



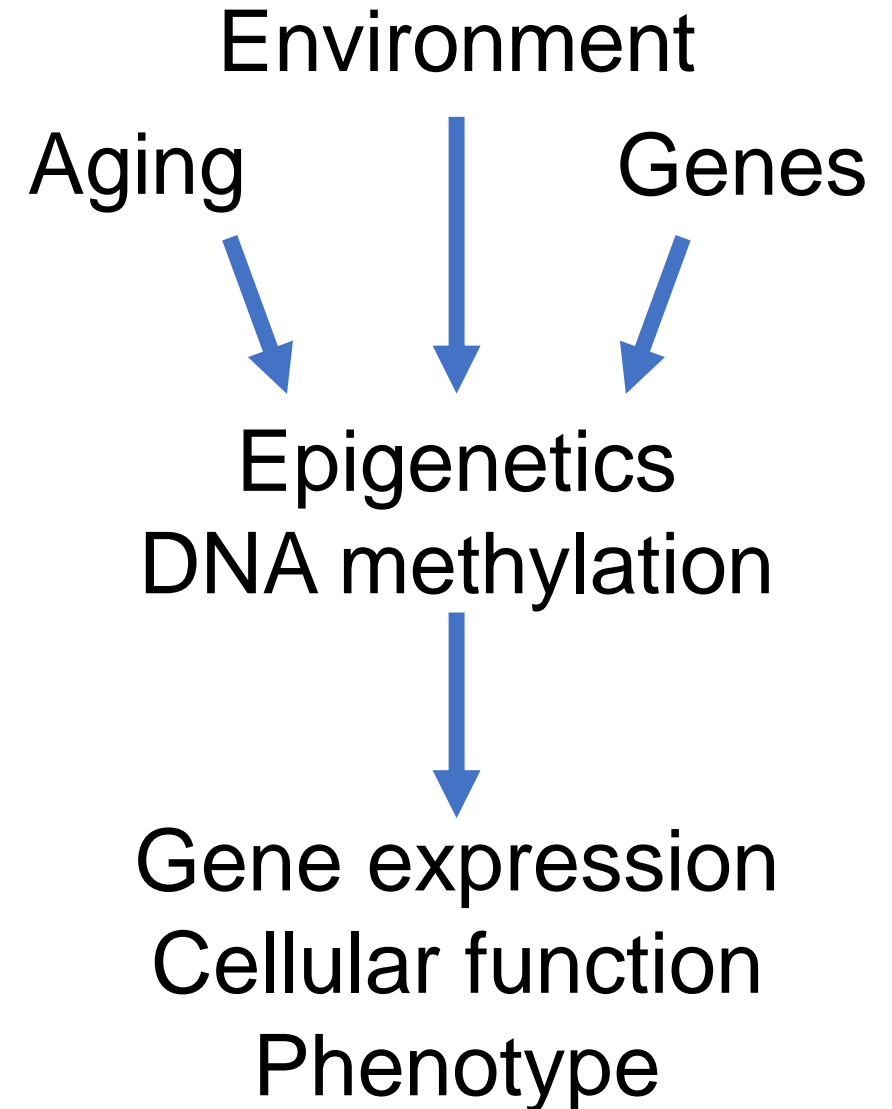
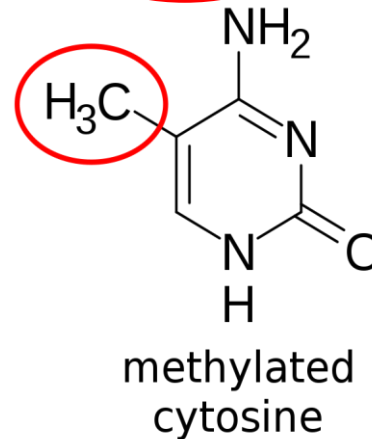
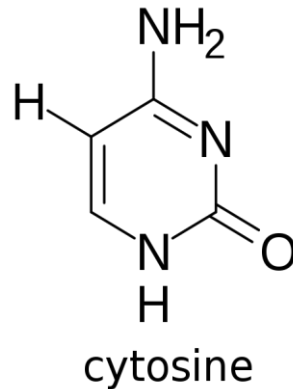
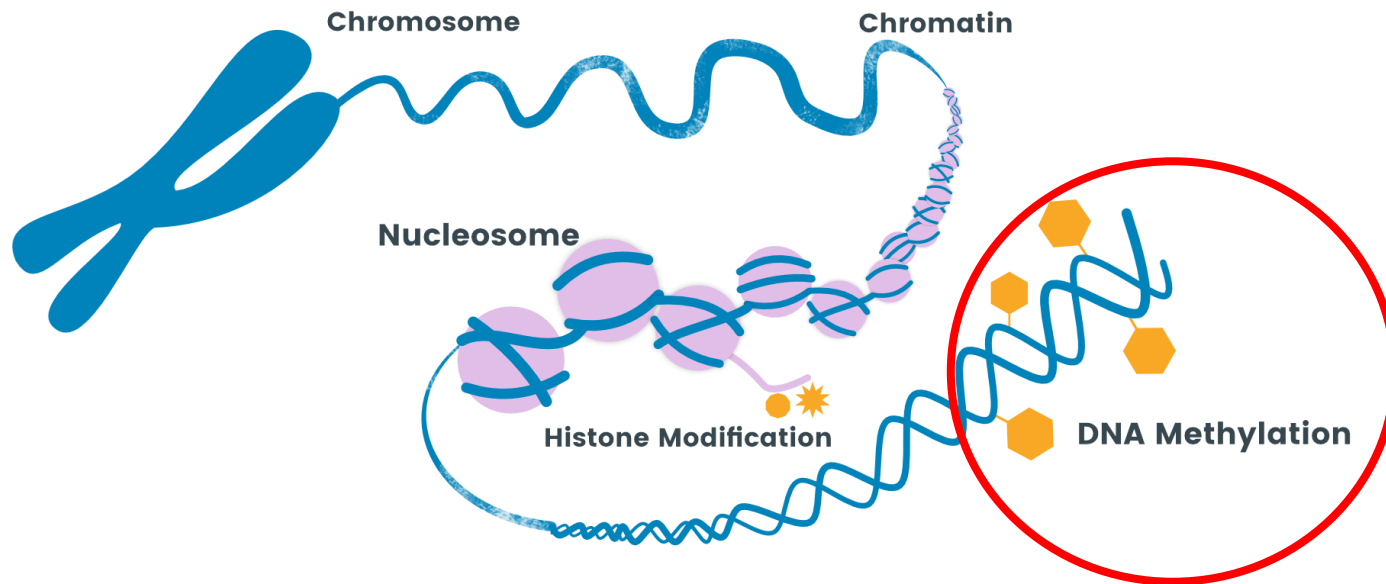
Methylomic Changes: Can we trust what we measure?

Albert Higgins-Chen, MD, PhD
Department of Psychiatry
Yale University

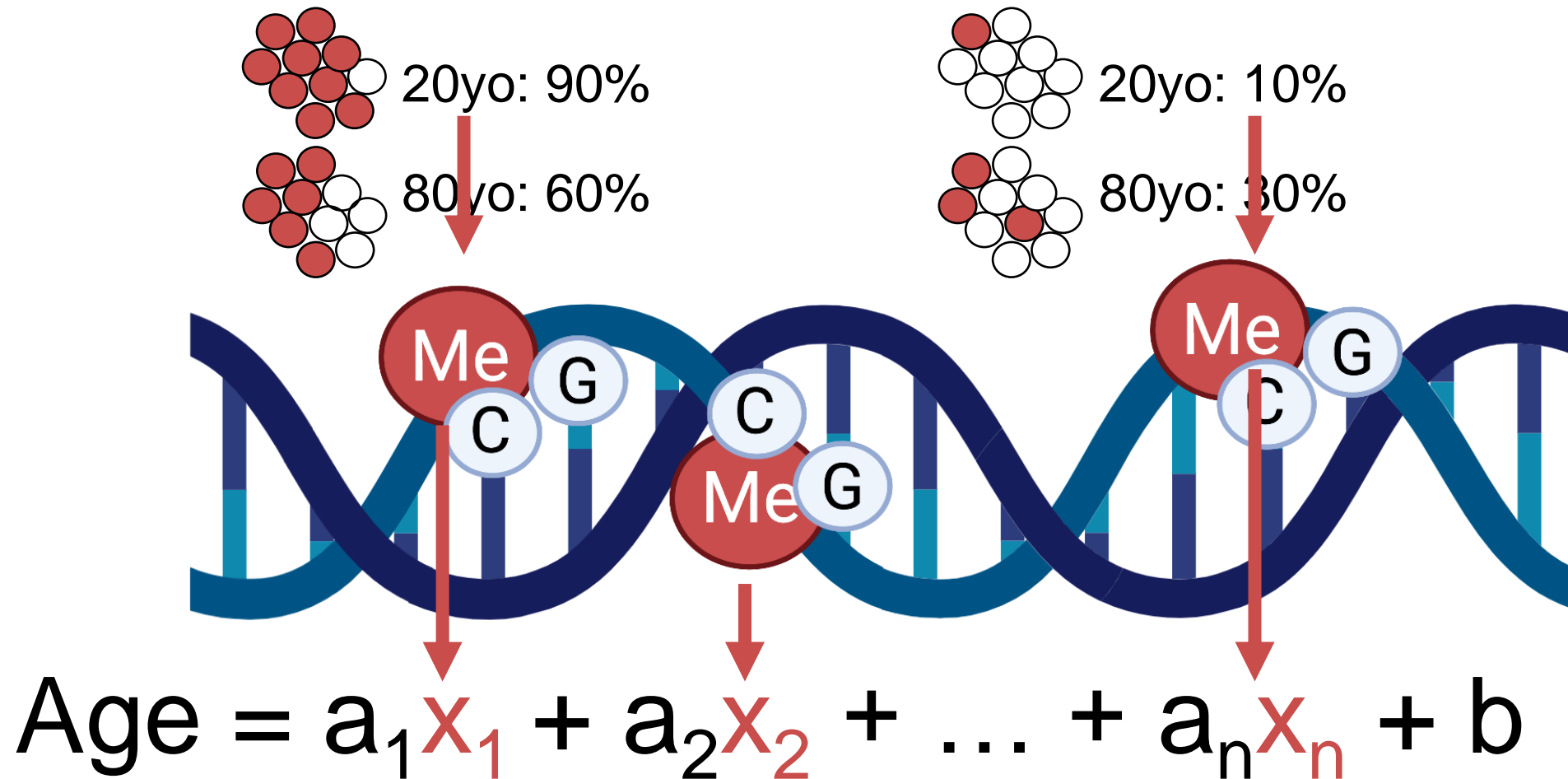
Disclosures

- The epigenetic clock methodology described in this talk was developed by Albert Higgins-Chen and Morgan Levine, and has been used to build epigenetic aging metrics licensed by Elysium Health, Inc.
- I received consulting fees from FOXO Technologies, Inc. from 2019-2021
- I am currently engaged in research collaborations with TruDiagnostic, Inc. examining epigenetic clocks

Epigenetics and DNA methylation



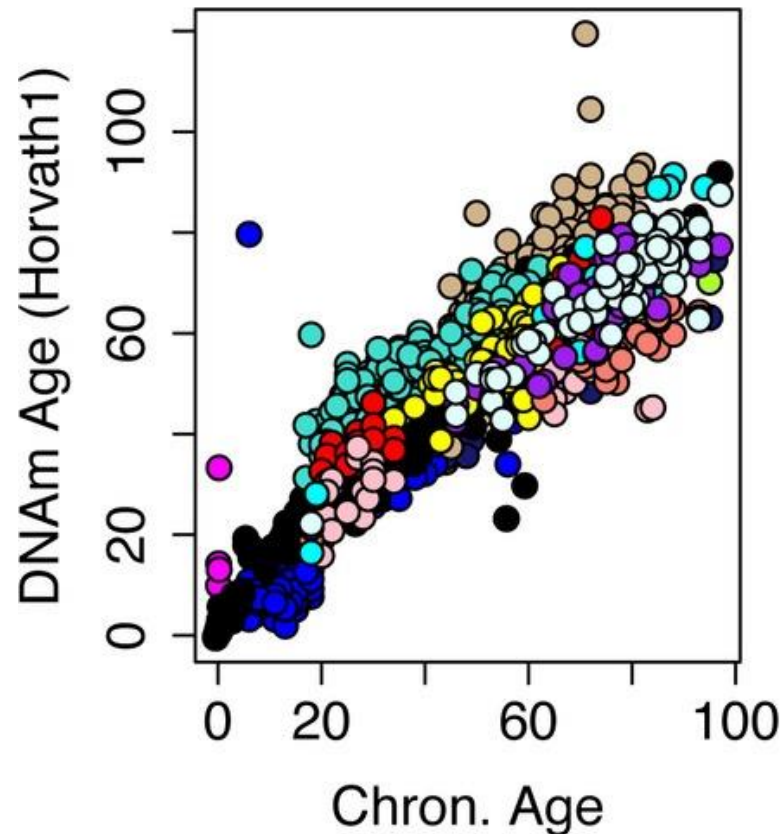
DNA methylation changes with age



Machine learning algorithms sift through ~850,000 methylation sites in thousands of samples and select a few hundred methylation sites as a robust biomarker of age

Epigenetic clocks predict age with very high accuracy in independent validation data

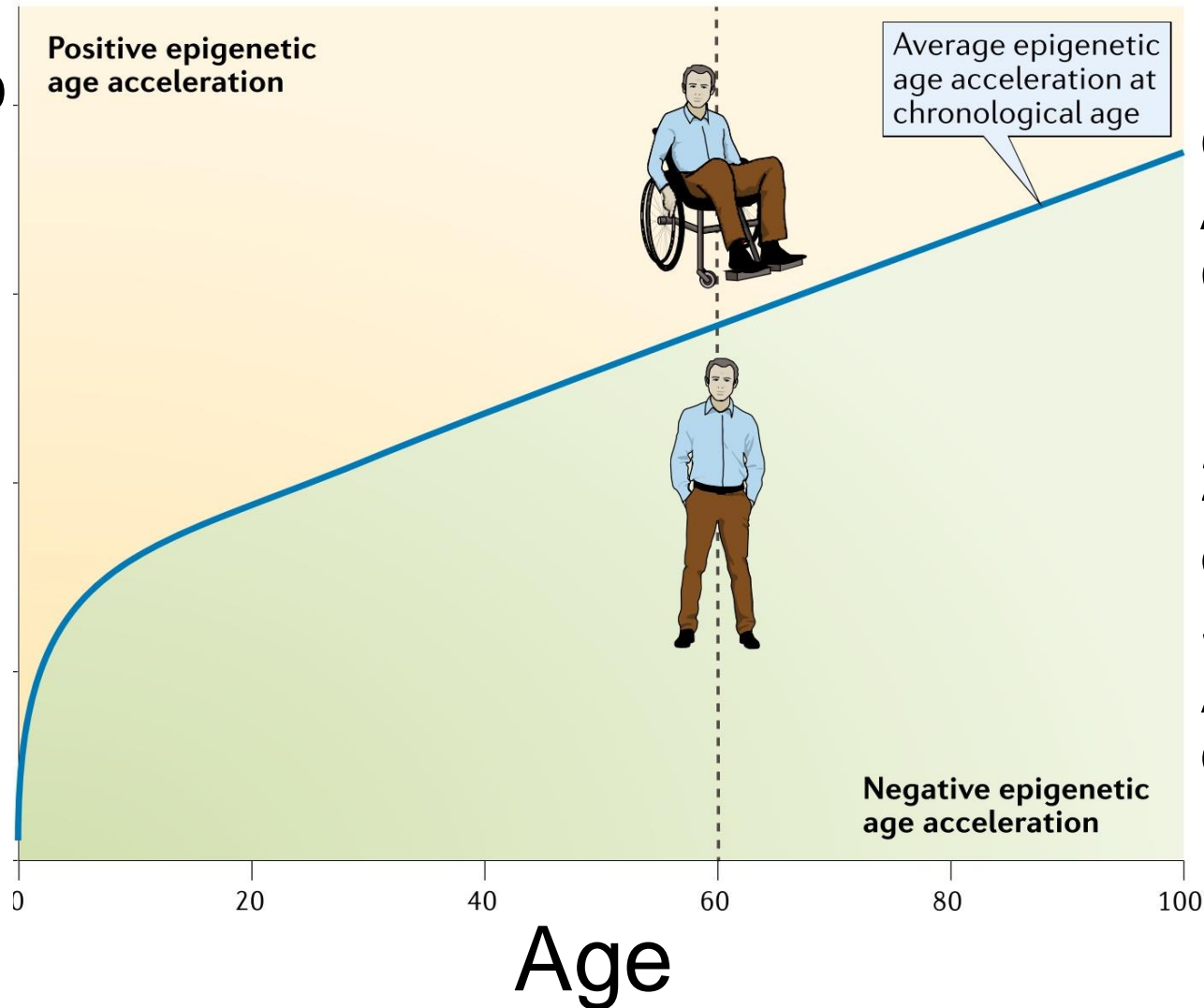
Horvath
Pan-tissue clock
cor = 0.94



	Breast
	Buccal
	Cerebellum
	Colon
	Cord Blood
	Dermis
	DLPFC
	Epidermis
	Fibroblast
	Frontal Cortex
	Hippocampus
	Monocyte
	Glia Occipital Coretx
	Neuron Occipital Cortex
	Striatum (Putamen)
	Temporal Cortex

Epigenetic clocks predict aging outcomes

DNAm Predicted Age



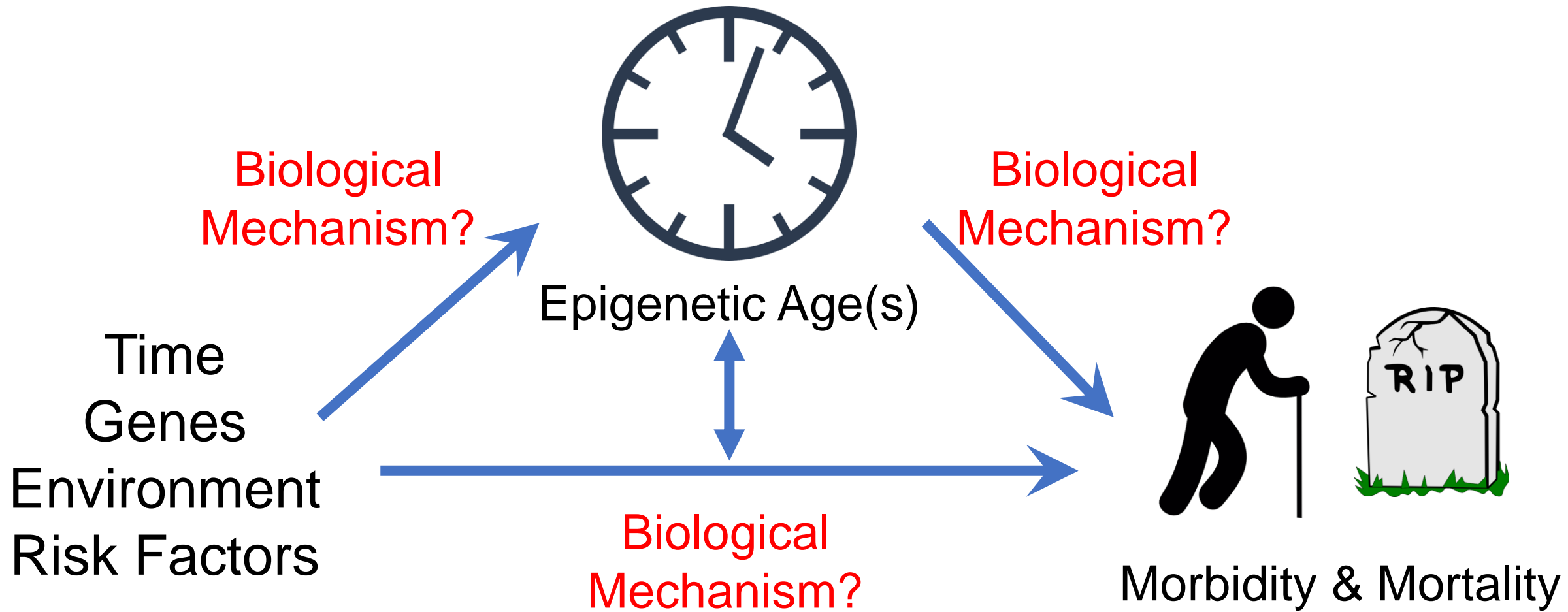
1) Predicts disease risk

Cardiovascular disease	Metabolic syndrome
Alzheimer's disease	Physical frailty
Cancer	Multimorbidity
Lung disease	All-cause mortality

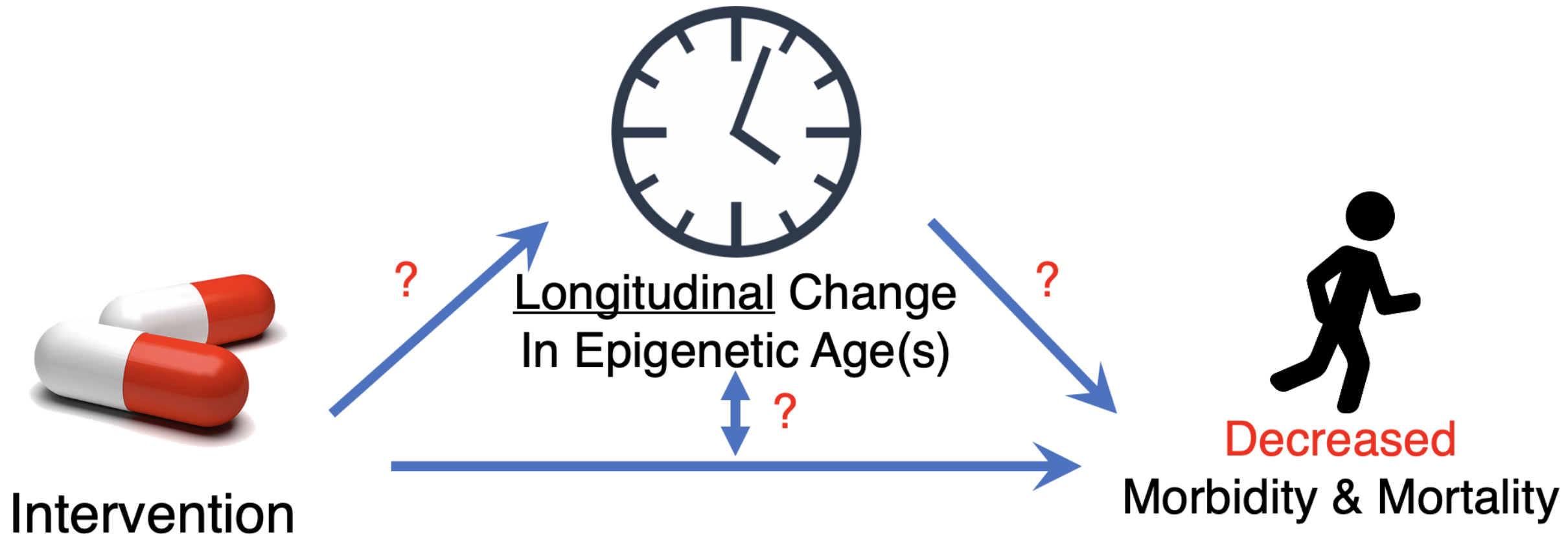
2) Correlate with known causes of accelerated aging

Smoking	Low physical activity
Alcohol	HIV
Obesity	Stress/trauma
Poor sleep	Socioeconomic disadvantage

The Unknowns



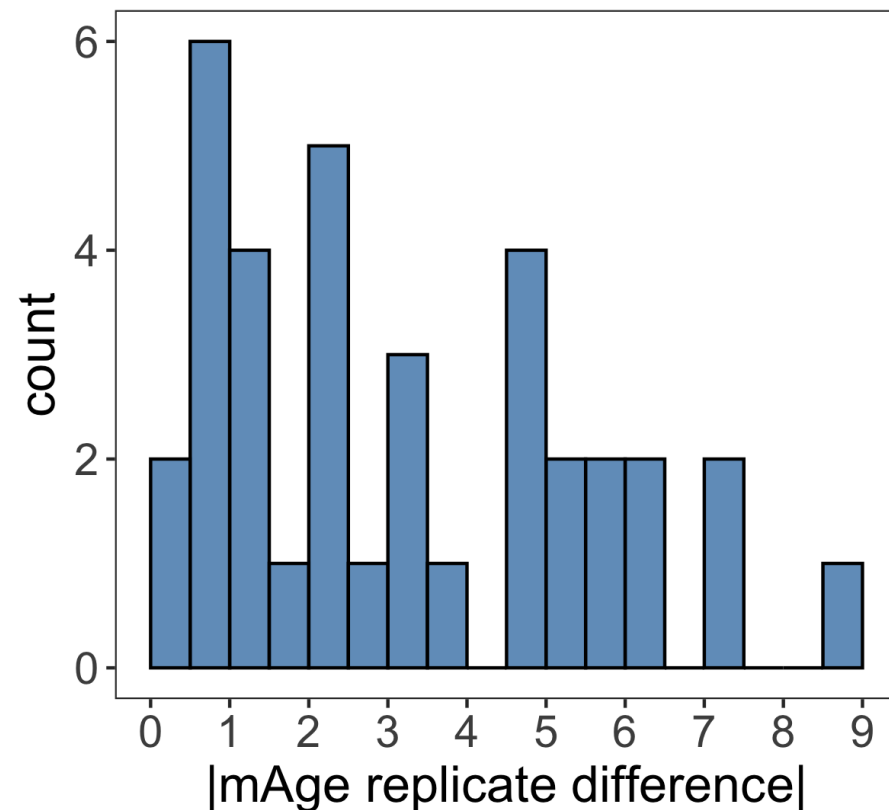
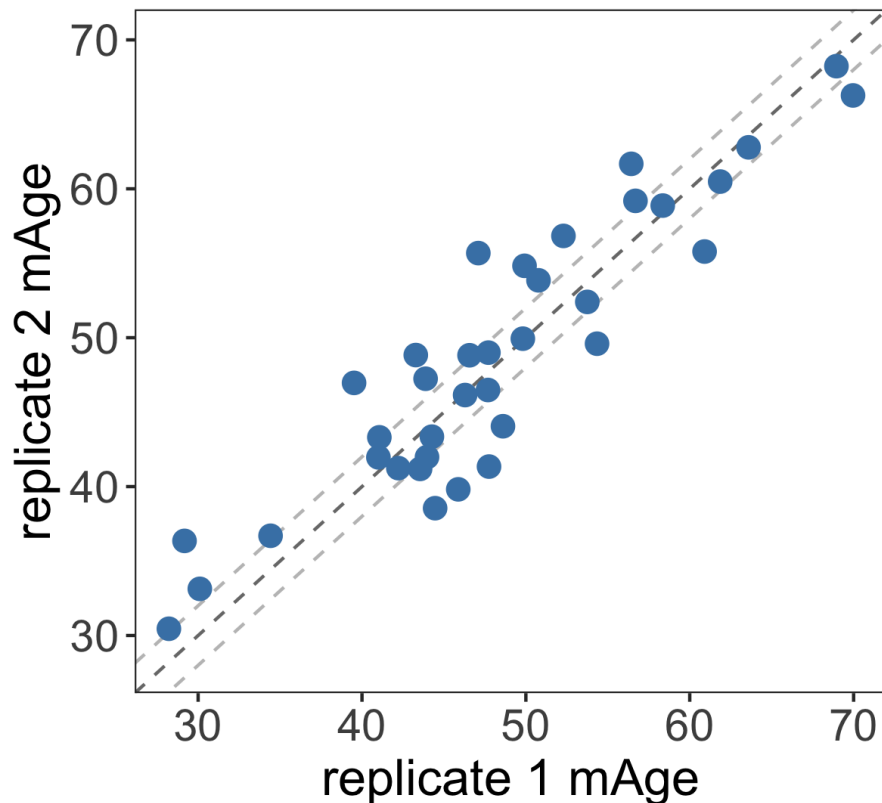
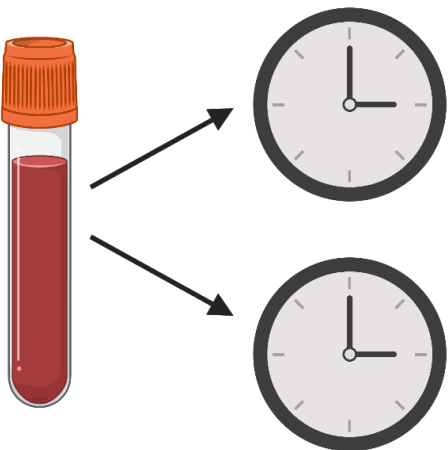
The Unknowns



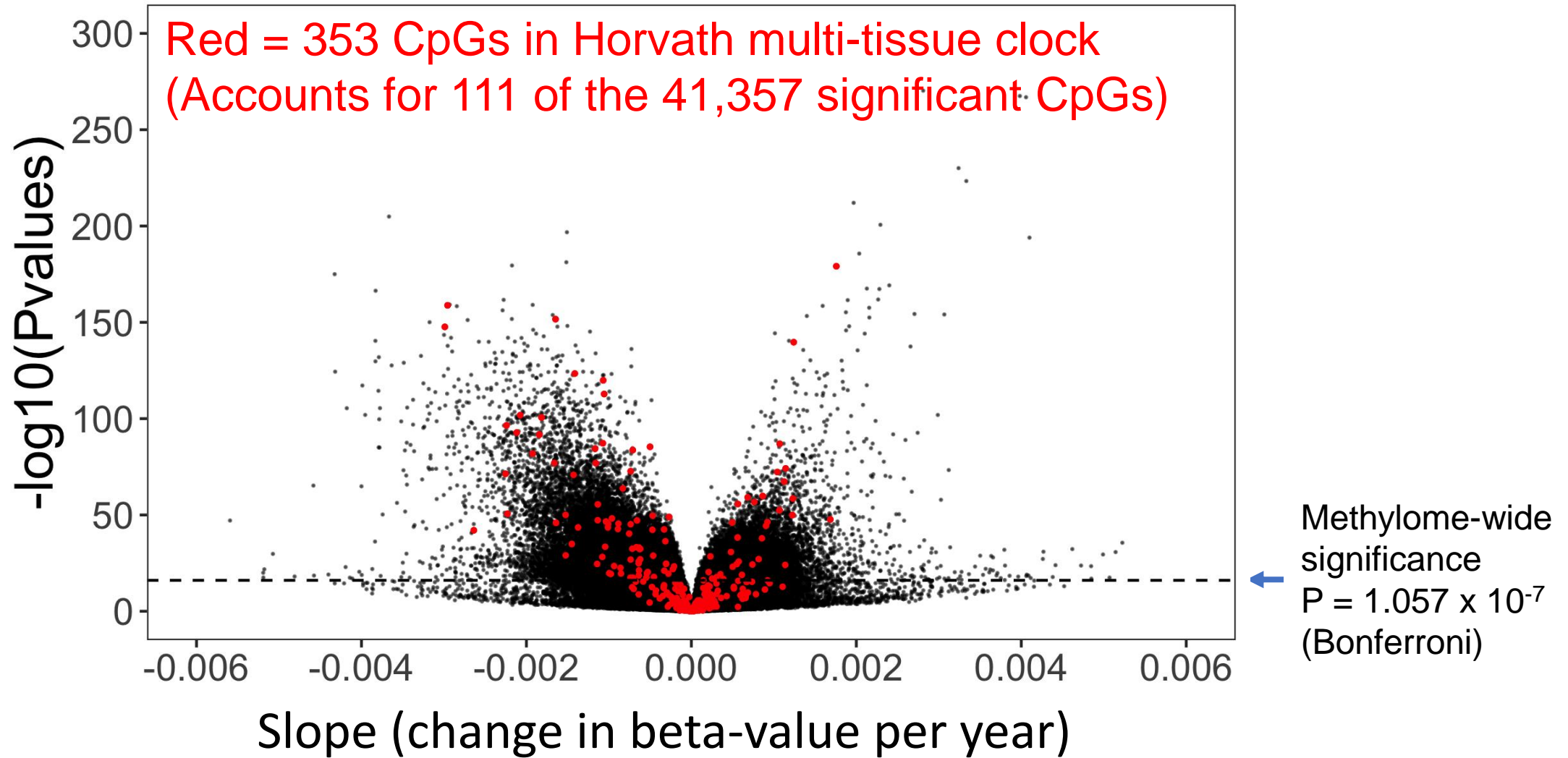
Big problem: DNA methylation data is VERY noisy

36 blood samples,
each measured twice

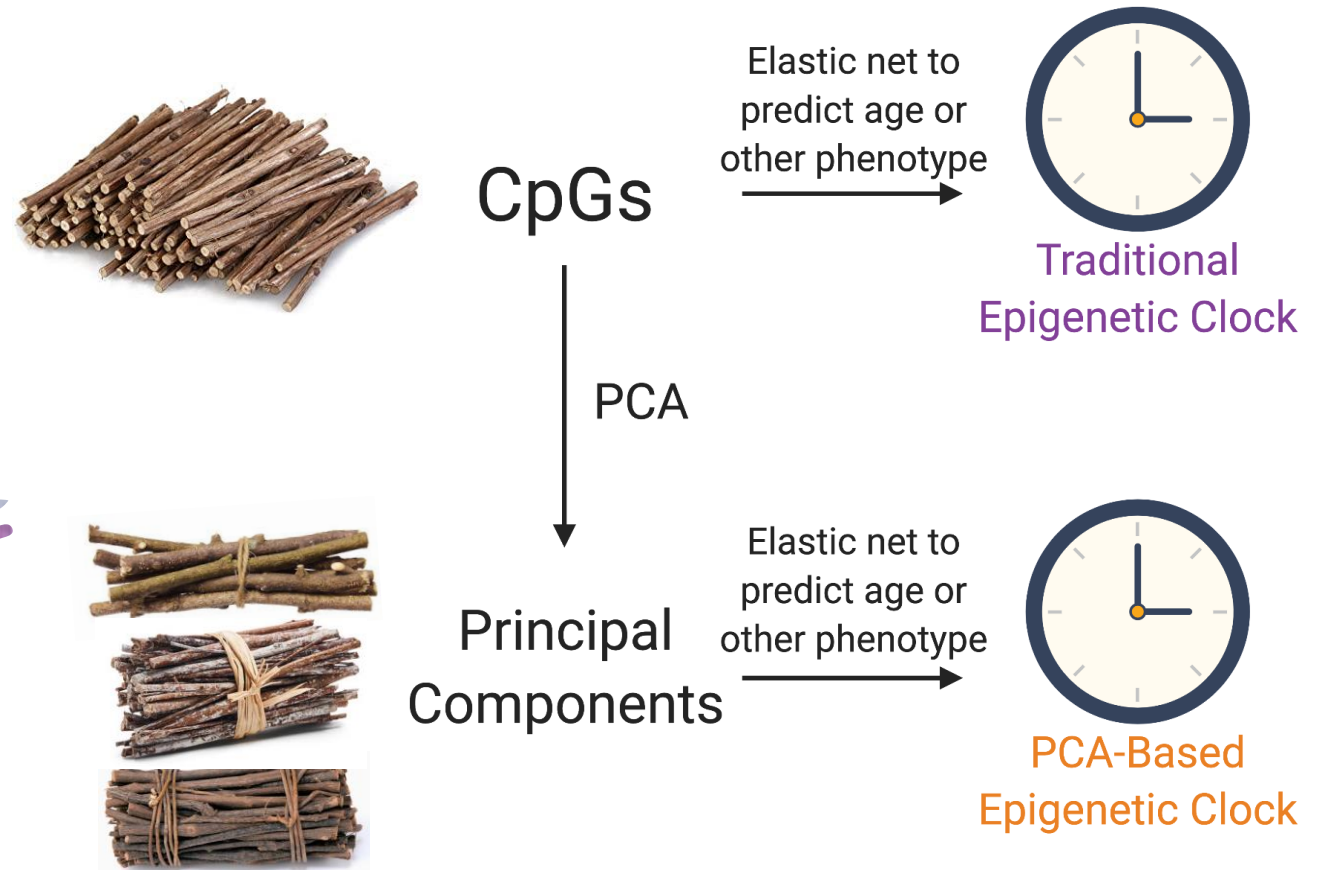
Age range 37-75



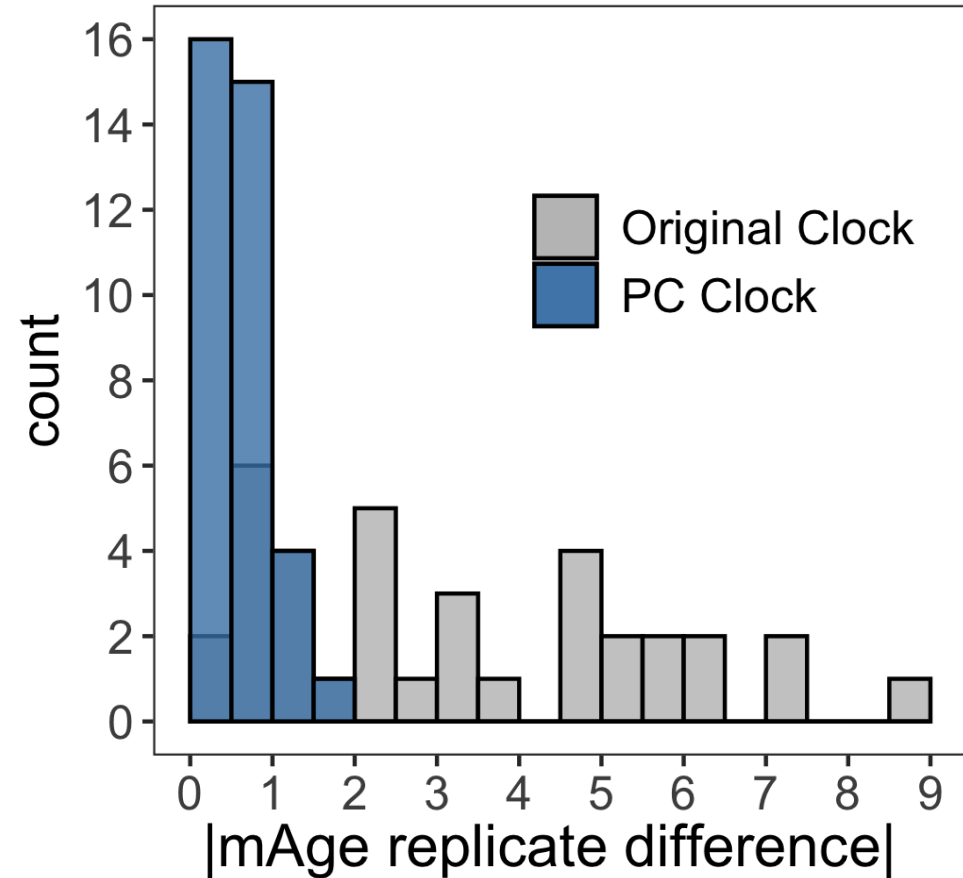
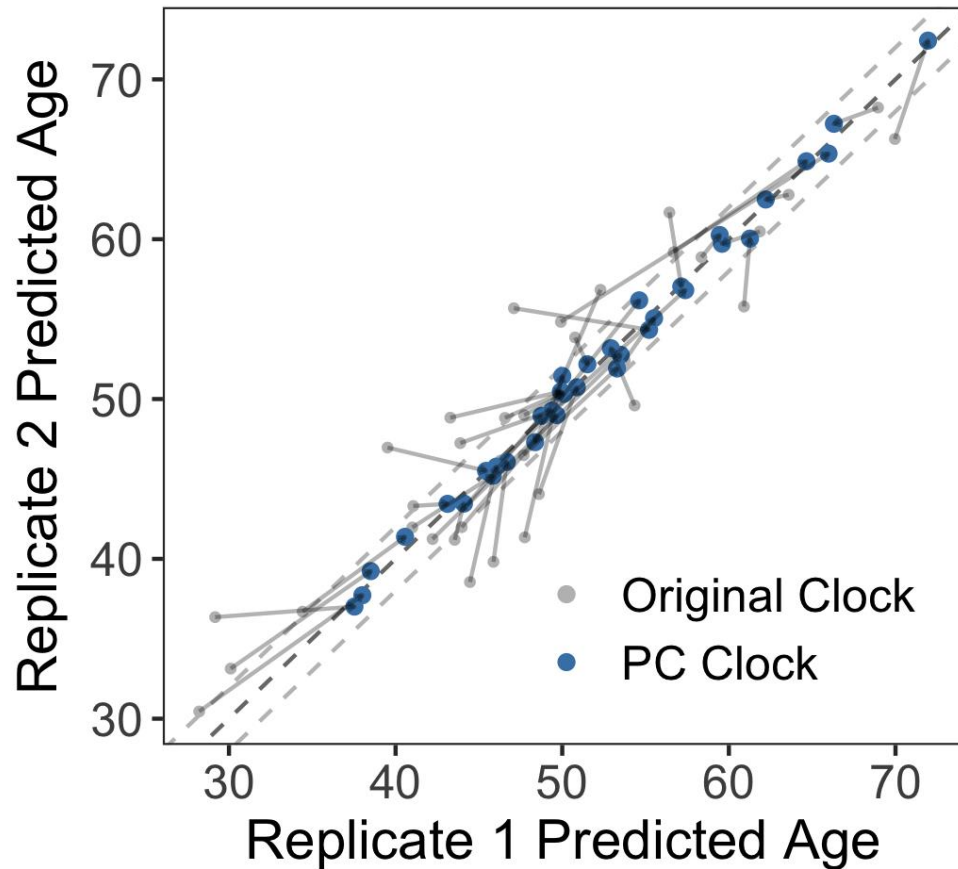
Age-related DNA methylation changes are widespread



Principal component analysis (PCA) bolsters reliability



Principal component-based clocks are highly reliable

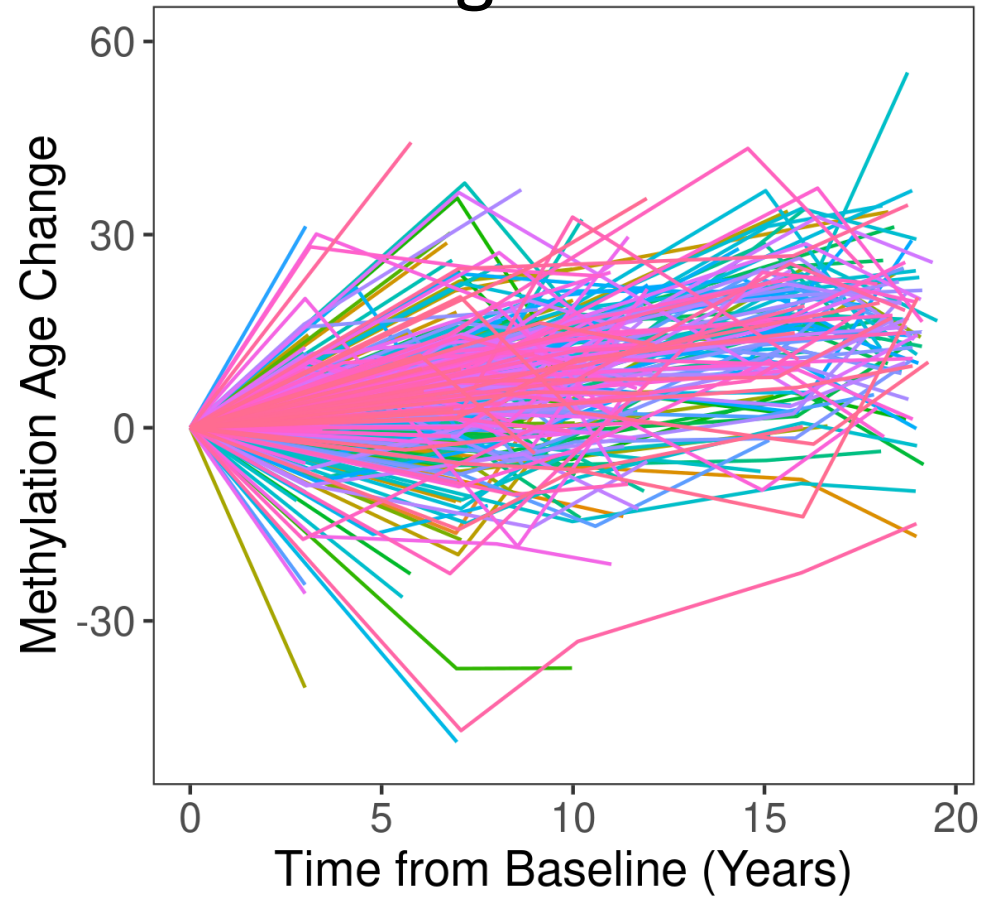


We applied this method to 6 commonly-used clocks with similar improvements.

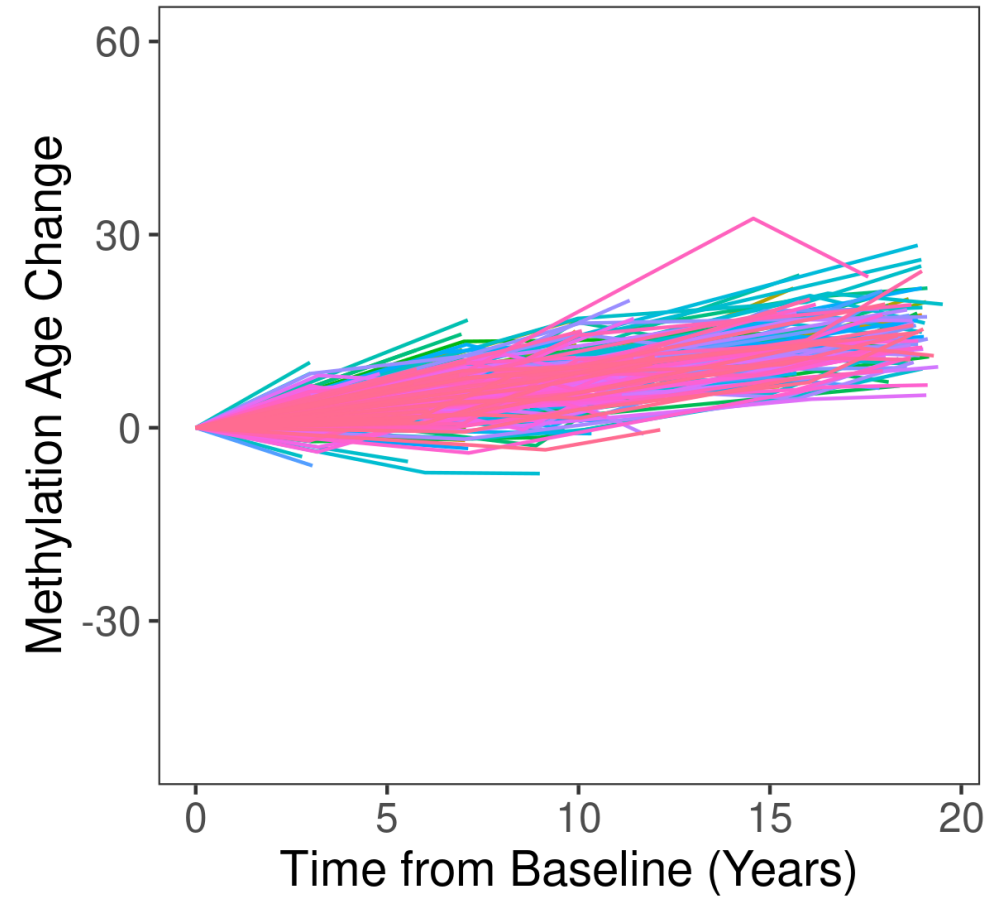
Longitudinal trajectories



Original Clock

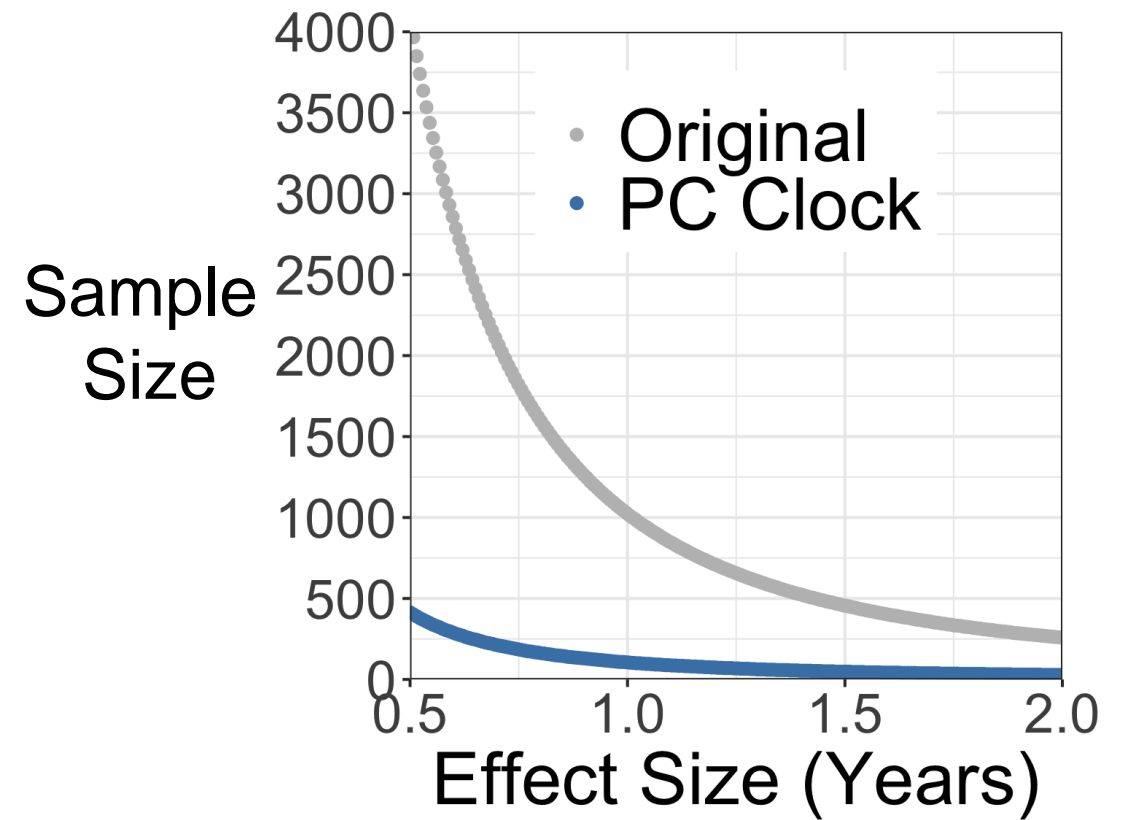
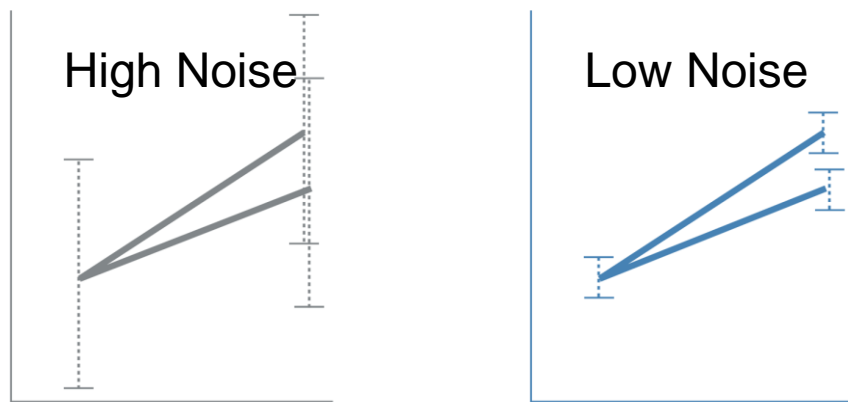
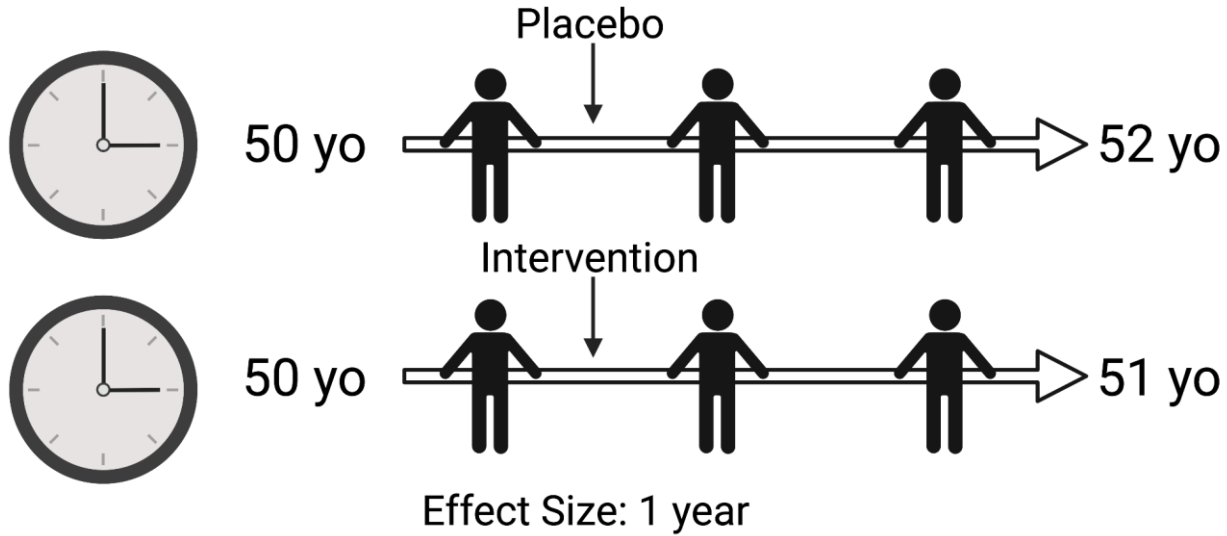


PC Clock



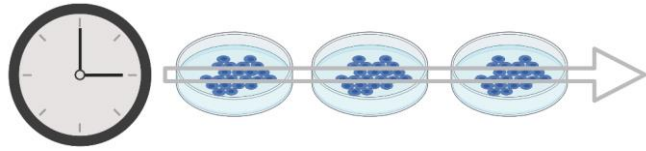
Results are similar for other PC clocks

PC clocks reduce sample size needed for clinical trials utilizing epigenetic clocks as surrogate endpoints

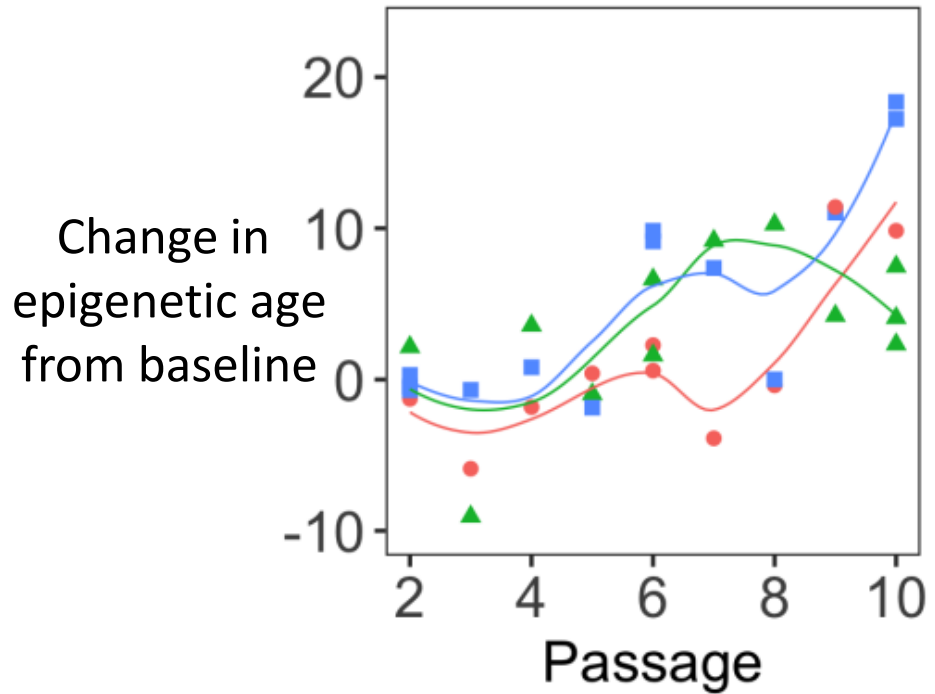


Results are similar for other PC clocks

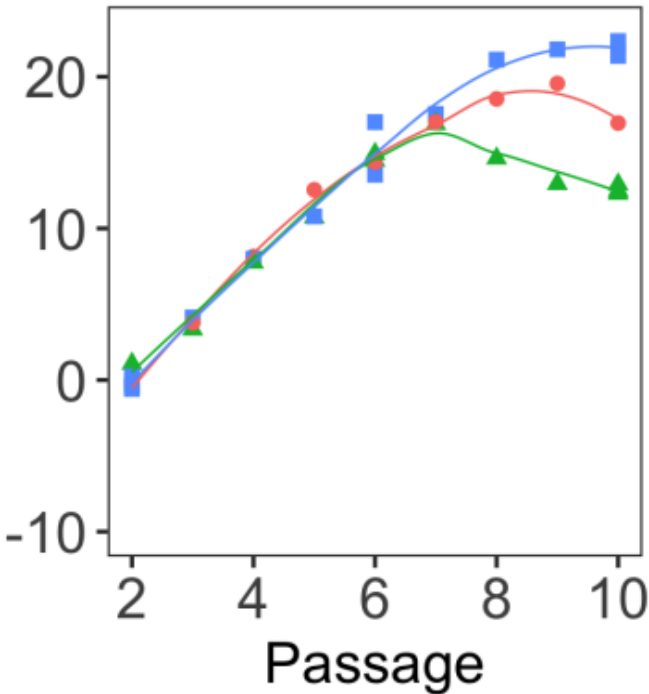
In vivo epigenetic aging is recapitulated *in vitro*



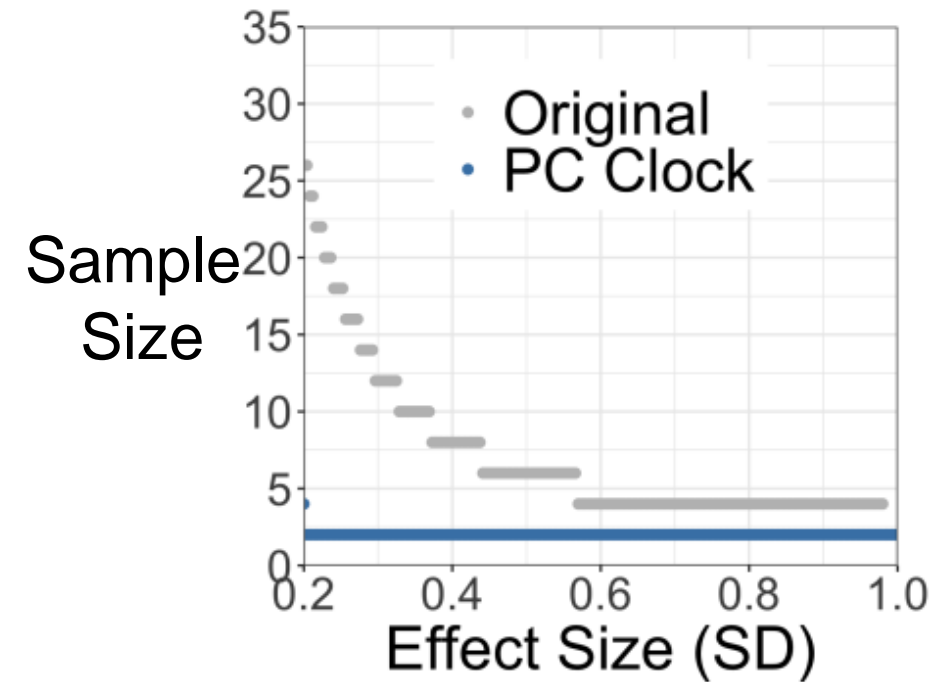
Original Clock



PC Clock

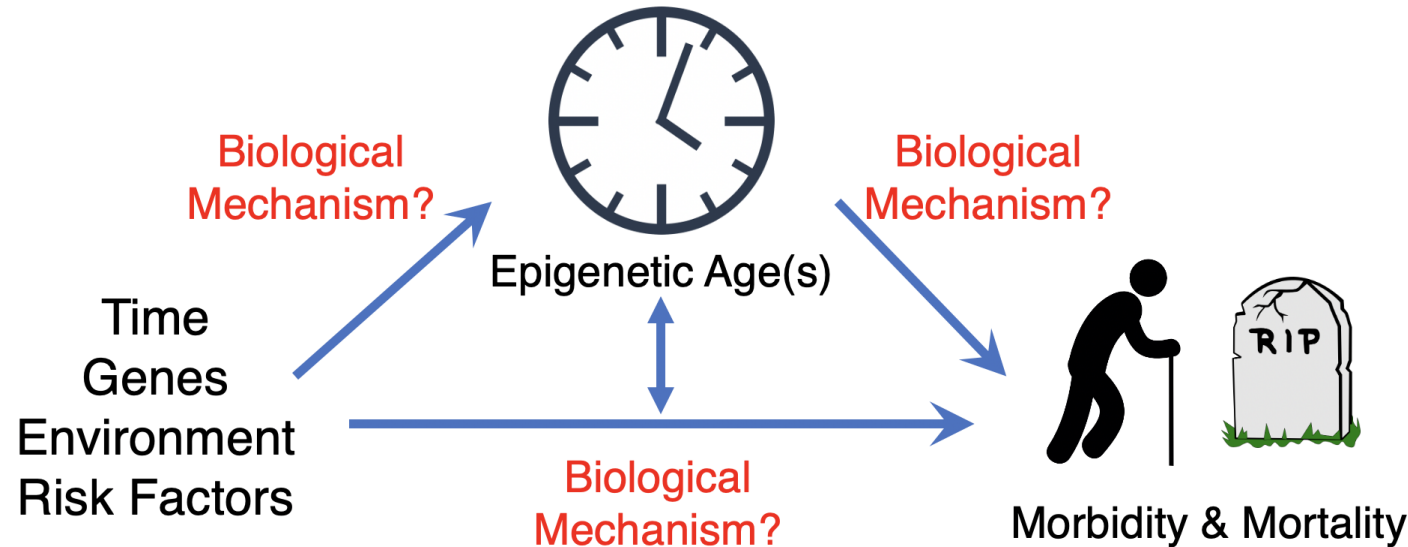


Power Analysis



Results are similar for other PC clocks

New technologies needed to investigate mechanism



- Principal component-based clocks for clinical trials, longitudinal tracking, and cell culture (Higgins-Chen 2021, Biorxiv)
- Single cell epigenetic clocks (Trapp 2021, Nature Aging)
- Pan-mammalian clocks (Lu 2021, Biorxiv)
- Ultra-low-cost epigenetic clocks (Griffin 2021, Biorxiv)
- DNA methylation editing with CRISPR (Nuñez 2021, Cell)

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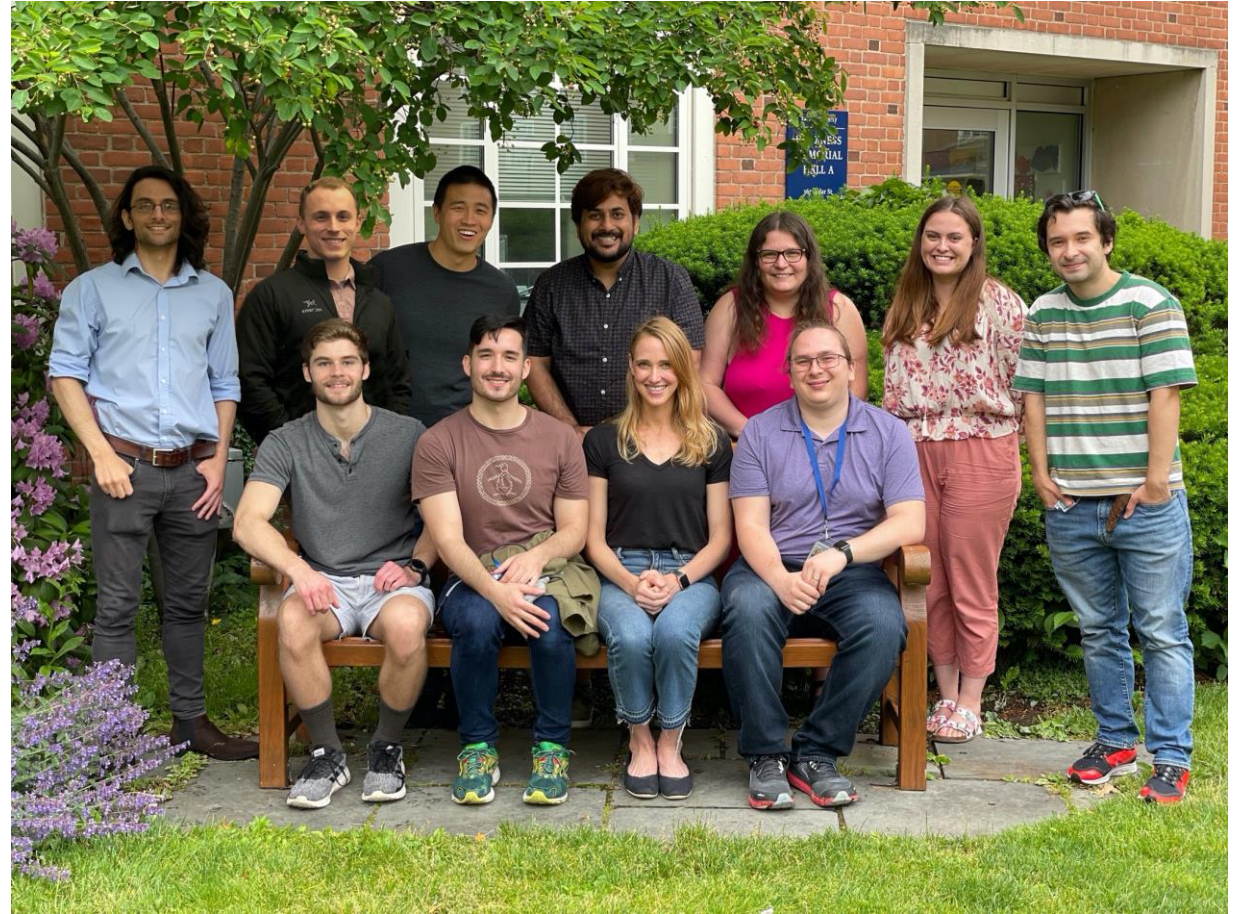
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