Brigham and Women's Hospital
Founding Member, Mass General Brigham

Aging Biomarkers

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DISCLOSURES

I have no relevant financial relationships with ineligible companies.

OBJECTIVES

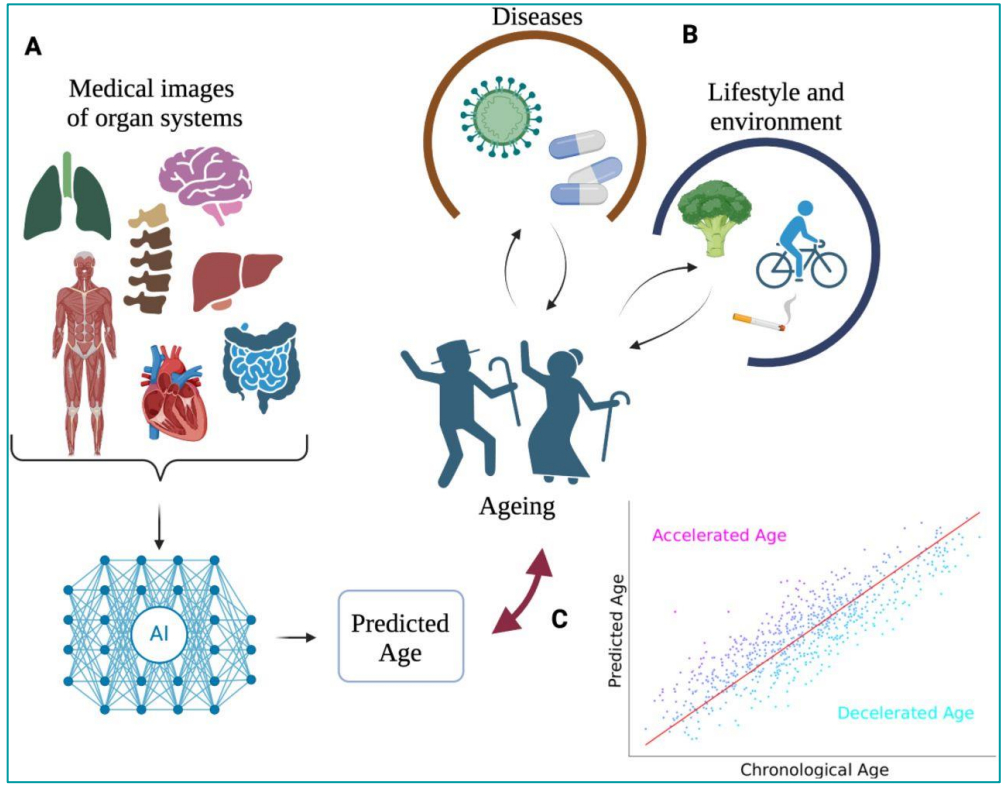
- To understand the various types of biomarkers, their limitations, and clinical potential.
- To learn about the fundamental hallmarks of aging that may predict the development of disease and disability and serve as potential targets for preventive and therapeutic interventions.
- To recognize the value and clinical relevance of several existing biomarkers that can easily be incorporated into clinical practice.

Biomarkers of aging are rapidly gaining attention

Scientists find 10 'markers' in blood that predict people's chances of reaching 100

Opinion By Karin Modig published October 10, 2023

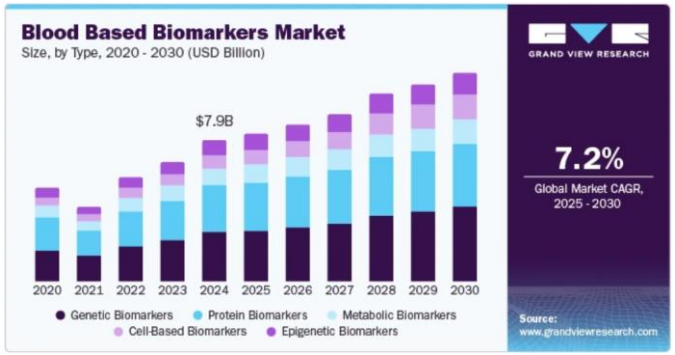
A recent study pinpoints measurable differences in the blood of people who survived to age 100 and those who died younger.



Longevity Blogs: For example:

Top 10 Longevity Biomarkers That Reveal How Well You're Ageing

November 6, 2025



Lots of Hype about Biomarkers for Cancer

$949, 2026 Super Bowl ad

Now there's a proactive tool to screen for cancer

The Galleri test can be taken annually as a simple blood test and screens for a "fingerprint" of many of the deadliest cancers before they become symptomatic, including those with no recommended screening tests today.[1,2,3]

About the Galleri test

What does Galleri screen for?

The Galleri test does not detect a signal for all cancers and not all cancers can be detected in the blood. False positive and false negative results do occur. The Galleri test should be used in addition to healthcare provider recommended screening tests.

Uses of Biomarkers

Predictive

Assess risk of disease or mortality (e.g., BRCA, LDL Cholesterol, ApoE4, BP, polygenic risk scores)

Prognostic

Identify prognosis and monitor functional decline (gait speed, grip strength, 6 min. walk, frailty)

Disease detection

(e.g., pTau217, Amyloid PET scans, CA125, CEA, PSA)

Response

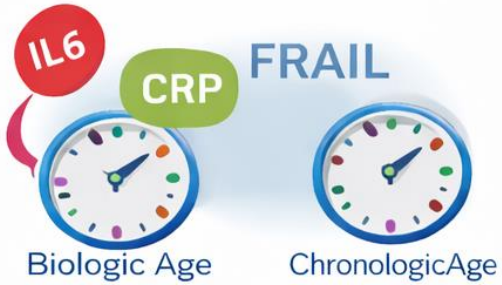
Monitor treatment outcomes and guide treatment intensity (CRP, HbA1C, Bone Density, FEV1, BNP, TSH)

Mechanistic and Discovery

Omics and biological pathways suggest targets for treatment. Largely investigational.

Surrogate

proxy measures of intervention effects (inflammatory markers - IL6, CRP, FRAIL, epigenetic clocks: Biologic vs. chronologic age)



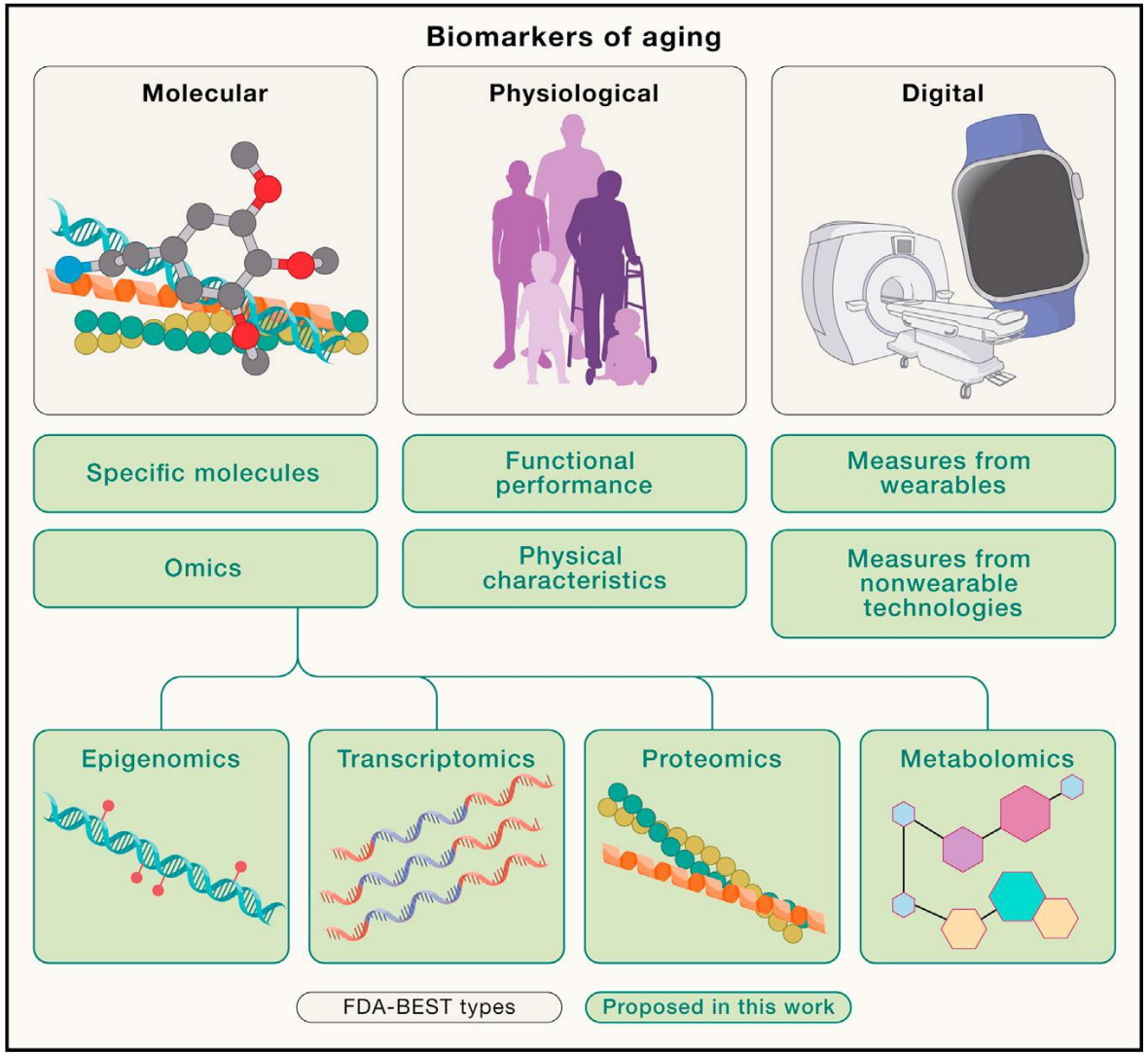
Images created with the help of Chat GPT.

Common Clinical Scenario

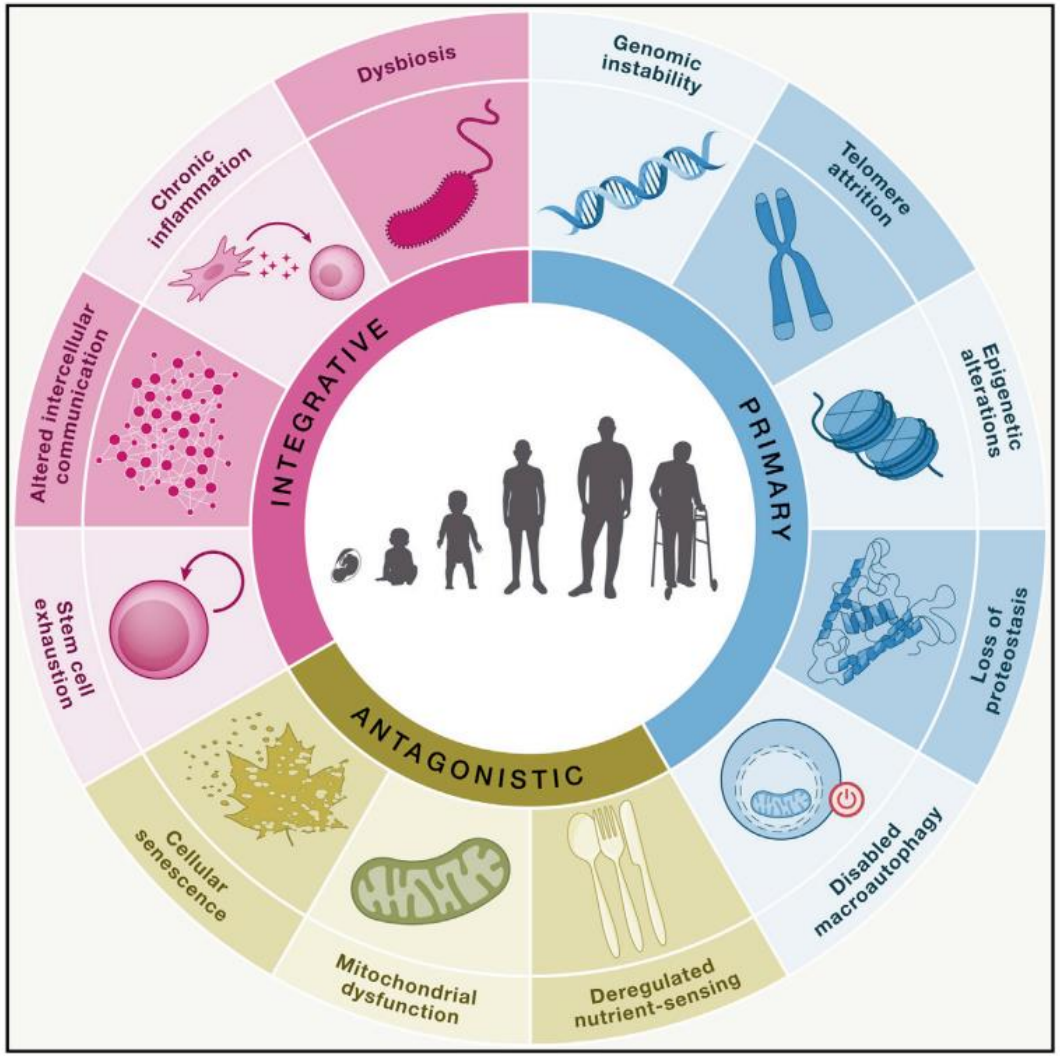
A 60 year old sedentary man wants to know his biological age to determine his life expectancy and what he can do to improve it. Would this be helpful?

Common types of biomarkers of aging

Moqri et al, Cell, 2023. doi.org/10.1016/j.cell.2023.08.003



Hallmarks of Aging – Targets for Translational Geroscience



López-Otín, Cell, 2023

Marcus Institute for Aging Research
Hebrew SeniorLife
HARVARD MEDICAL SCHOOL AFFILIATE

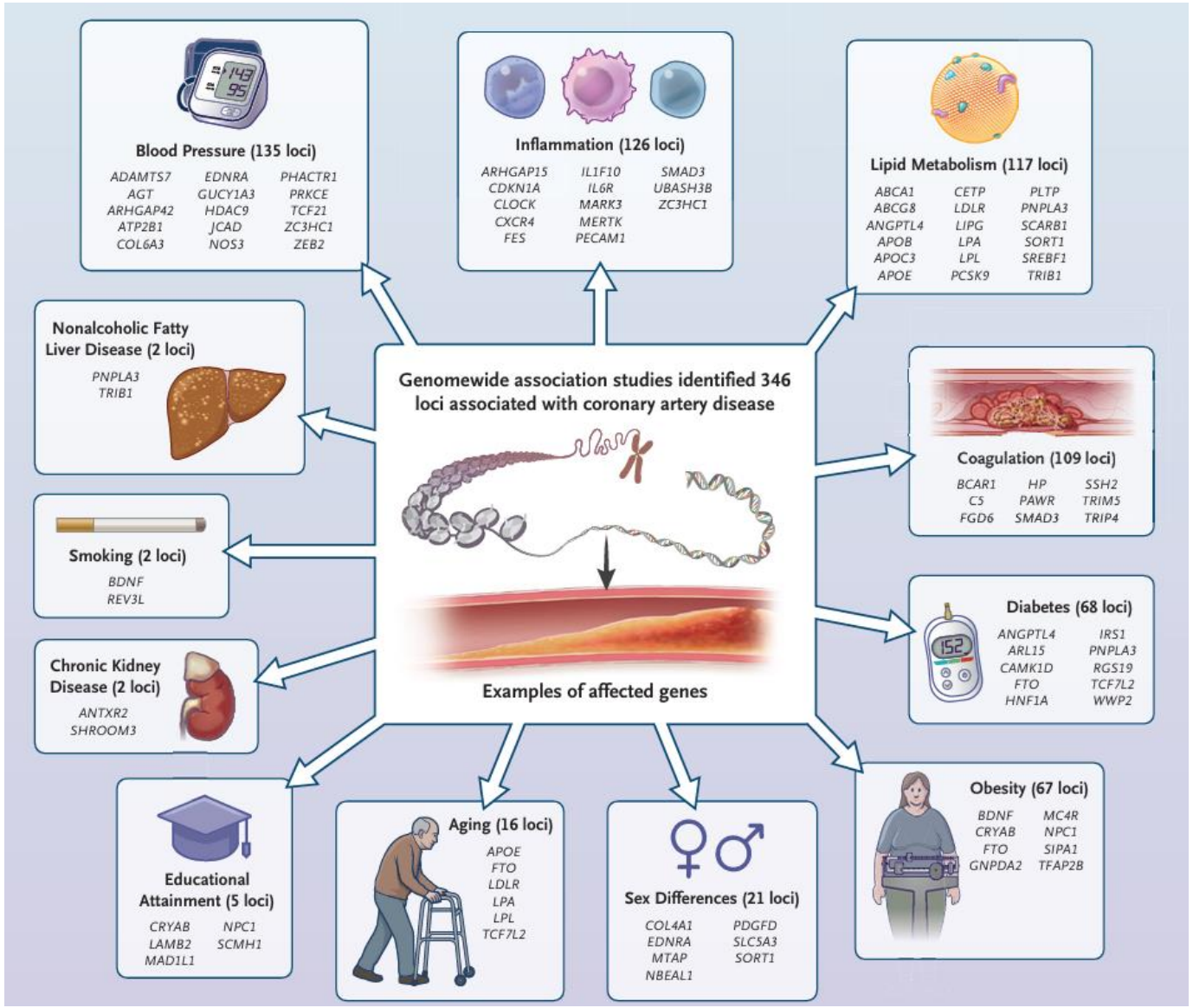
DNA Methylation Biomarkers and Biological Clocks.

Are they ready for clinical use?

Biomarker Criteria	Horvath epigenetic age	Hannum epigenetic age	GrimAge	PhenoAge	DunedinPoAm
DNA Methylation Biomarker Calibrated to Detect:	Chronologic Age	Chronologic Age	Biomarkers, Smoking, Death	Phenotypic Age	Pace of Aging (change)
Feasible for use in a clinical trial in older adults?	✓	✓	✓	✓	✓
Robustly associated with chronological age across independent cohorts?	✓	✓	✓	✓	✓
Predict age-related change in function, chronic disease, or death?	✓	✓	✓	✓	✓
Responsive to interventions that beneficially affect the biology of aging?	--	--	--	--	--

Polygenic Risk Scores (PRS)

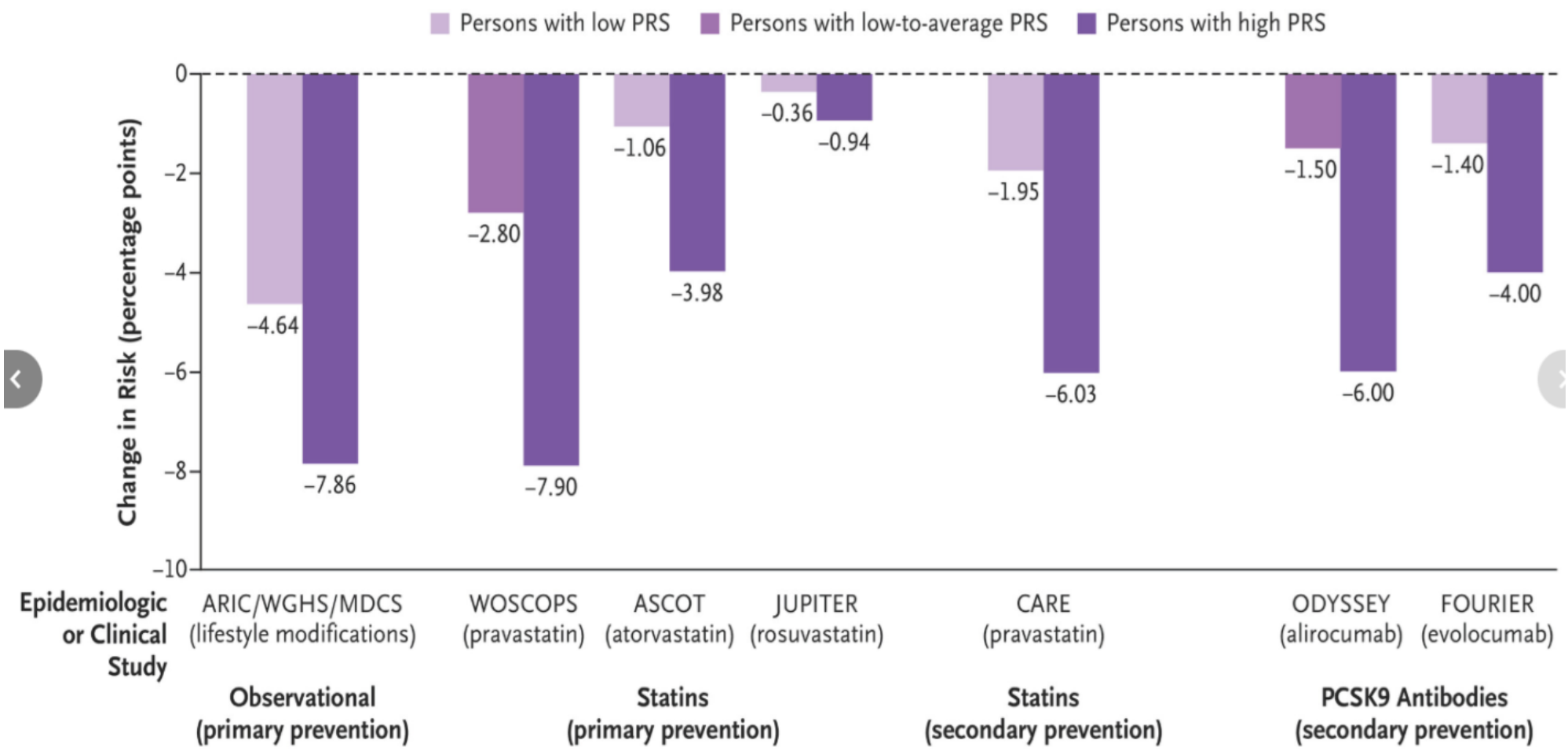
Genetic Loci associated with coronary artery disease



Schunkert et al,, NEJM, 2026

PRS integrate the cumulative effects of common genetic variants into a single measure.

Polygenic Risk Scores (PRS):
Risk Reduction through Lifestyle Modifications or Lipid-Lowering Treatment According to the PRS



Schunkert et al, NEJM, 2026

Polygenic Risk Scores

- Polygenic risk scores can provide information independent of conventional clinical risk factors.
- Although genetic risk alleles are fixed at conception, their expression and clinical consequences are modifiable through lifestyle interventions and environmental exposures.
- For example, lipid-lowering therapy can attenuate risk among persons with high polygenic risk scores.
- Their incremental value above conventional risk factors, applicability to different populations, cost-effectiveness, and implementation are unclear and in need of further study.

Problems and pitfalls of biomarkers

- Lack of clinical validation
- Dynamics, Variability – disease, drug, environmental, age interactions
- Population heterogeneity (influenced by age, sex, frailty, race, culture)
- Renal and hepatic clearance
- Many good ones already exist (BP, LDL, BMI, etc. for CVD)
- Assay time and expense
- Poor sensitivity, specificity, and predictive value. Many false positives and negatives

Common Clinical Scenario

A 60 year old sedentary man wants to know his biological age to determine his life expectancy and what he can do to improve it. Would this be helpful?

- Traditional risk factors may be more predictive of adverse outcomes than biological clocks. (BP, LDL, BMI, smoking, sleep, alcohol, social isolation)
- We already know that lifestyle interventions will help improve many aspects of health.
- It may be motivational to know that his biological age is above his chronological age (accelerated aging), but it may not be sensitive to change with lifestyle interventions.
- A biological age below his chronological age may be misleading, falsely suggesting that lifestyle interventions are not necessary.

What biomarkers can clinicians use today?

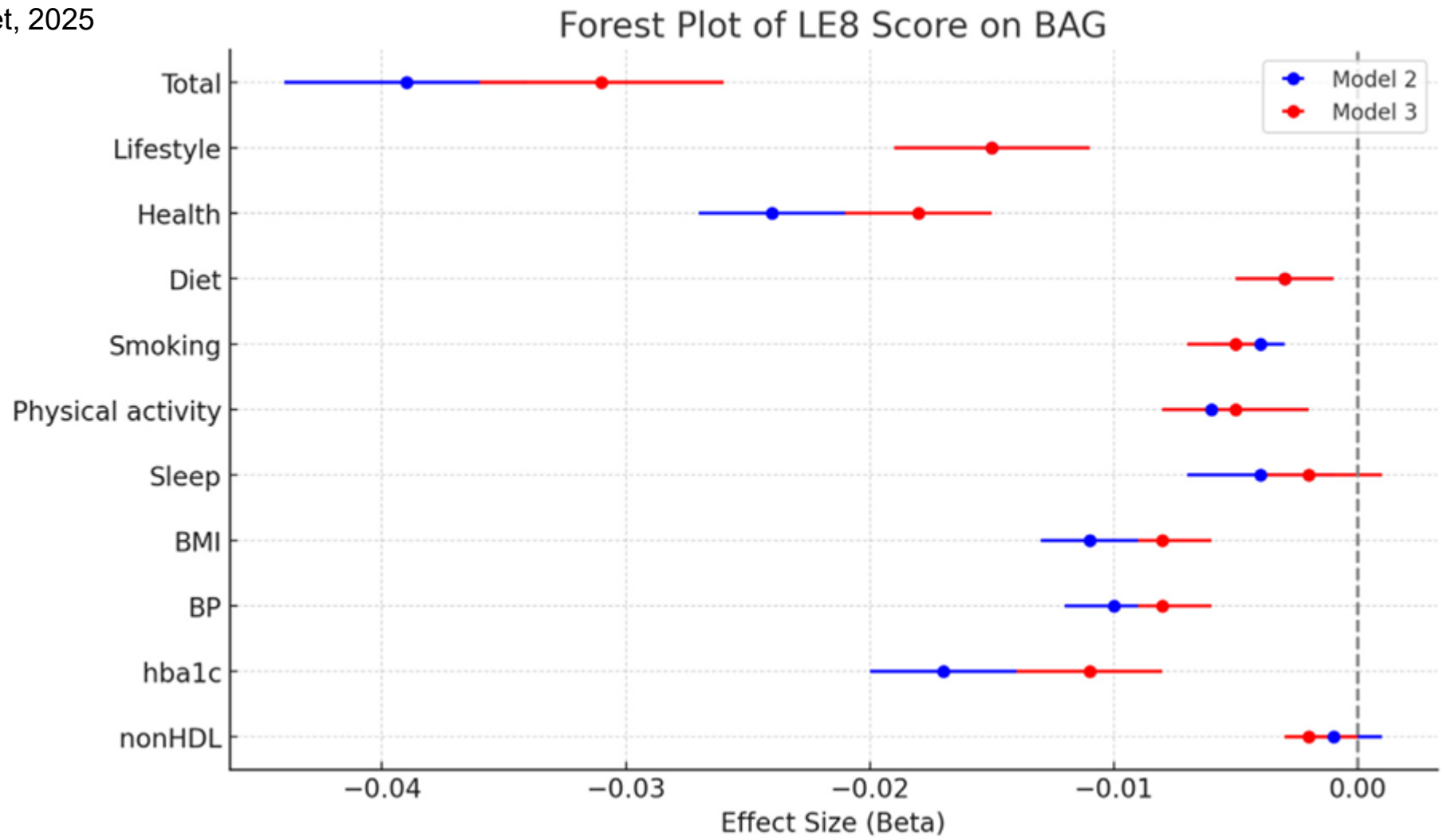
- Gait speed
- “Life’s Essential 8”
- Frailty (https://efrailty.hsl.harvard.edu/)
- Functional and cognitive assessments (ADLs, IADLs, “Timed Up and Go”, Mini-Cog, integrated into Annual Wellness Visit)
- Wearable monitors (Ambulatory BP, Glucose monitors)

Life’s Essential 8

1. Diet: Whole foods, fruits, vegetables, lean protein, nuts, and olive or canola oils.
2. Activity: Aim for 150 minutes of moderate or 75 minutes of vigorous physical activity weekly.
3. Smoking.
4. Sleep: 7–9 hours nightly for adults; more for children.
5.Body Weight: Maintain a healthy Body Mass Index (BMI).
6.Cholesterol: Manage non-HDL cholesterol levels.
7.Blood Sugar
8.Blood Pressure

Effect of Lifestyle Interventions on Brain Aging Gap (BAG)

Feng, Lancet, 2025



14 Modifiable Risk Factors for Dementia
Lancet Commission, 2024

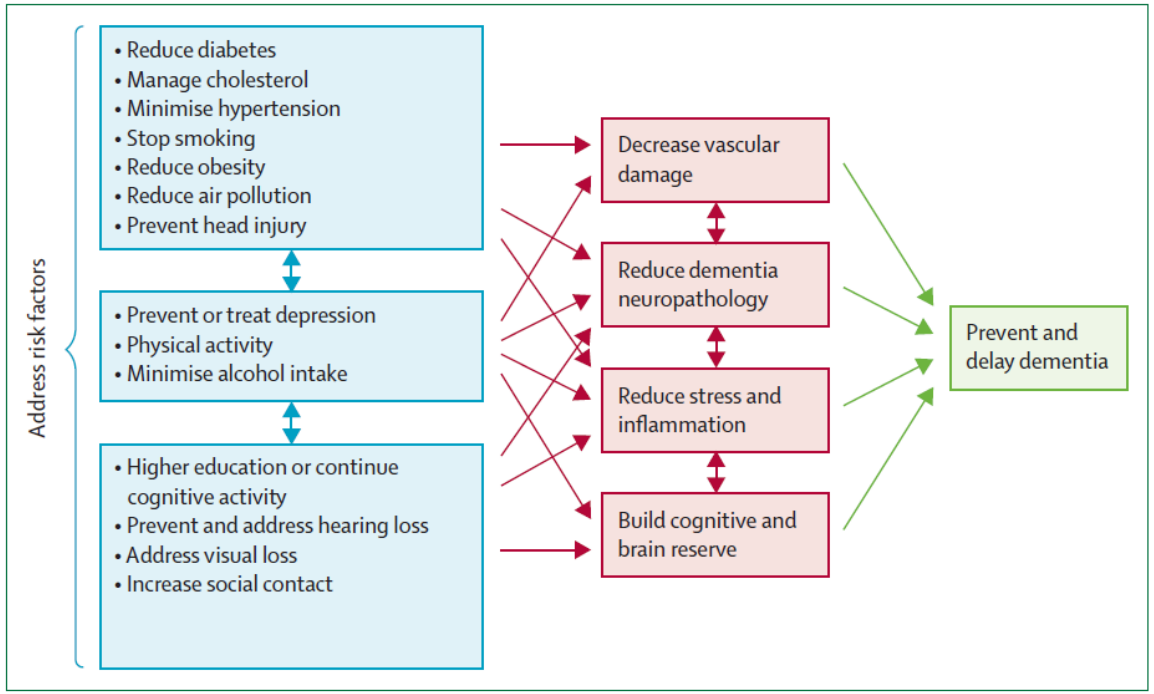


Figure 2: Possible brain mechanisms for enhancing or maintaining cognitive reserve and risk reduction of potentially modifiable risk factors in dementia

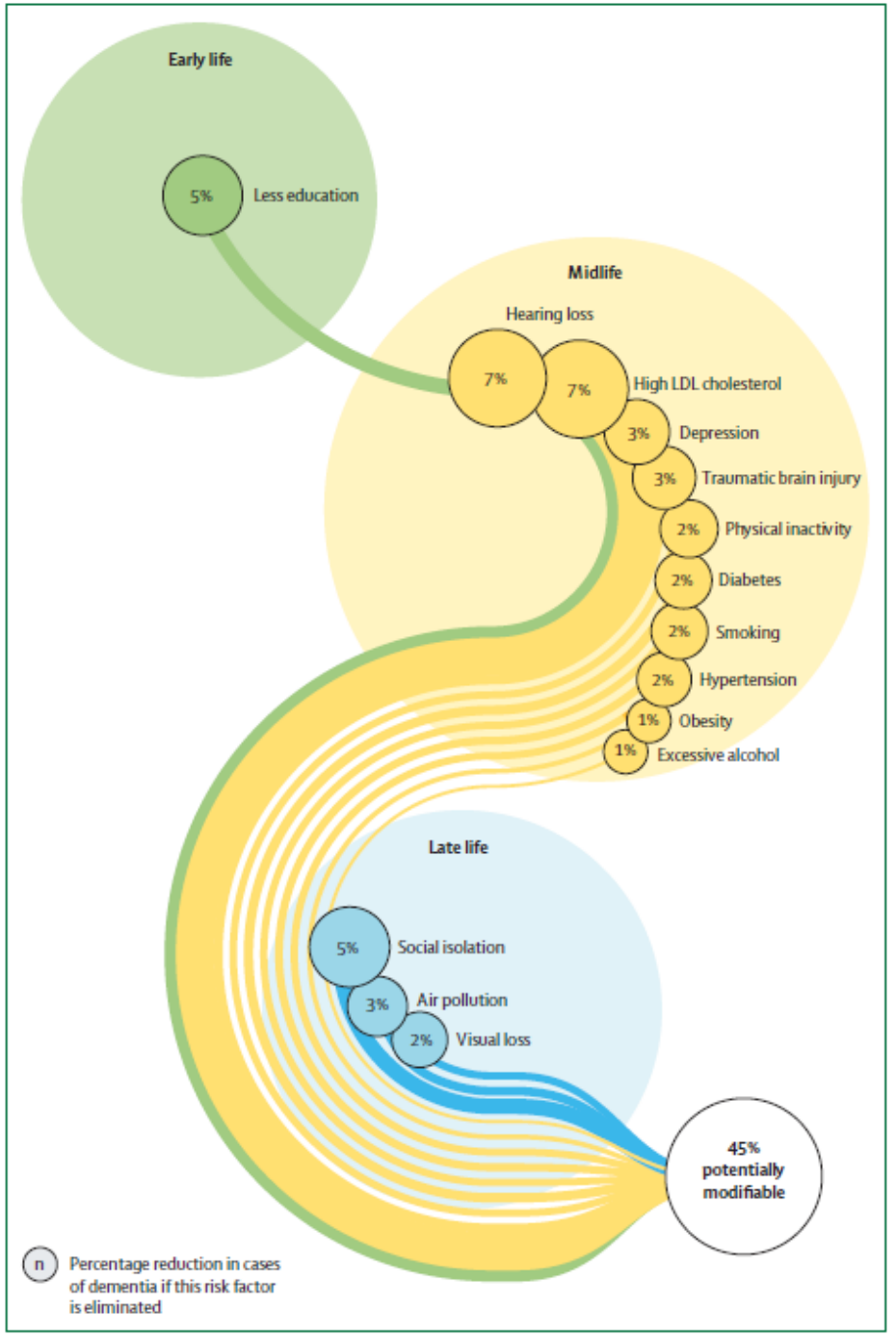
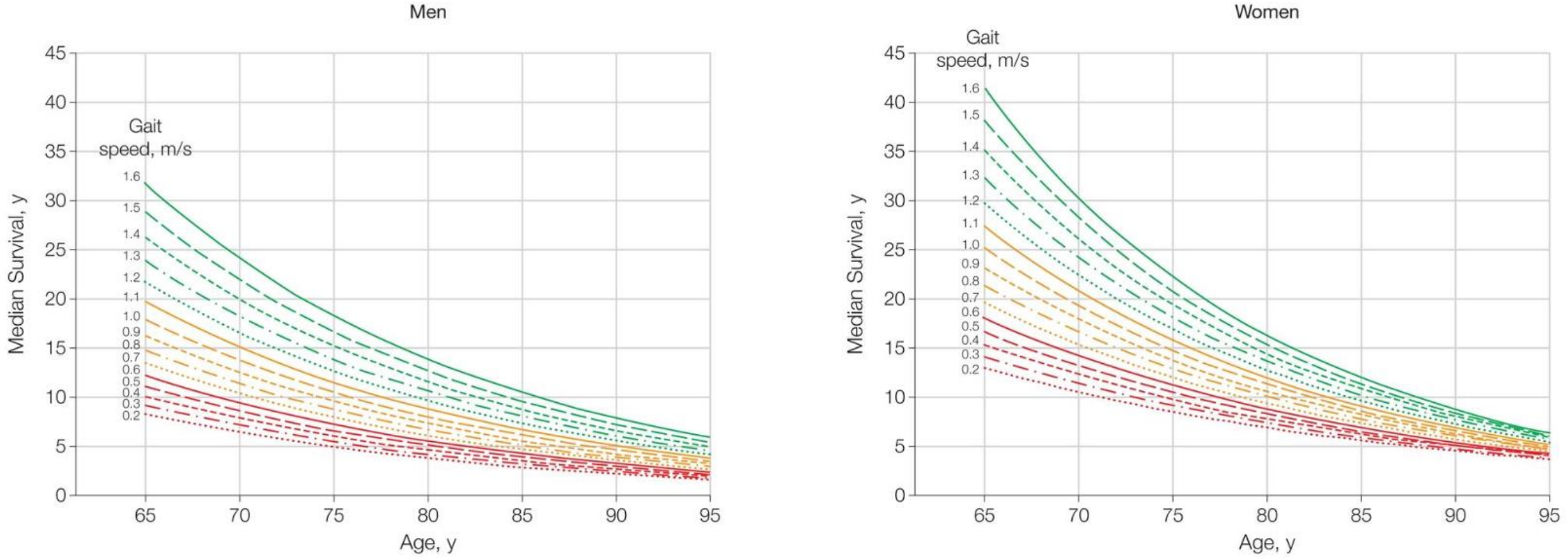


Figure 9: Population attributable fraction of potentially modifiable risk factors for dementia

Livingston et al, ***Lancet* 2024; 404: 572–628**
https://doi.org/10.1016/

Gait Speed and Survival in Older Adults

Studenski et al, JAMA, 2011, PMC3080184



Frailty: A Summary Measure of Multiple Age-Related Processes That Reduce Physiologic Reserve

Subcellular/cellular aging → **Altered physiological systems** → **Clinical manifestation**

CELLULAR SENESCENCE

MITOCHONDRIAL DYSFUNCTION

DEREGULATED NUTRIENT SENSING

↑ mTOR

↓ SIRTUIN/AMPK

INFLAMMATION

SARCOPENIA

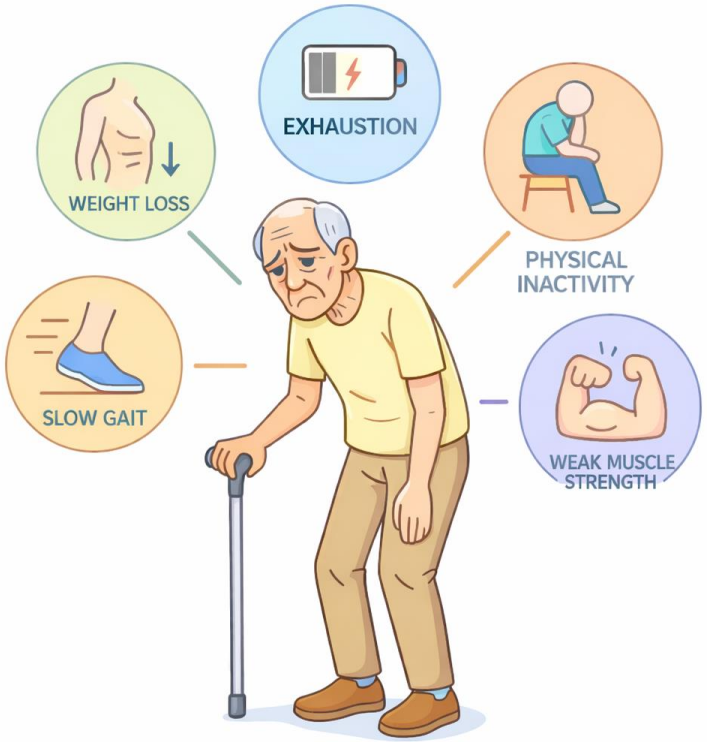
↑ CORTISOL

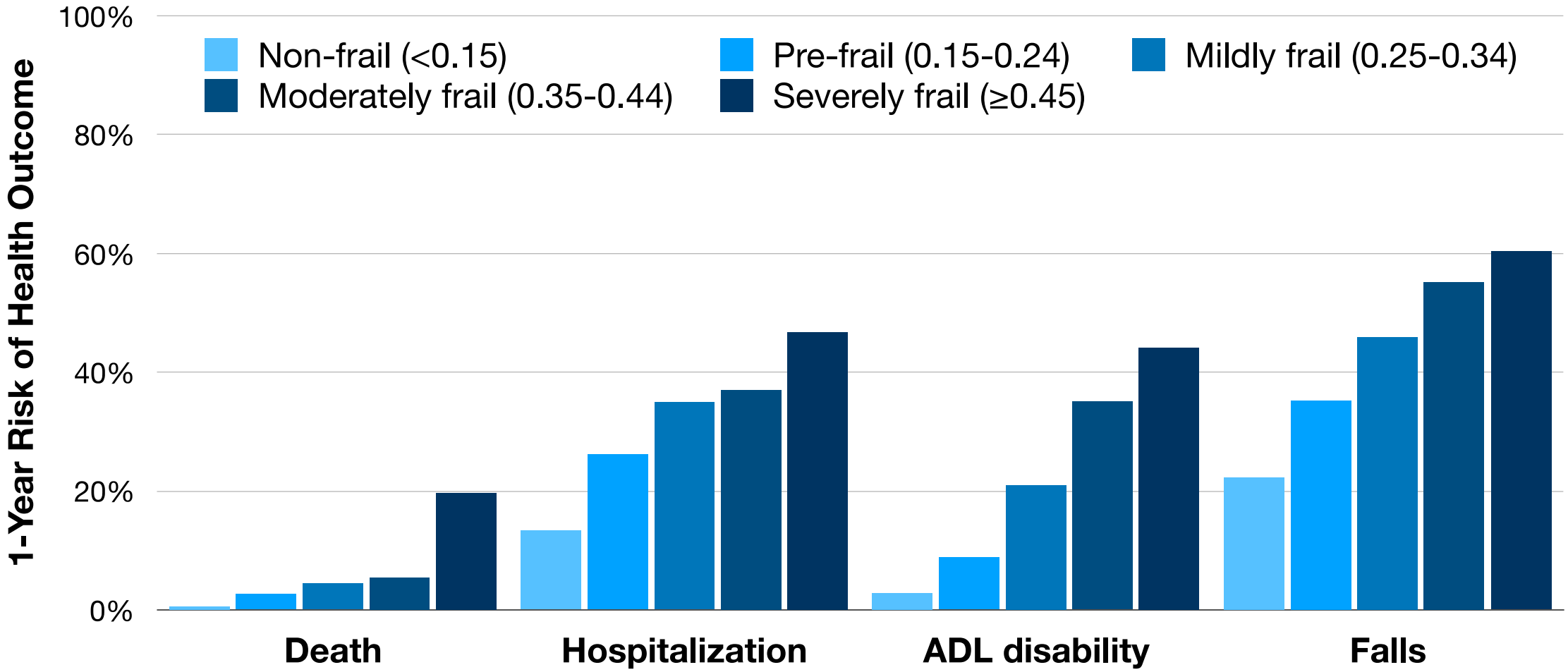
↓ GROWTH HORMONE

AUTONOMIC DYSFUNCTION

↓ ANTIBODY RESPONSE

FRAILTY



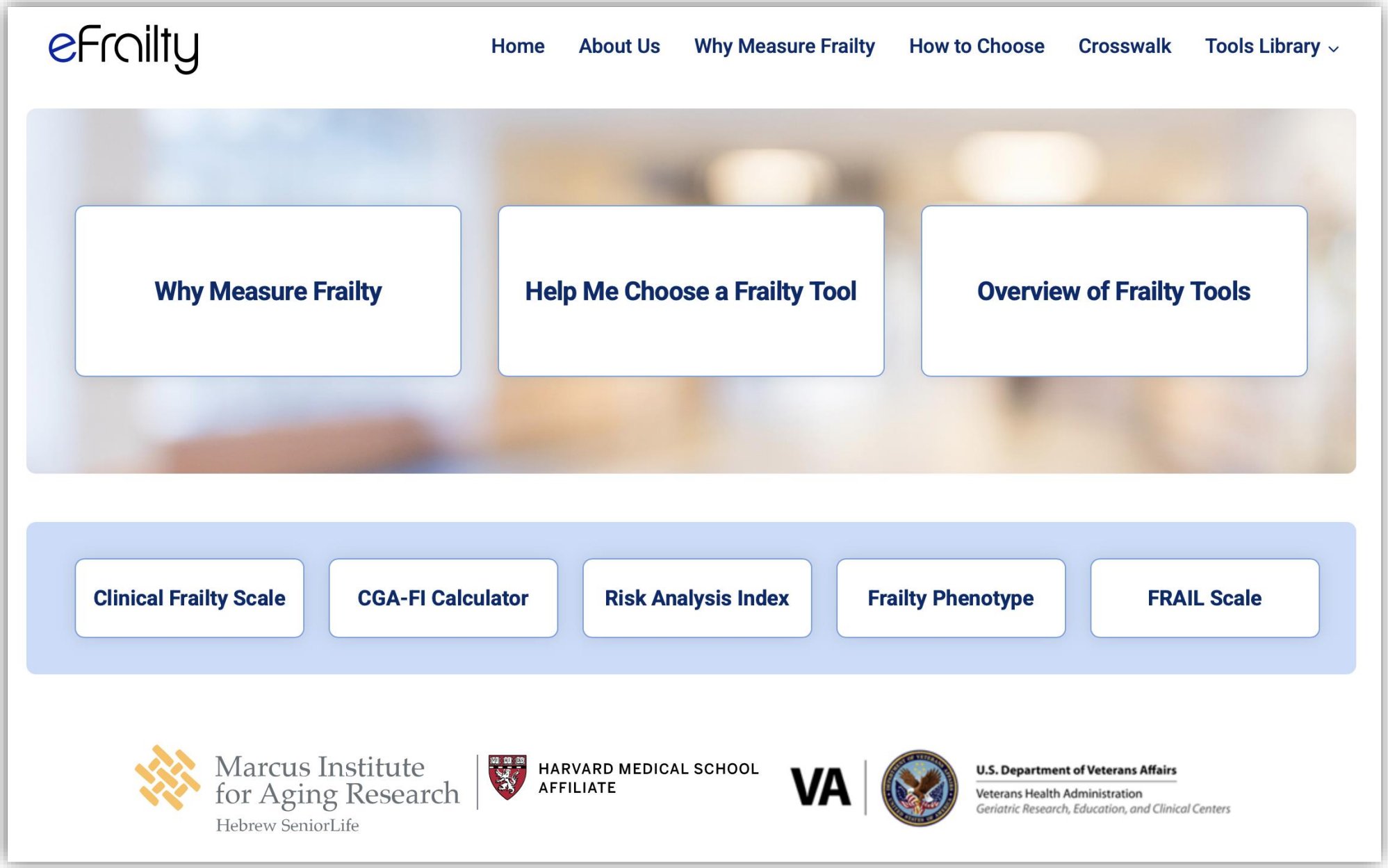


Shi et al. J Gen Intern Med. 2020; 35: 1516-1522

Frailty at early older adulthood predicts broad health risks over the next decade

Death	X 4.4	Cancer	X 1.1
Heart failure	X 2.9	Dementia	X 3.6
Coronary disease	X 2.0	Fall	X 2.8
Stroke	X 2.2	Fracture	X 1.5
Diabetes	X 2.3	Disability	X 11.0

Jang et al. JAMA Netw Open. 2023 03 01; 6(3):e2248995



efrailty.org

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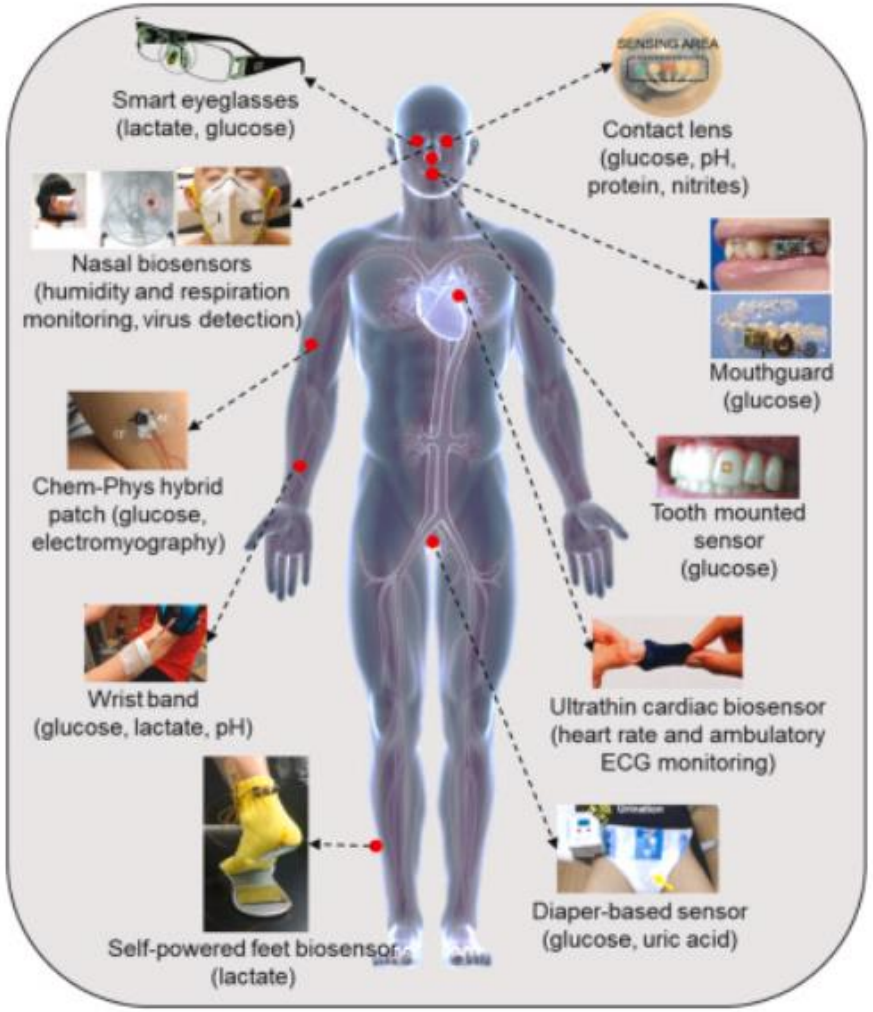
The Future of Biomarkers in Clinical Practice

- Digital phenotyping. : “The clinic in your home.”
- Audio biomarkers: Early detection of disease from voice or linguistics.
- Body tracking and gait analysis for sarcopenia, falls risk, osteoporosis.
- “Age-meter” smartphone for measurement of biological age.
- Facial biomarker of aging and disease.
- Multimodal data collection Kiosk.



MOC REFLECTIVE STATEMENT – TAKE-HOME NOTES

- Personal and commercial interests in biomarkers are rapidly growing to help detect preclinical disease, predict future health outcomes, and guide therapeutic interventions.
- While biomarkers based on fundamental mechanisms of aging, including DNA methylation clocks and polygenetic risk scores, are promising for risk assessment, their validation in different clinical populations and incremental value over existing tools is lacking.
- Measures of lifestyle, physical and cognitive function, gait speed, and frailty are easily accessible, practical, and proven useful in identifying risk and prognosis.

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