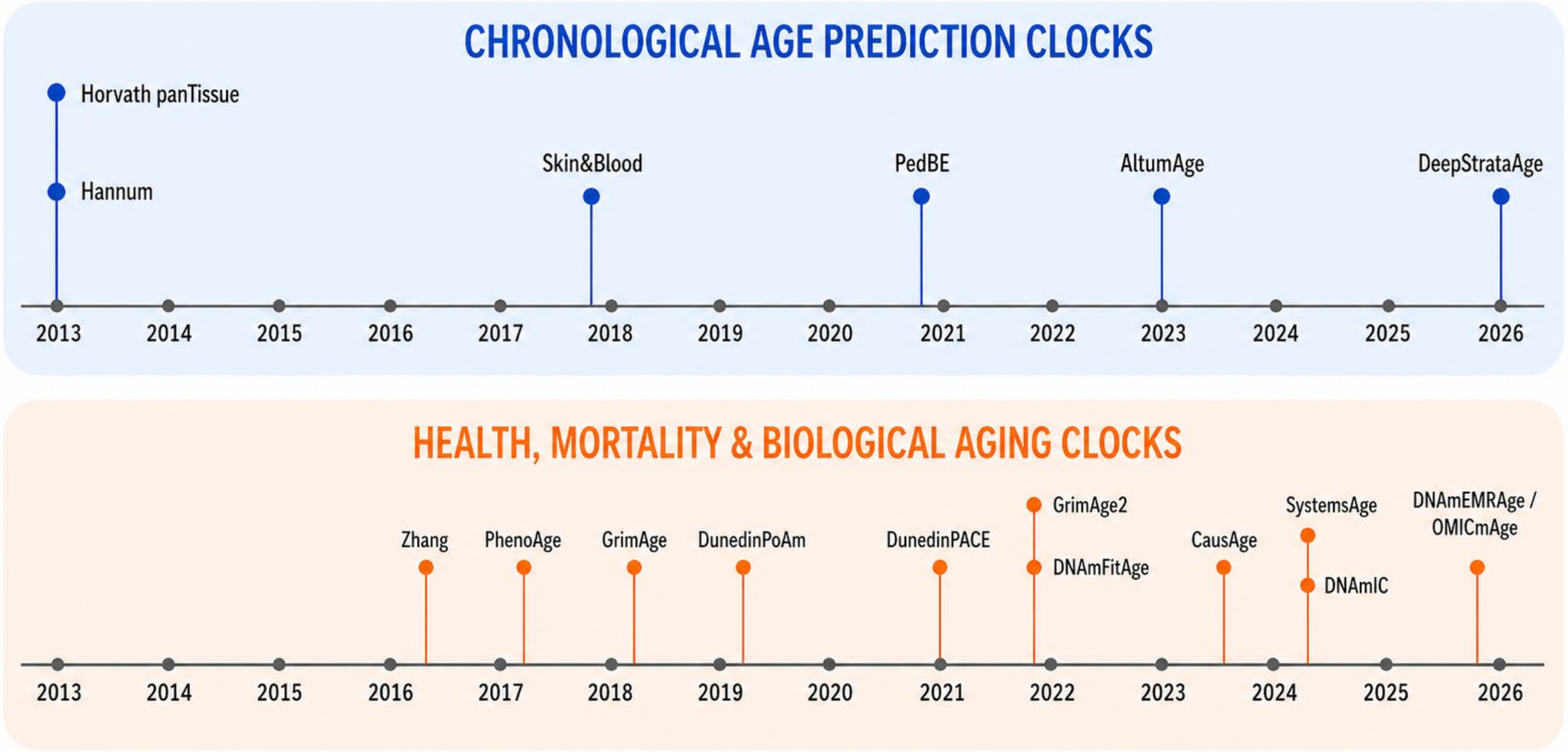
Epigenetic Biomarkers of Aging



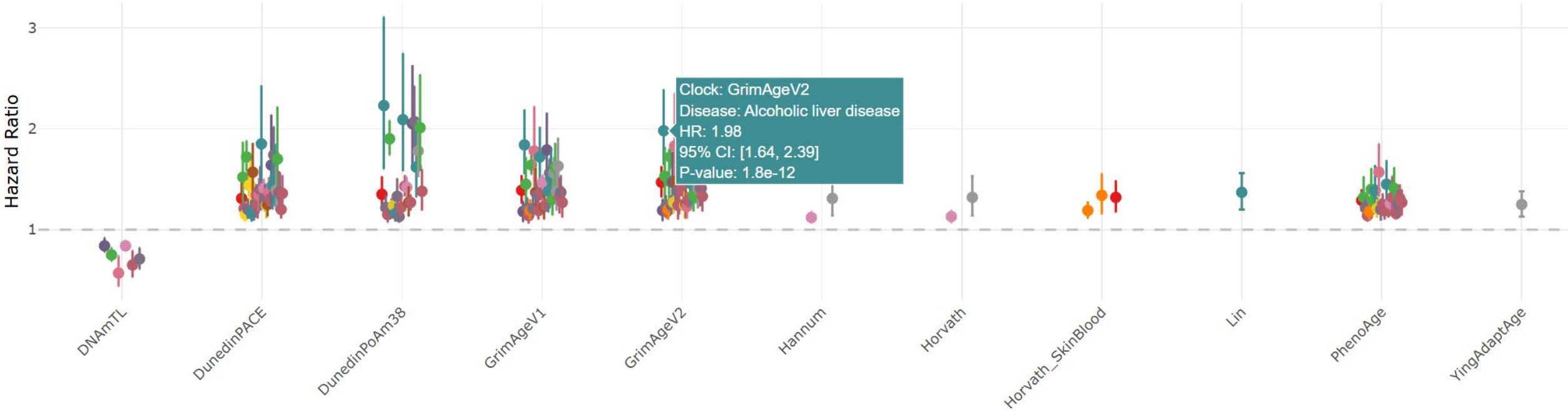


Adapted from Horvath & Raj 2018

Epigenetic Biomarkers of Aging



Widescale Validation Efforts



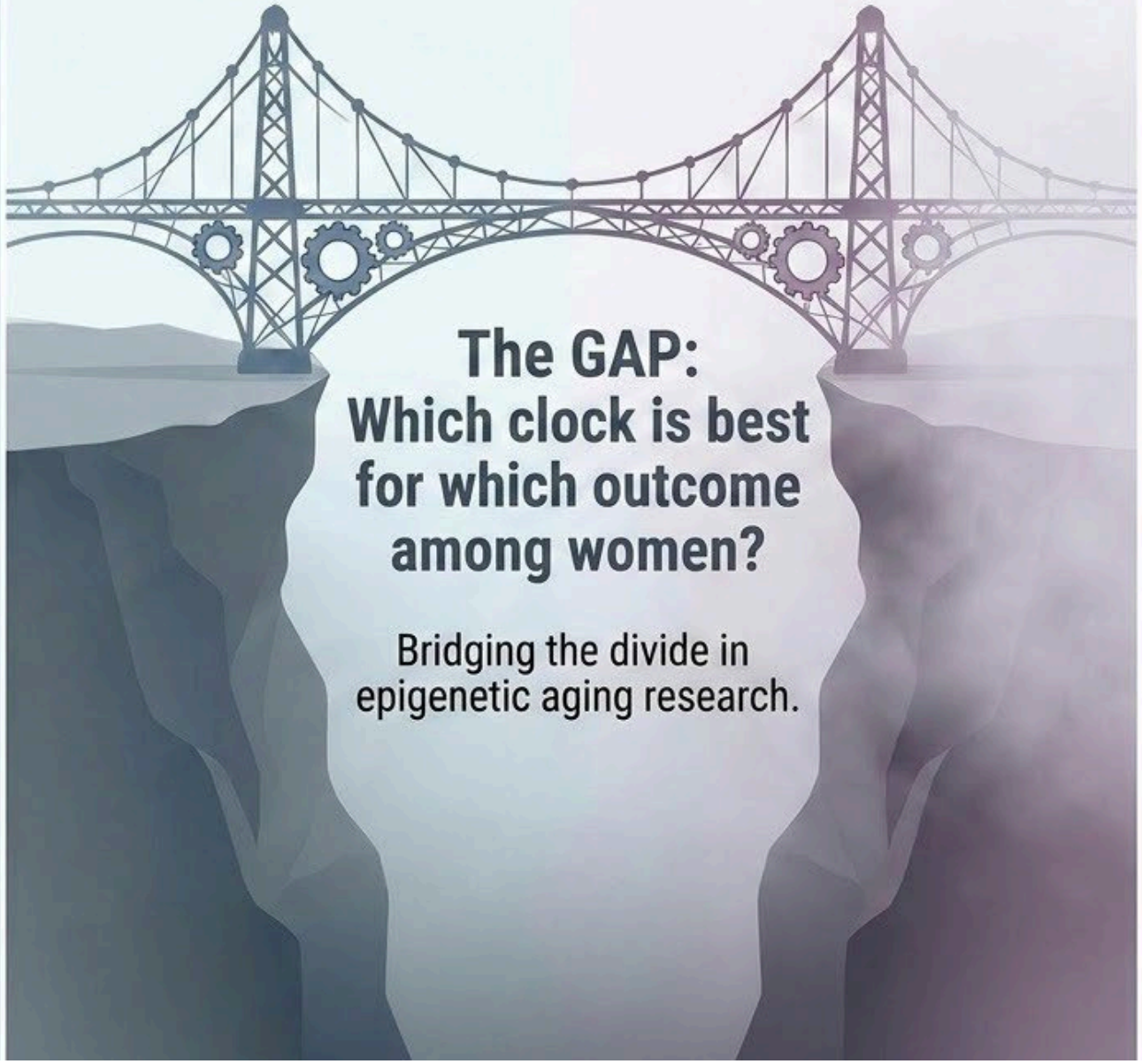
Mavrommatis et al. Nature Communications. 2025

THE CURRENT STATE

* epigenetic clocks are versatile

* Strong predictors of morbidity and mortality

* widely adopted



The GAP: Which clock is best for which outcome among women?

Bridging the divide in epigenetic aging research.

THE UNKNOWN

* Overwhelming number of available clocks

* Differing training samples

* Differing aging phenotypes

* Limited validation

* Not specifically validated among women only

* Often European only

WHI DNAm Data

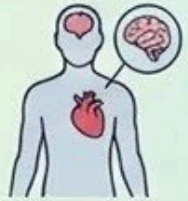
Study	PI	Study design	Timepoint	Platform	Total N after QC
AS311	Parveen Bhatti	Bladder Cancer Cases and Controls	Baseline	450K	882
AS315	Eric Whitsel	Cohort	Baseline	450K	2400
BA23	Tim Assimes	CVD cases and controls	Baseline	450K	2151
AS564	Charles Kooperberg	Cohort	LLS	EPICv1	1336
AS690	Aladdin Shadyab	WHIMS participants	Baseline	EPICv2	6089
AS690	Aladdin Shadyab	WHIMS participants	LLS	EPICv2	1837
AS717	Nora Franceschini/Andres Cardenas	African American participants	Baseline	EPICv2	~5318

- Use of WHI in Validation Samples
  - PhenoAge (Levine, et al. 2018): mortality, aging-related morbidity
  - GrimAge (Lu, et al. 2019): dietary/lifestyle factors
  - SystemsAge (Sehgal, et al. 2025): varying disease outcomes
- Use of WHI in Training Samples
  - DNAmTL (Lu, et al. 2019): BA23

VALIDATION FRAMEWORK

AREAS FOR BIOLOGICAL VALIDATION

Assessing real-world biological impact



PREVALENT DISEASE:
Establishing associations with existing health conditions

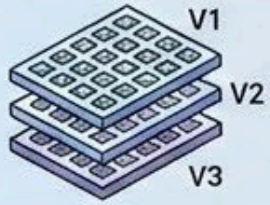
RISK PREDICTION:
Forecasting future disease development

EFFECT MODIFICATION BY RELEVANT FACTORS:
Understanding how external factors influence biological markers

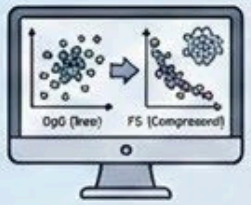
VALIDATION & ROBUSTNESS

AREAS FOR TECHNICAL VALIDATION

Evaluating robustness and consistency



ARRAY VERSION:
Comparing consistency across different platform generations



CpG vs. PC TRAINING:
Evaluating models trained on raw features vs. dimensionality-reduced data

PERFORMANCE IN DIVERSE SAMPLES: Testing applicability and robustness across different populations

LOOKING FOR COLLABORATORS TO GET THIS PROJECT STARTED

2026 WHI INVESTIGATORS MEETING

THE WOMEN'S HEALTH INITIATIVE

Are Postmenopausal Women One Group?

Discovery of hidden cardiovascular phenotypes in the WHI data using machine learning

Shabitri B. Dasgupta DrPH, MPH, RCIS

Epidemiologist · Clinically Certified in Interventional Cardiology

Founder & CEO, Dasnovate Women's Health Analytics LLC

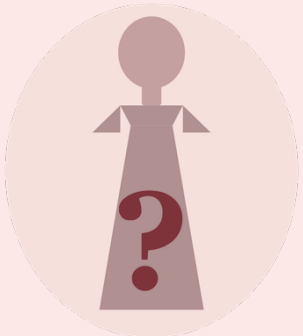
Dasnovate

WOMEN'S HEALTH ANALYTICS

One Population. Different Risk Profiles.

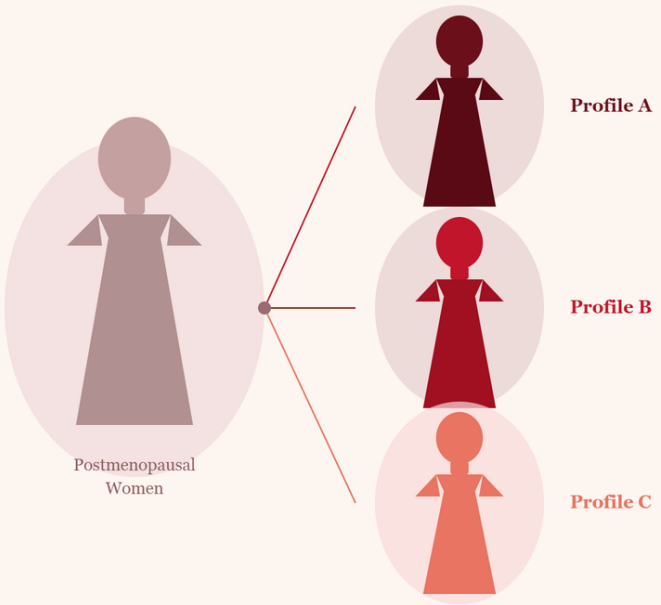
Multidimensional Risk

Postmenopausal women are not all experiencing the same pathophysiological changes equally or simultaneously that determine risk.



One group — or many?

Distinct Cardiovascular Profiles



Profile A | **Profile B** | **Profile C**

Traditional Methods Can Miss This

Hypothesis-driven approaches are designed to test **prespecified relationships.**

Rely on **predefined risk categories** and **single associations.**

- Multi-domain biological interactions
- Latent subgroup structure
- Patterns not anticipated at study design

Instead of testing one relationship at a time...
we let the data reveal the underlying structure

Traditional Statistical Approaches

- Start with a hypothesis
- Test one relationship at a time
- Require predefined risk categories
- Constrained by study design assumptions

VS

Unsupervised Machine Learning

- No hypothesis required — patterns emerge from data
- Processes all domains simultaneously
- Discovers structure without predefined categories
- Surfaces patterns

1

Preliminary Cluster Analysis
Full WHI cohort (N = 161,808)

2

Domain-Level Characterization
Refine and interpret emergent patterns across domains

3

Follow the Signal
Analytic direction informed by findings (e.g., biomarker predictive analysis)

4

Validate with External Data
Assess replication in independent postmenopausal cohorts

Building on Previous WHI ML-Based Work

Gorodeski, Ishwaran & colleagues used **Random Survival Forests (RSF)** to demonstrate the **prognostic value** of resting **ECG parameters** for **all-cause mortality** in WHI.

01 **14 out of 477 ECG biomarkers were identified as independent predictors of long-term all-cause mortality.**

02 **RSF made high-dimensional ECG analysis possible. Cox regression modeling failed to converge.**

03 **Study Limitations:**
No blood biomarker integration.
No external validation.

Circulation: Cardiovascular Quality and Outcomes
Volume 4, Issue 5, September 2011; Pages 521-532
https://doi.org/10.1161/CIRCOUTCOMES.110.959023

American Heart Association.

ORIGINAL ARTICLE

Use of Hundreds of Electrocardiographic Biomarkers for Prediction of Mortality in Postmenopausal Women

The Women's Health Initiative

Eiran Z. Gorodeski, MD, MPH*, Hemant Ishwaran, PhD*, Udaya B. Kogalur, PhD, Eugene H. Blackstone, MD, Eileen Hsich, MD, Zhu-ming Zhang, PhD, Mara Z. Vitolins, DrPH, RD, JoAnn E. Manson, MD, DrPH, J. David Curb, MD, Lisa W. Martin, MD, Ronald J. Prineas, MD, PhD, and Michael S. Lauer, MD

Background— Simultaneous contribution of hundreds of electrocardiographic (ECG) biomarkers to prediction of long-term mortality in postmenopausal women with clinically normal resting ECGs is unknown.

Methods and Results— We analyzed ECGs and all-cause mortality in 33 144 women enrolled in the Women's Health Initiative trials who were without baseline cardiovascular disease or cancer and had normal ECGs by Minnesota and Novacode criteria. Four hundred and seventy-seven ECG biomarkers, encompassing global and individual ECG findings, were measured with computer algorithms. During a median follow-up of 8.1 years (range for survivors, 0.5 to 11.2 years), 1229 women died. For analyses, the cohort was randomly split into derivation (n=22 096; deaths, 819) and validation (n=11 048; deaths, 410) subsets. ECG biomarkers and demographic and clinical characteristics were simultaneously analyzed using both traditional Cox regression and random survival forest, a novel algorithmic machine-learning approach. Regression modeling failed to converge. Random survival forest variable selection yielded 20 variables that were independently predictive of long-term mortality, 14 of which were ECG biomarkers related to autonomic tone, atrial conduction, and ventricular depolarization and repolarization.

Conclusions— We identified 14 ECG biomarkers from among hundreds that were associated with long-term prognosis using a novel random forest variable selection methodology. These biomarkers were related to autonomic tone, atrial conduction, ventricular depolarization, and ventricular repolarization. Quantitative ECG biomarkers have prognostic importance and may be markers of subclinical disease in apparently healthy postmenopausal women.

Key Words: electrocardiography ■ epidemiology ■ women ■ prognosis

* Drs Gorodeski and Ishwaran are joint first authors.

Three Domains. One Analysis.

No variable preselected as the driver — all entered simultaneously

01

477

features

ECG Data

- Autonomic tone
- Atrial conduction
- Ventricular depolarization
- Ventricular repolarization

02

TBD

variables

Reproductive & Clinical History

- Reproductive & hormonal history
- Demographic characteristics
- Lifestyle factors
- Clinical / anthropometric measures

03

TBD

biomarkers

Clinically Actionable Biomarkers

- Inflammatory markers
- Metabolic / insulin resistance
- Lipid panel + hormonal
- Renal, gut-cardiovascular

The goal is not to be exhaustive — **but intentional.** Distinct biological systems that we know matter for cardiovascular health in postmenopausal women.

Cluster Analysis for Phenotyping Retrieval

INPUT FEATURE SPACE

ECG Biomarkers
477 features → PCA-reduced

Blood Biomarkers
Inflammatory · Metabolic · Lipid · Hormonal

Demographic / Clinical / Reproductive / Hormonal
Life course + clinical context

ANALYTIC PIPELINE

1. DISCOVERY
   Pre-process
   Log-transform, z-score, Gower distance for mixed data
2. **Dimensionality reduction**
   Domain-specific PCA, retain ≥80% variance
3. **Unsupervised clustering**
   K-means → GMM, optimal k via silhouette + BIC
4. VALIDATION
   Stratified survival analysis
   Do clusters differ in mortality outcomes?
5. **External validation**
   Reproducibility in independent cohorts

HYPOTHETICAL PHENOTYPE PROFILES

Cluster A
↑ hsCRP · IL-6
P-wave conduction changes
Late menopause · long HRT use

Cluster B
↑ Glucose · HbA1c
Repolarization changes
↑ BMI · triglycerides

Cluster C
↓ Estradiol · ↑ FSH · low SHBG
Autonomic tone changes
Early menopause · oophorectomy

Cluster D
↑ Fibrinogen · PAI-1
ECG: atrial conduction
Hx gestational HTN / preeclampsia

**Profiles are hypothetical — actual phenotypes determined by data*

Cluster interpretation requires scientific judgment — cannot be replaced by machines

Machine learning **AUGMENTS** traditional epidemiologic methods — **NOT** replace.

Leveraging AI/ML for the WHI

1. Identify Subgroups

Hidden phenotypes may emerge that redefine how we study subgroups within this population

2. Improve Modeling

Empirical profiles may reveal which domains matter most informing smarter covariate selection

3. Address WHI Data-Specific Confounding

Latent structures may surface population-specific patterns

4. Enable Replication

A transferable analytical framework that can be benchmarked across independent cohorts

NEXT STEPS

Let's Work Together

- Principal Investigator
- Collaborators
- Funding Sources
  - *Biospecimen/ECG Access*
- External Validation Datasets
  - Physionet + UK Biobank?

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Epidemiologist

Clinically Certified in Interventional Cardiology

Founder & CEO Dasnovate

Connect with the presenter

Thank You!

WITH GRATITUDE TO

- **Dr. JoAnn E. Manson**
- **Dr. Marcia Stefanick**
- **Ms. Lindsey Bull**
- **WHI Community**

WOMEN'S HEALTH INITIATIVE

Life and Longevity After Cancer (LILAC)
A national resource for studies of cancer and aging

IGNITE SESSION: Expanding Treatment-Aware Cancer Survivorship Research in WHI

UNIVERSITY OF HAWAI'I CANCER CENTER

Alexandra M. Binder, ScD, ScM

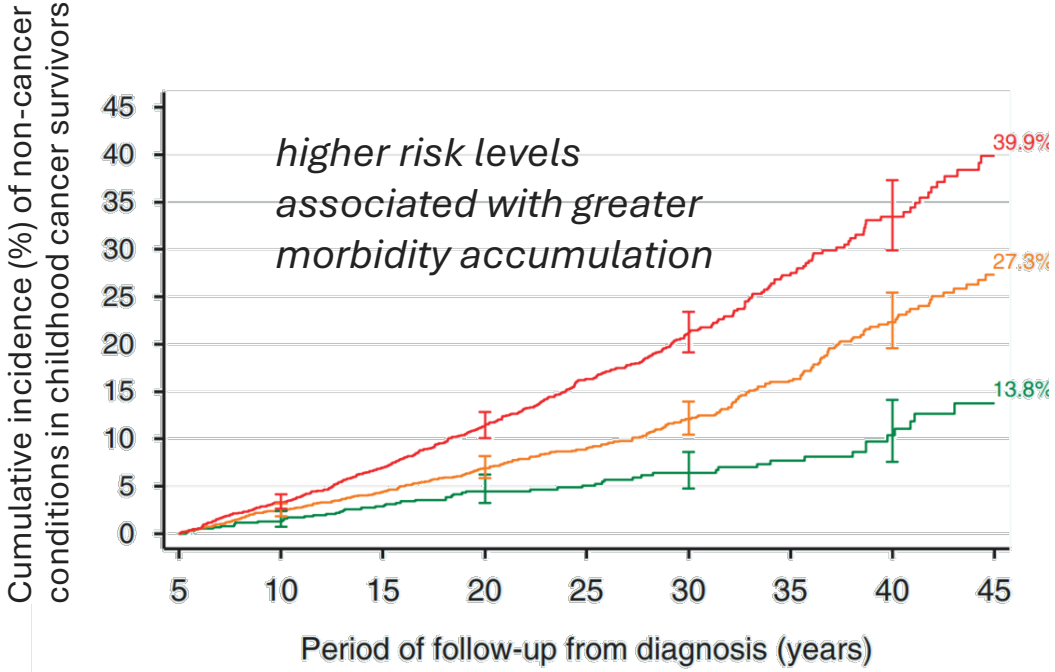
Associate Professor of Cancer Epidemiology
University of Hawai'i Cancer Center

Treatment Shapes Aging After Cancer

- Cancer survivors exhibit heterogeneous aging trajectories shaped by treatment
- More adults are living long after cancer, with quality of life a central priority
- Treatment-informed risk stratification enables targeted supportive care

Opportunity: *A newly harmonized, multi-source cancer treatment dataset in WHI that can be integrated into survivorship studies to* ***refine treatment-informed risk categories***

Risk-stratified survivorship care based on treatment profile



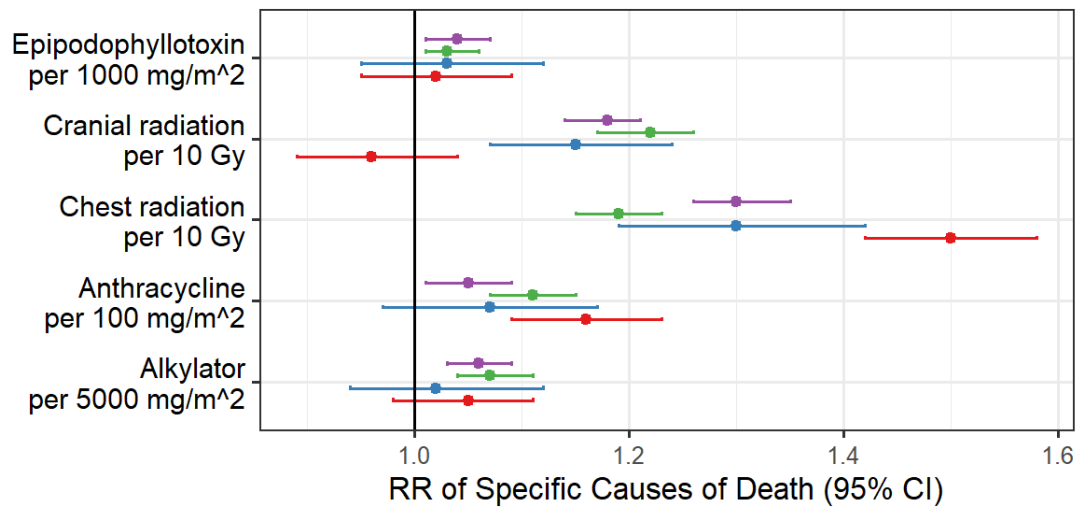
Level 3: specialist-led clinical care

Level 2: nurse- or primary care-led follow-up

Level 1: supported self-management

Adapted from:
Frobisher *et al* (2017)
Br J Cancer

Treatment intensity & health-related mortality in childhood cancer survivors



Adapted from:
Dixon *et al* (2023)
Lancet

Medical Record Abstraction (LILAC) *(gold standard)*

- Rich detail on **first-course treatment**
- Includes **non-Medicare participants**
- Limited to diagnoses after 2000

Medicare (FFS A/B/D claims)

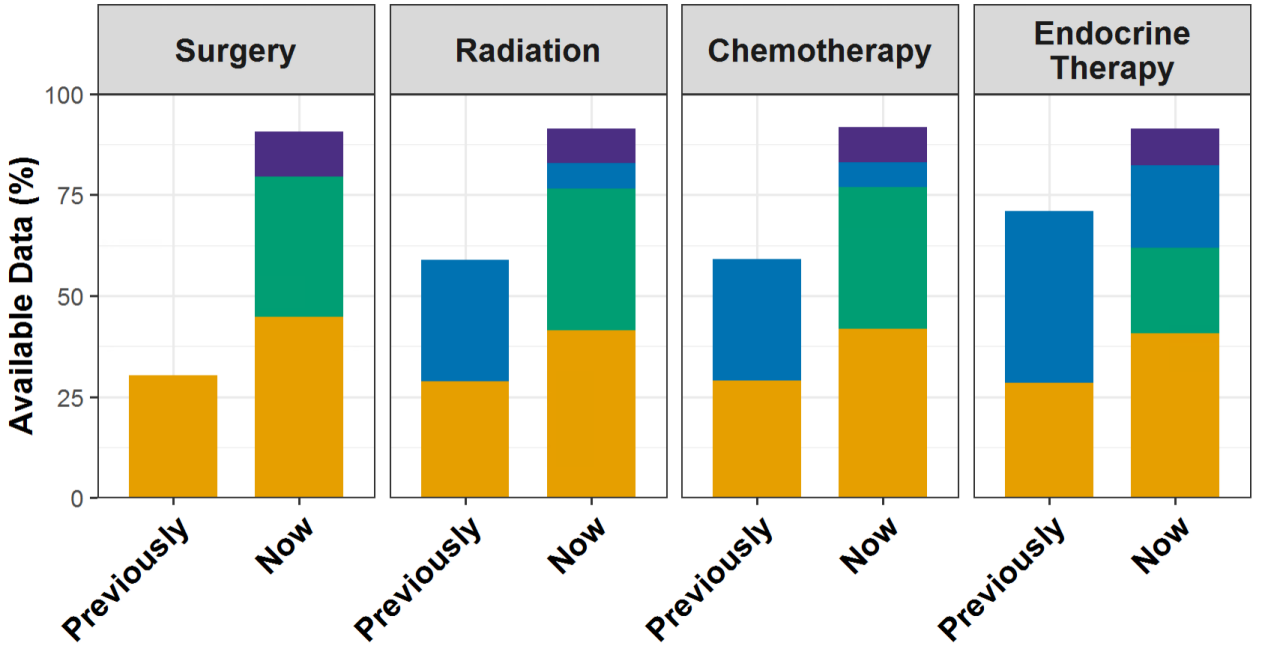
- Detailed **agents, dosing, timing** (ICD, CPT, NDC codes)
- Captures **oral therapies (Part D)**; Part D starting in 2006
- Limited to ≥65 and continuous enrollment

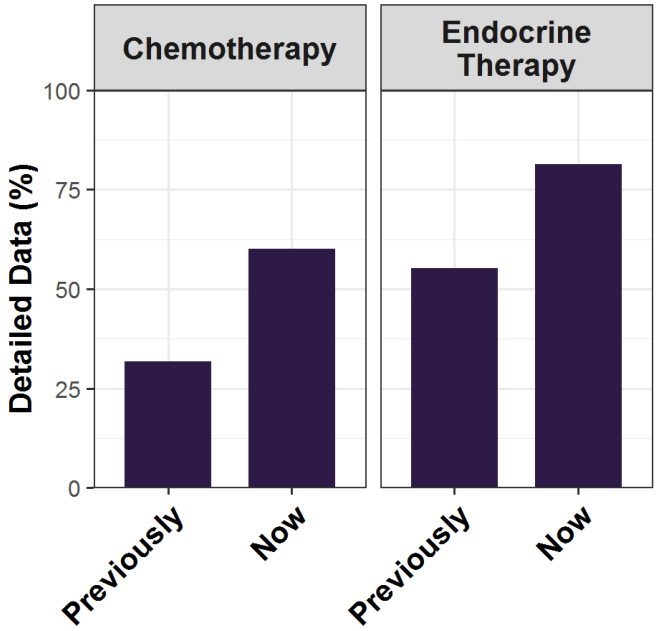
Self-Report (WHI + LILAC surveys)

- Supplements **treatment receipt (yes/no)**
- Adds detail for **hormonal therapies**

NCI Virtual Pooled Registry-Cancer Linkage System

- Nationwide registry linkage (**45 registries**)
- Captures **first-course treatment + timing**
- Less granular (e.g., chemo: single vs multi-agent)
- Fills gaps (pre-2000, non-Medicare, missing abstraction)





Invasive Breast Cancer

Available treatment info:

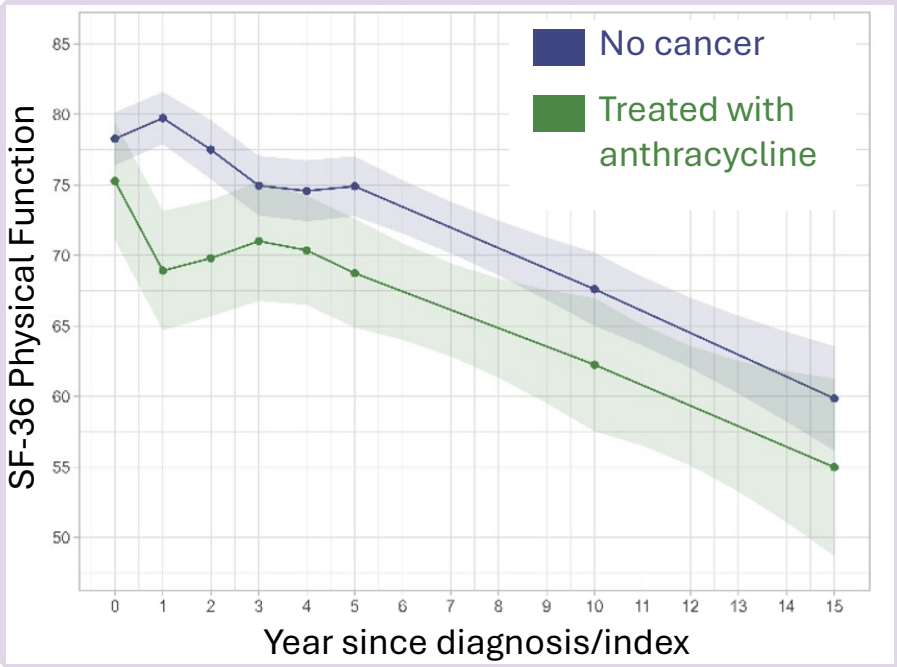
- ***Surgery***: 30% → 91%
- ***Radiation***: 59% → 91%
- ***Chemo***: 59% → 92%
- ***ET***: 71% → 91%

Detailed information:

- ***Chemo***: 32% → 60%
- ***ET***: 55% → 81%

Long-Term Trajectories of Accelerated Biological Aging and Functional Decline Associated with Breast Cancer and its Treatment

R01CA283839
MPIs: Feliciano & Binder



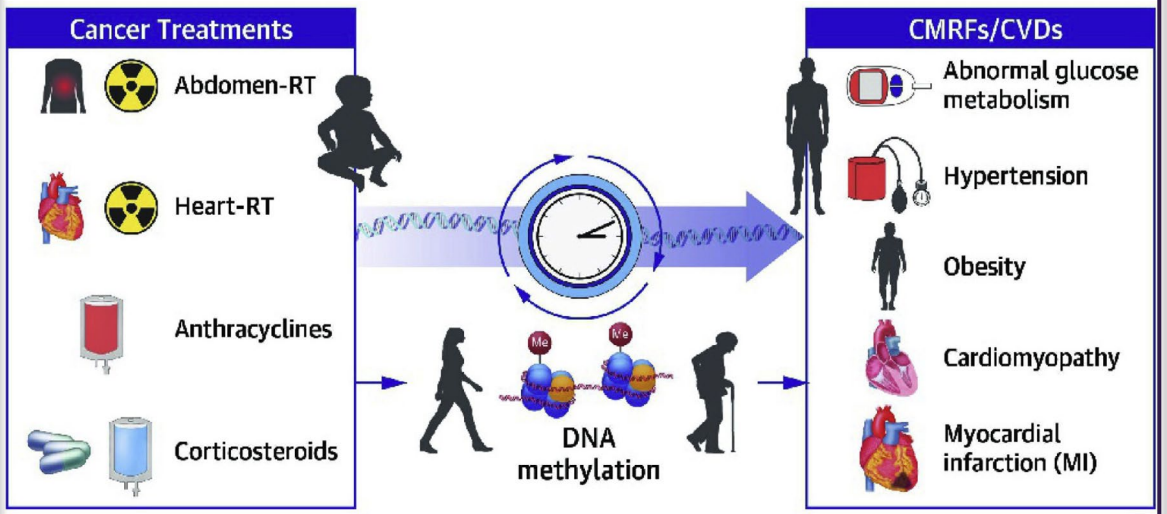
Chemotherapy recipients show sharp early decline, partial recovery, and persistent deficits vs. cancer-free comparators

Next steps: *Evaluate how treatment shapes trajectories of epigenetic aging*

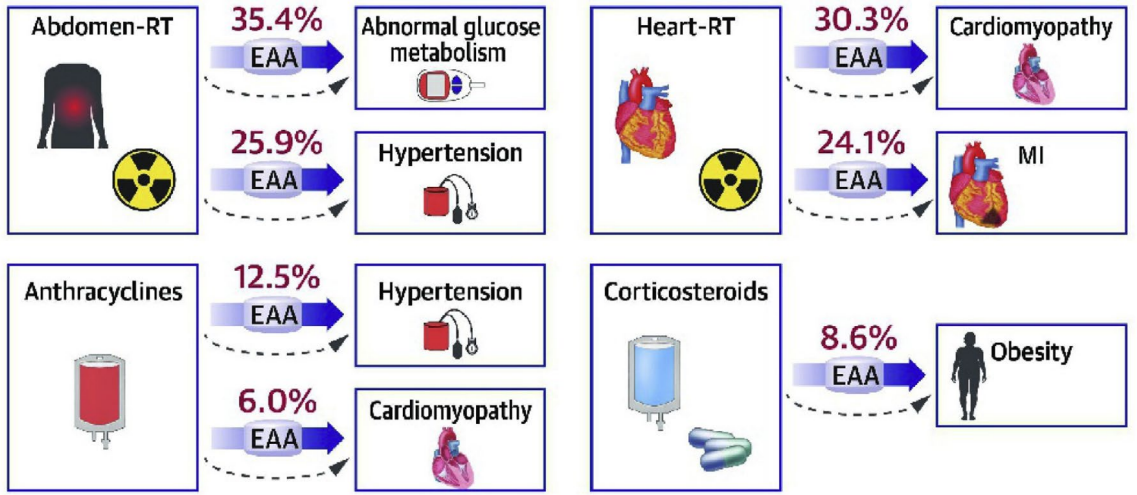
Opportunities: *Integrate treatment data with multiple domains of aging (e.g. disease, cognition, & quality of life)*

Epigenetic age acceleration partially mediates treatment-related cardiometabolic & CVD risk

Epigenetic age acceleration (EAA)



EAA as a mediator of treatment-related CMFRs/CVDs



Adapted from: Meng *et al* (2025) JACC CardioOncol

THANK YOU

WHI/LILAC Study Collaborators: Elizabeth M. Cespedes Feliciano, Sophie Fuller, Josh Nugent, Anlan Cao, Garnet Anderson, Electra Paskett, Bette Caan, Andrea LaCroix, Hailey Banack, Carolyn Presley, Jude Carroll, JoAnn Manson, Aladdin Shadyab, Sowmya Vasan, Roberta Ray

NIH NATIONAL CANCER INSTITUTE

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U01CA173642; MPIs: Anderson, Caan, Paskett

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Prolonged Grief and Mortality Risk Among Aging Adults: Evidence from the Women's Health Initiative

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WHI Investigator Meeting Ignite Session · May 7–8, 2026 · Bethesda, MD

HARVARD T.H. CHAN SCHOOL OF PUBLIC HEALTH

POPULATION WELLNESS LAB

STANLEY CENTER FOR PSYCHIATRIC RESEARCH AT BROAD INSTITUTE

The Problem

Bereavement & Mortality

↑ 87%

excess mortality risk in first 3 months after spousal loss (Moon et al., 2013)

15–17%

excess risk in subsequent months (Shor et al., 2012)

Yet results have been mixed — one study has shown that widowhood is protective for women with prior CVD (Stahl et al. (2016) Cardiovascular Health Study)

Prolonged Grief Disorder

~3.9–10%

PGD prevalence in older adults (increases with age)

Prolonged Grief Disorder (PGD)

- Persistent yearning, preoccupation with the deceased, and impairment in functioning
- Sleep disturbance, emotional dysregulation, dietary changes
- Comorbid with suicidal ideation, treatment-resistant depression, PTSD
- Now a diagnostic code: ICD-11 & DSM-5-TR

Is Prolonged Grief Disorder a key mechanism explaining excess mortality in bereaved older women?

Why WHI? A Unique Scientific Opportunity

Grief Symptoms Assessed

Validated PGD measures in Forms 151B (2019), with >43,000 participants — one of the only large longitudinal cohorts worldwide with grief-specific data.

Longitudinal Design

Bereavement events tracked from 1992 baseline through 2023+, enabling prospective assessment of PGD → mortality pathways with 3–7 year follow-up.

Women's Health Focus

Women live longer but carry greater multimorbidity burden relative to men. PGD effects may differ by layered social determinants that are yet to be characterized and identified.

Rich Covariate Data

Longitudinal data on sleep, diet, physical activity, depression, anxiety, social support, CVD, hypertension, diabetes, cancer — enabling precise confounder adjustment.

Aligns with ORWH Strategic Goal 1, Obj. 2: Life-course perspective on women's health, integrating biological, behavioral, and social determinants, and NIMH aging and mental health

Specific Aims

Aim 1 — All-Cause Mortality

Compare the magnitude of excess all-cause and cause-specific mortality among bereaved vs. non-bereaved women using Cox proportional hazards models with time-varying covariates.

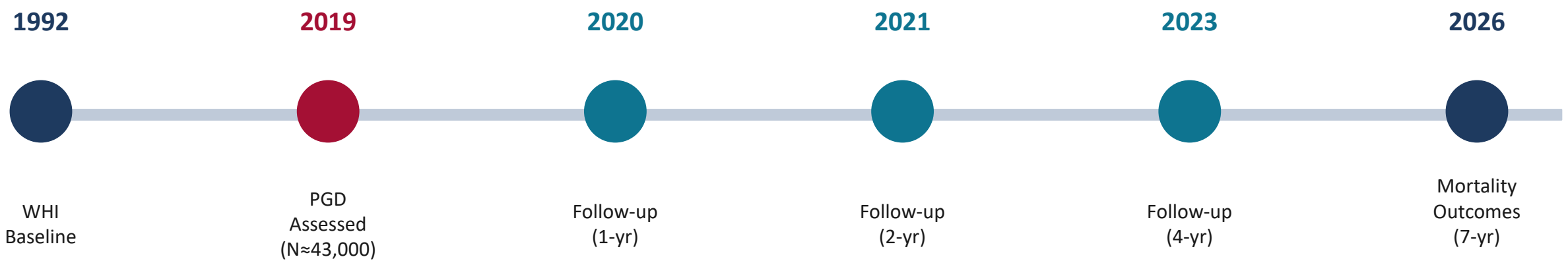
H1a: Bereaved women will exhibit excess mortality risk relative to non-bereaved women. **H1b:** Excess CVD mortality risk will be identified only among bereaved women with pre-existing CVD.

Aim 2 — The Role of PGD

Assess variation in excess mortality among bereaved women by post-bereavement psychopathology using Cox proportional hazards models, adjusting for pre-loss mental health, neurocognitive functioning, and sociodemographic factors.

H2: Excess all-cause mortality among bereaved women with PGD symptoms will be elevated relative to bereaved women without PGD symptoms.

Study Design & Sample



Inclusion & Analysis Plan

- Bereavement event (spouse/partner loss)
- Completion of validated PGD measures (Form 151B)
- ≥1 year follow-up post-baseline grief assessment
- Cox models; Kaplan-Meier survival curves
- Sensitivity: IPCW, competing risk models

Key Covariates

- Demographics: age, race/ethnicity, education, income
- Health behaviors: sleep, physical activity, alcohol, smoking
- Clinical: hypertension, diabetes, CVD, cancer history
- Psychosocial: depression, anxiety, social support, loneliness

Impact & Invitation to Collaborate

01 Clinical Guidance

Identify modifiable grief-related risk factors to guide clinical screening, referral, and treatment for older women after spousal loss.

02 Public Health Significance

PGD has not been well characterized on the population-level given historical absence from psychiatric diagnostic manuals. This work will build evidence on the population-level mortality burden attributable to untreated PGD and related complications among aging women.

03 NIH Alignment

Directly addresses ORWH Strategic Goal 1, Obj. 2 — life-course health of women. Also NIMH priorities on psychiatric conditions among aging adults.

04 Open Questions for Discussion

Use of LLS-II biorepository? Additional exposure windows? Novel mechanisms (neuroinflammation)? Collaborator interest in grief/aging?

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