

DunedinPACE

A new biomarker for gerontology & geroscience

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Disclosures

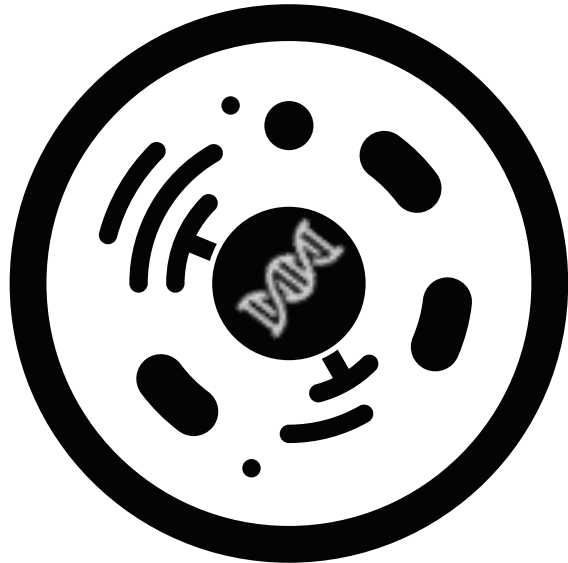
DunedinPACE is a Duke University & University of Otago invention licensed to a private company, Tru Diagnostic

DunedinPACE is freely available to researchers: <https://github.com/danbelsky/DunedinPACE>

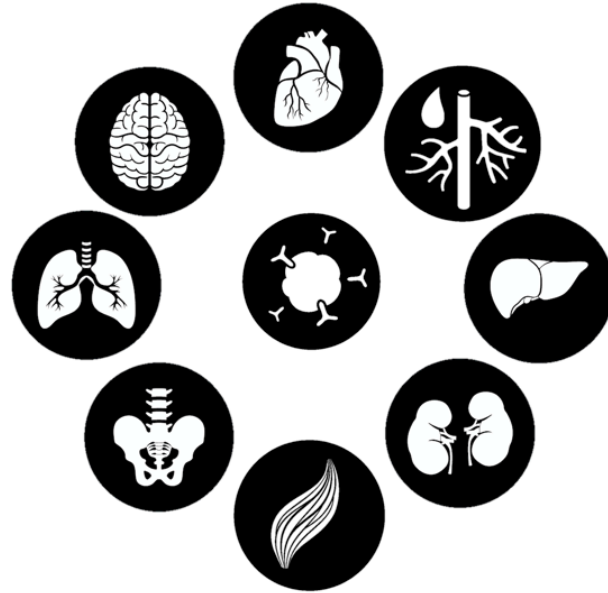
I receive consulting and/or SAB payments from the Hooke Clinic and Broad River Asset Management

The Geroscience Hypothesis

Molecular
Changes



Decline in
System
Integrity



Functional
Decline

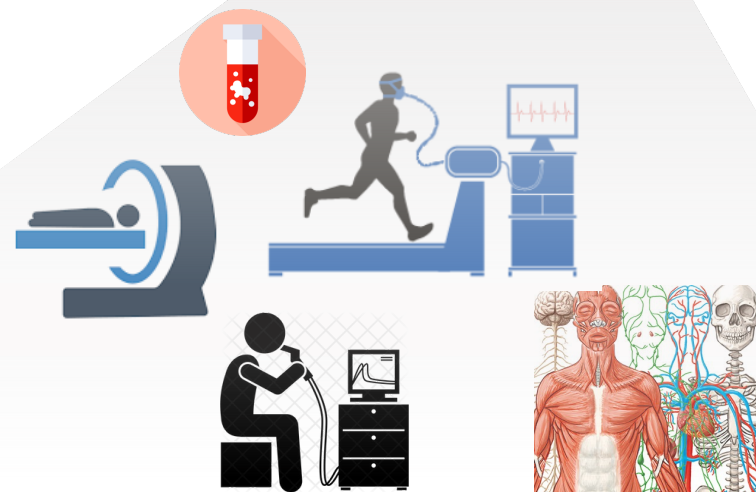
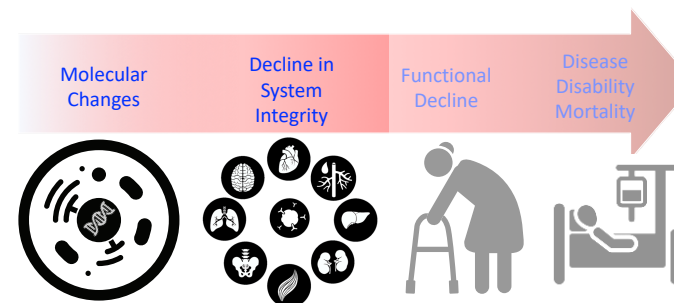
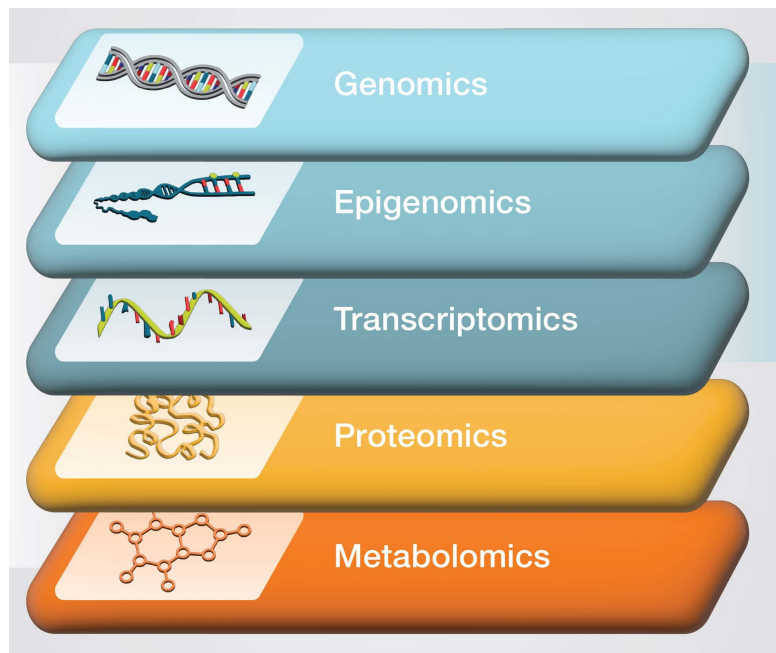


Disease
Disability
Mortality

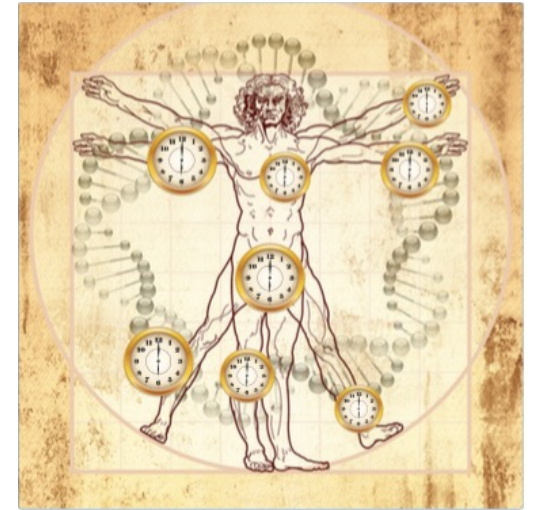
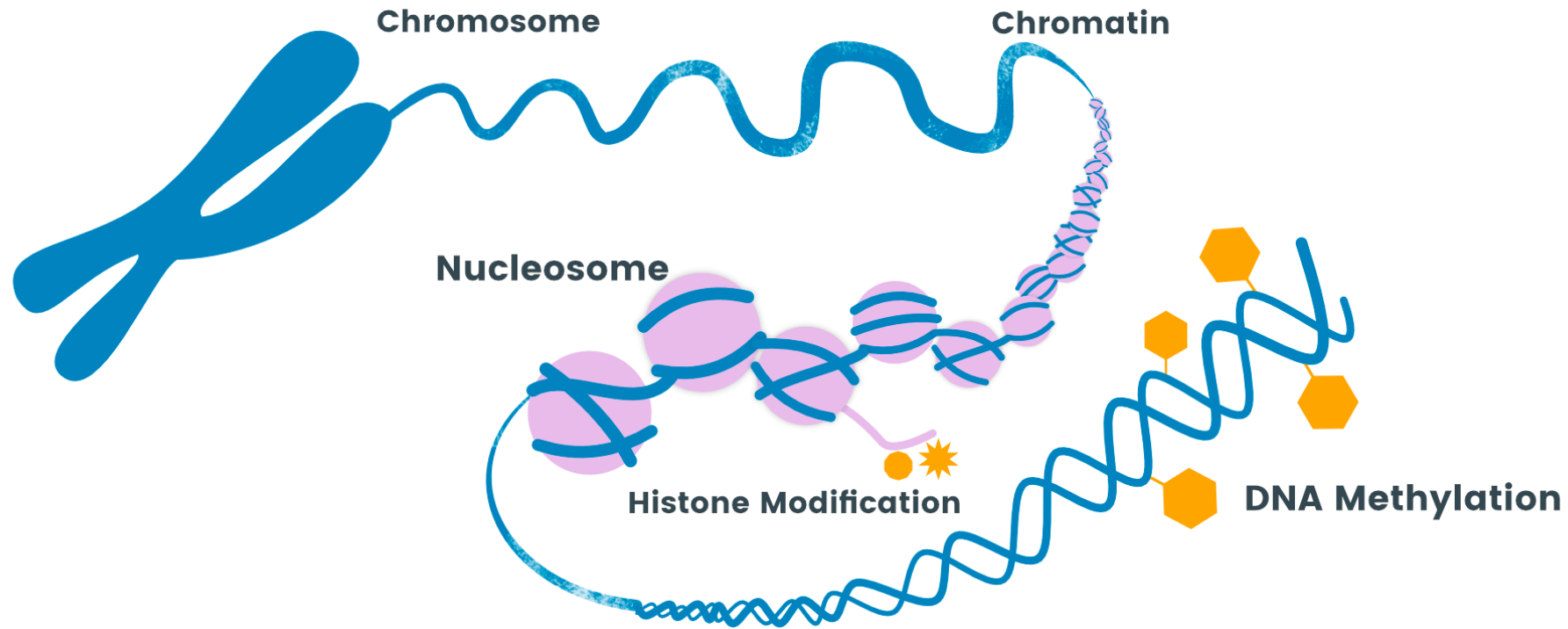


How do we measure biological aging?

Data-driven approaches

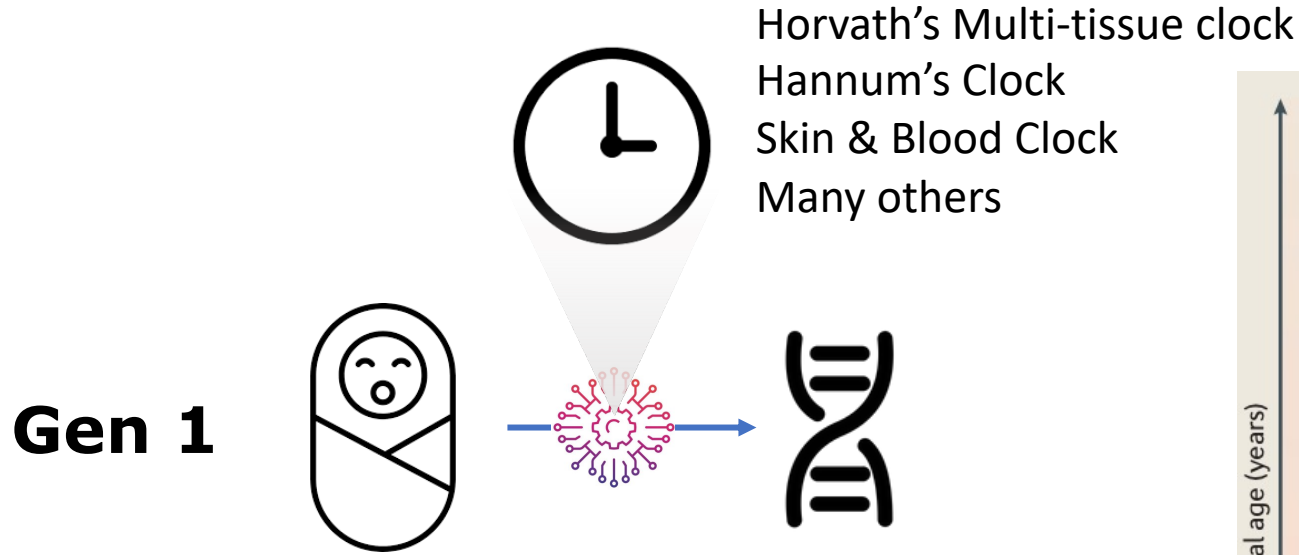


Epigenetic “clocks” estimate biological aging from DNA methylation



Horvath 2013 Genom Biol
Horvath & Raj 2018 Nat Rev Genet

1st gen Epigenetic “clocks” predict age from DNA methylation



Biological age is the age at which your biology would appear normal in a reference population

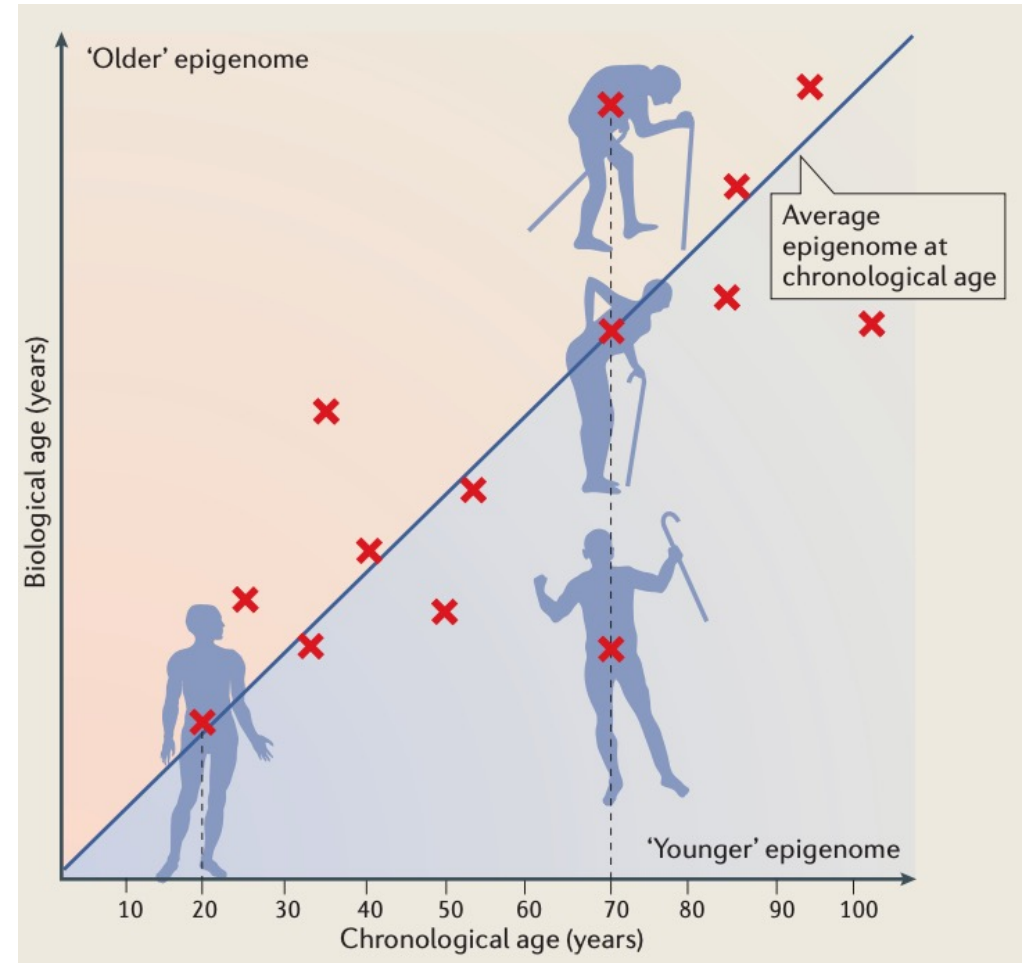
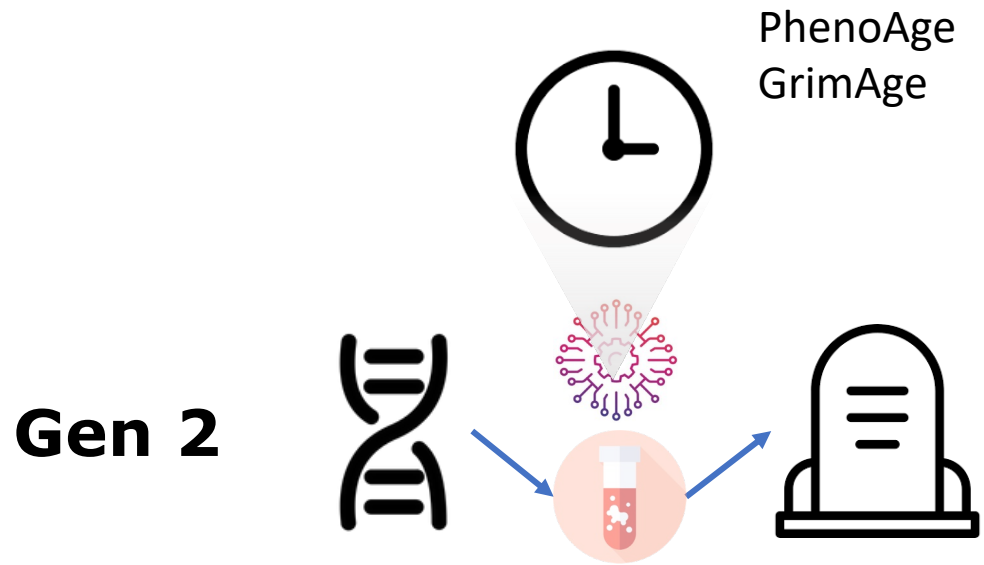
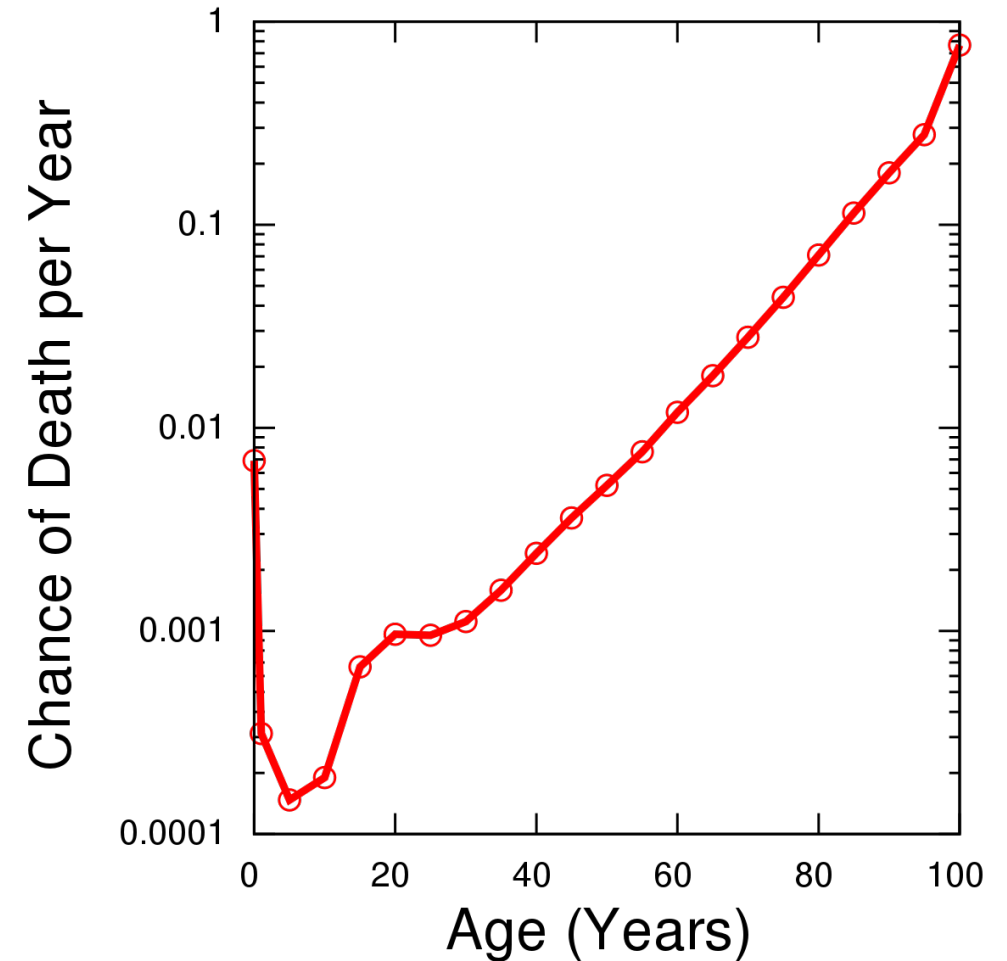


Figure – Benayoun et al. 2015 Nat Rev Mol Biol

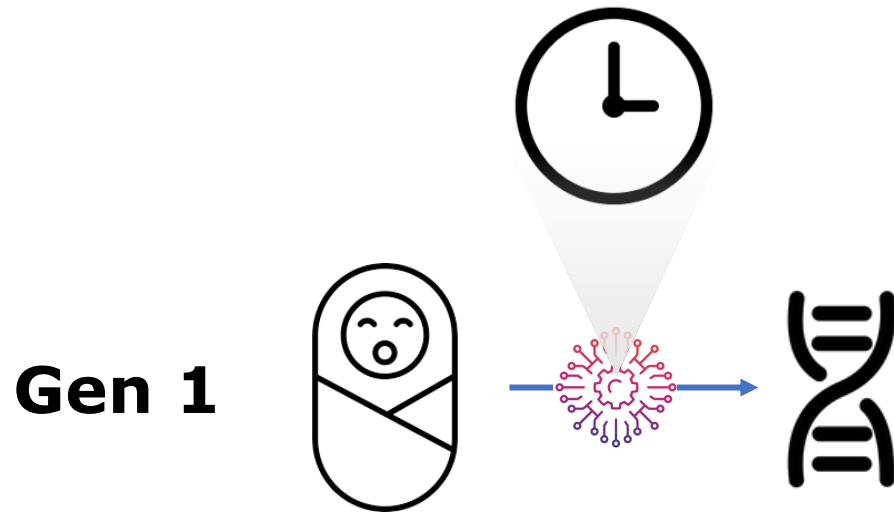
2nd gen Epigenetic “clocks” predict survival from DNA methylation



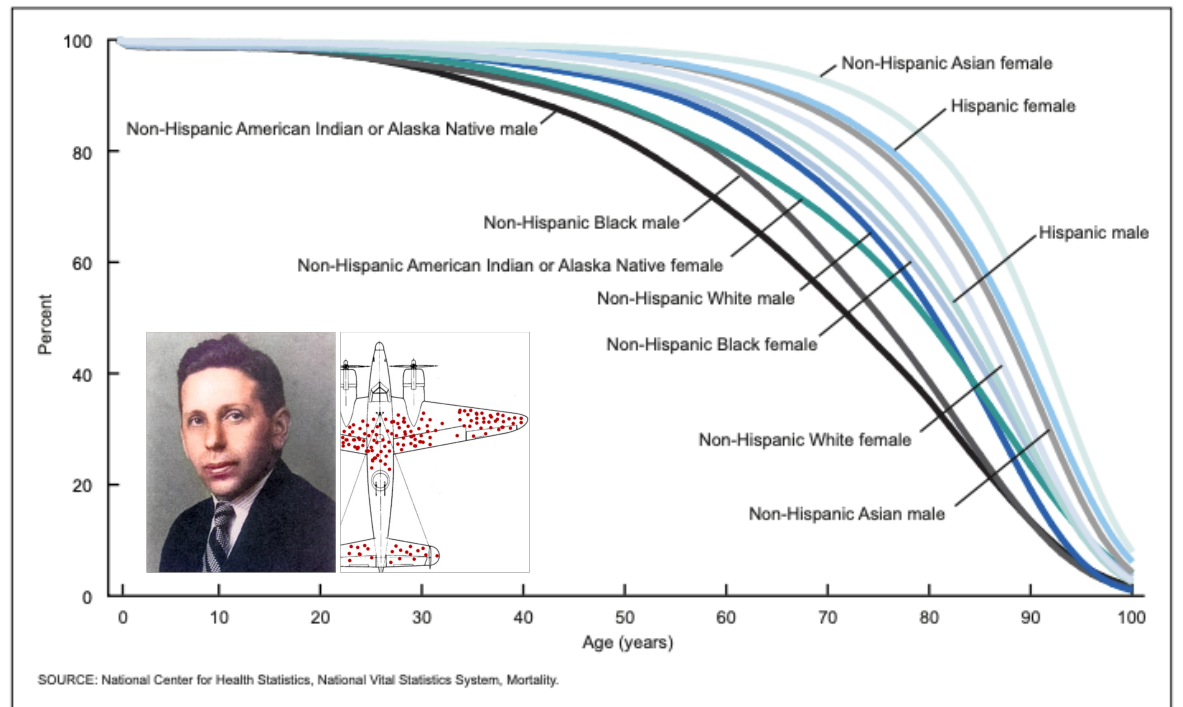
Biological age is the age at which your risk of death would appear normal in a reference population



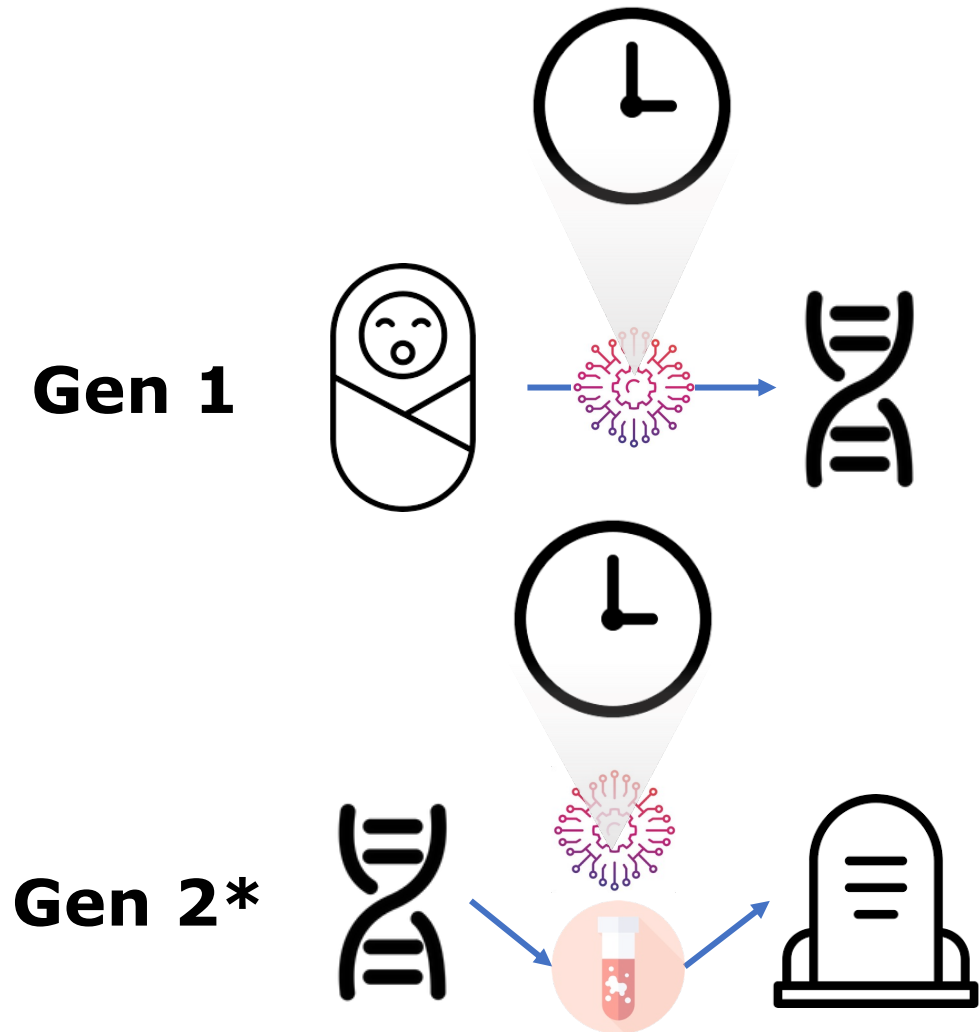
Limitations: *Survival Bias*



DNAm correlates of aging-related deterioration are not distinguished from DNAm correlates of resilience



Limitations: Cohort Effects



DNAm correlates of aging not distinguished from DNAm correlates of exposure history

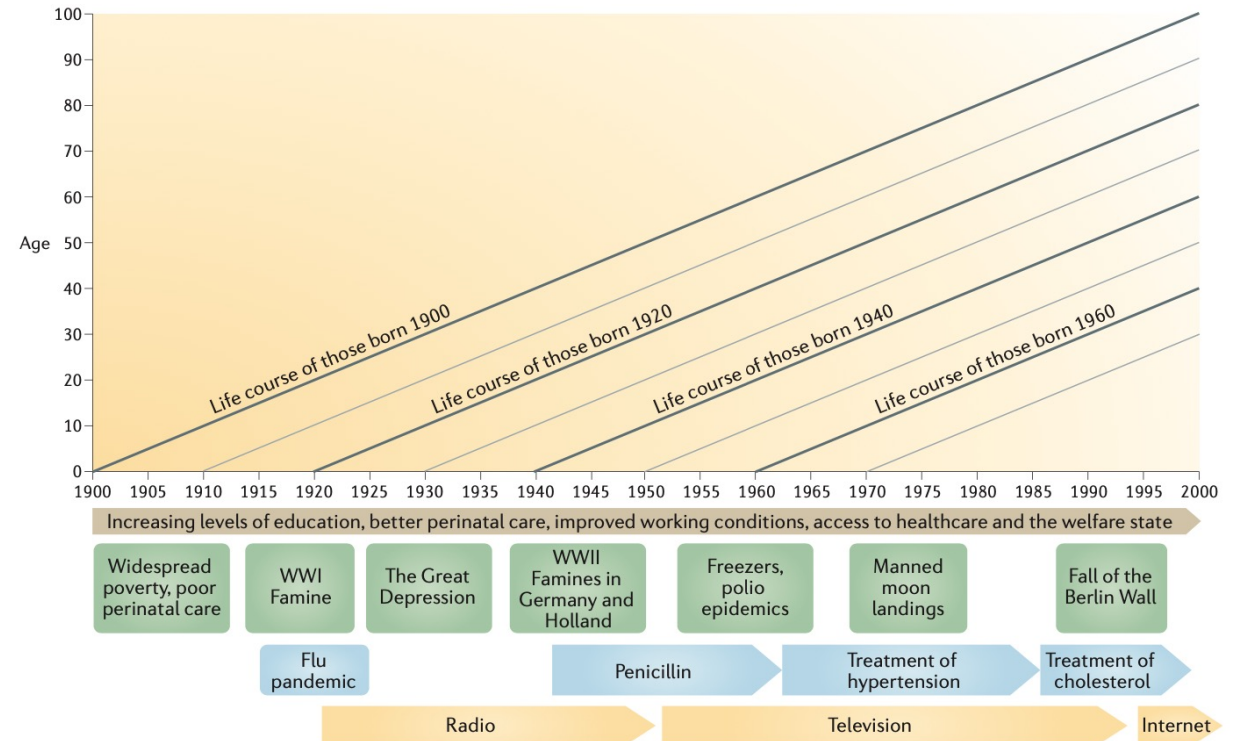
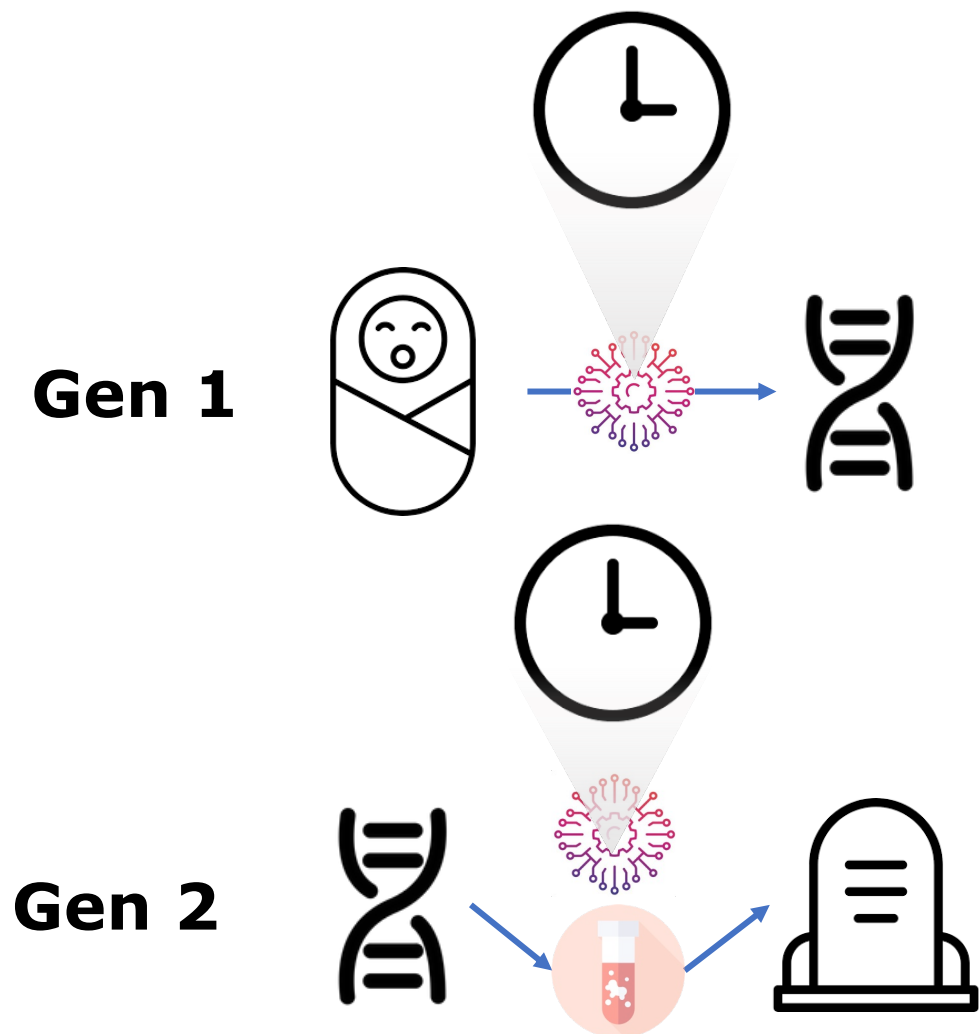


Figure - Skoog 2016 Nat Rev Neurol

Limitations: Uncertain Timing

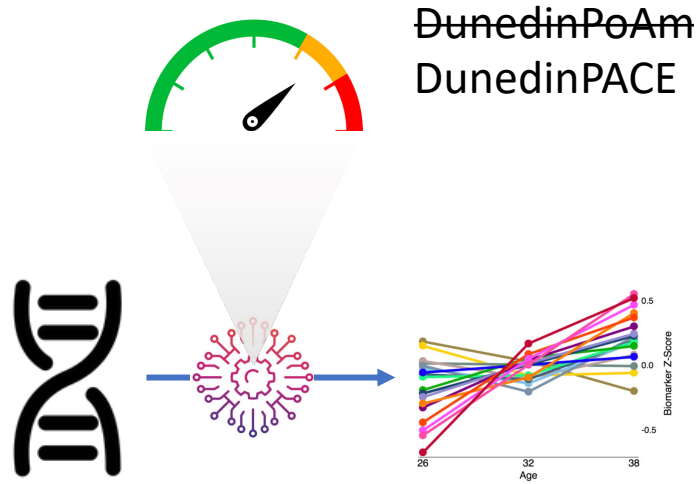
DNAm differences be established at any time following embryogenesis

Because most deaths are to older people, clocks are tuned to identify DNAm differences that have accumulated over many decades of adult life.



3rd gen Epigenetic “clocks” predict pace of aging from DNA methylation

Gen 3



Pace of Aging clocks are
“Speedometers”

They estimate rate of decline
in system integrity

Pace of Aging is the extent of
biological change occurring in a
single year in a reference population

Co-Inventors:

TE Moffitt, A Caspi, R Poulton, DL Corcoran, K Sugden

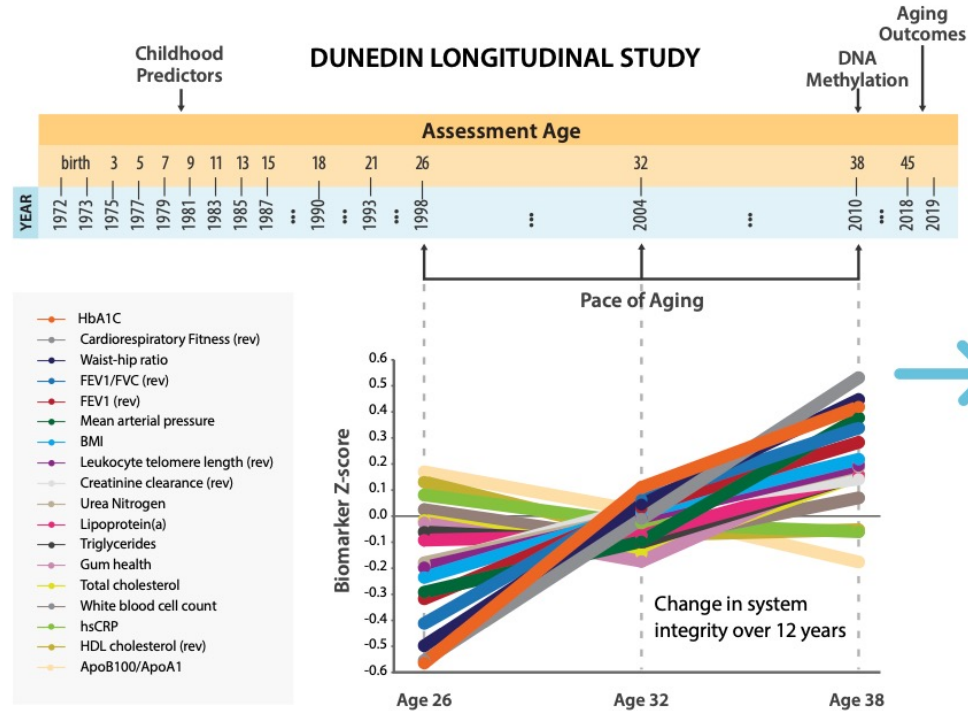


[Belsky et al. 2015 PNAS](#)

[Belsky et al. 2020 eLife](#)

[Belsky et al. 2022 eLife](#)

A DNAm biomarker of Pace of Aging: DunedinPoAm



Elastic net regression:
Analysis of age-38 DNA methylation data



DunedinPoAm is available from HRS with the v1 Epigenetic Clock dataset

HRS | HEALTH AND RETIREMENT STUDY

HRS Documentation Report

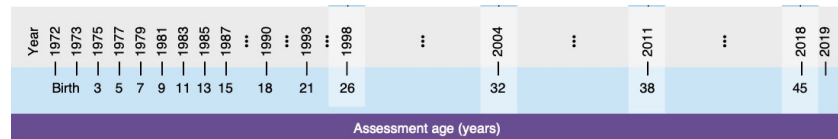
HRS Epigenetic Clocks

Report prepared by
Eileen Crimmins, University of Southern California
Jung Ki Kim, University of Southern California
Jonah Fisher, University of Michigan
Jessica Faul, University of Michigan

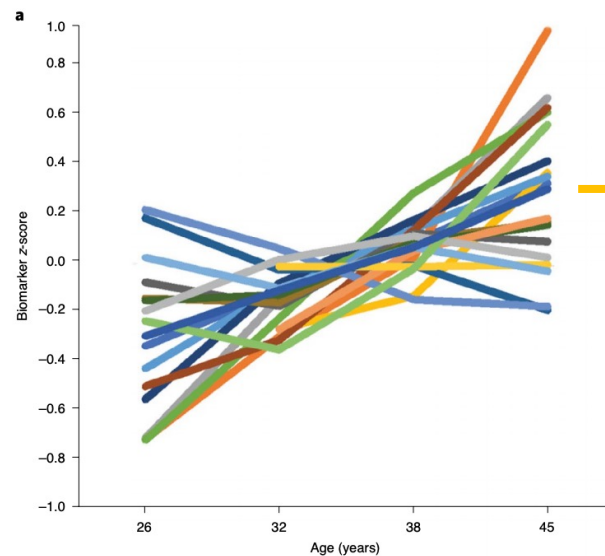
Survey Research Center
University of Michigan
Ann Arbor, Michigan
September 2020

A DNAm biomarker of Pace of Aging: DunedinPACE

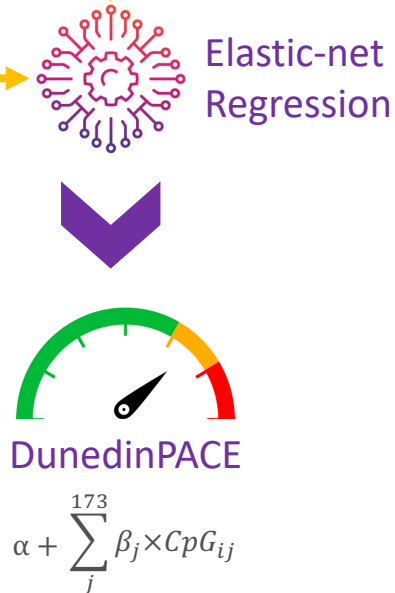
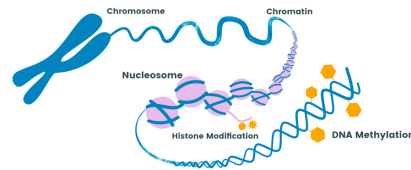
Dunedin Birth Cohort Follow-up



- BMI
- Waist-hip ratio
- Hemoglobin A1c
- Leptin
- Mean arterial pressure
- VO₂Max (rev)
- FEV₁/FVC (rev)
- FEV₁ (rev)
- Total cholesterol
- Triglycerides
- HDL cholesterol (rev)
- Lipoprotein(a)
- ApoB100/ApoA1
- eGFR (rev)
- Blood urea nitrogen
- hsCRP
- White blood cell count
- Mean periodontal attachmer
- Dental caries experience



Blood DNAm at age 45



DunedinPACE is developed from an expanded Pace of Aging phenotype

- Biomarkers measured at 4 timepoints
- over 20 years of follow-up

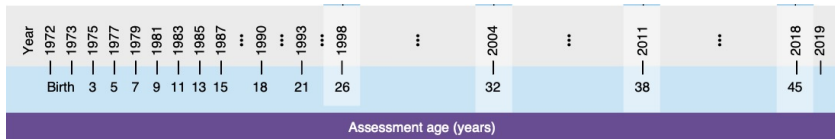
Details in Elliot et al. 2021 Nat Aging

AG032282 (Moffitt)

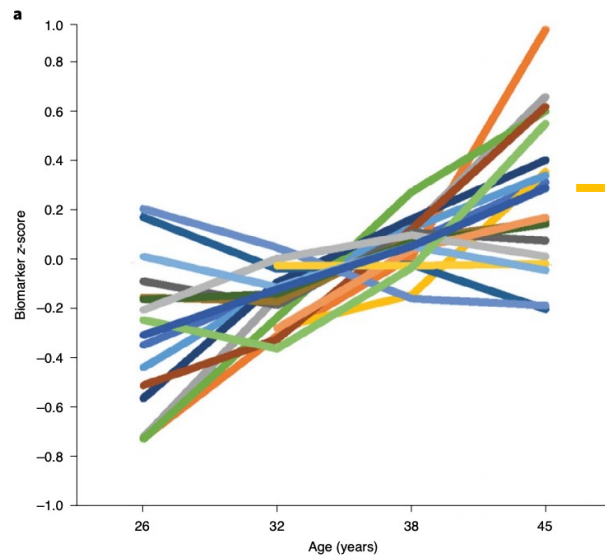


A DNAm biomarker of Pace of Aging: DunedinPACE

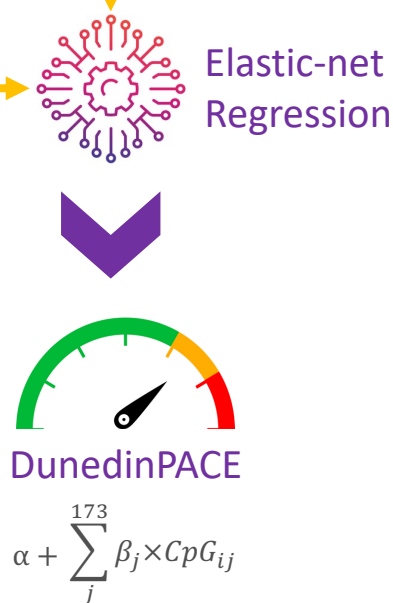
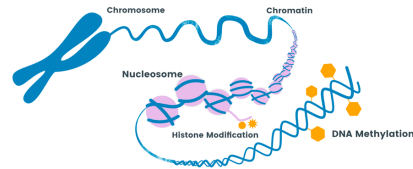
Dunedin Birth Cohort Follow-up



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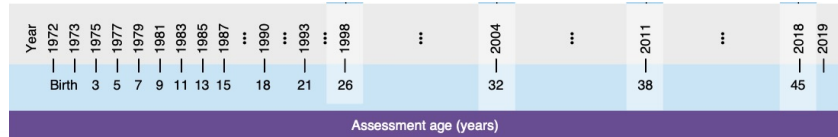
Blood DNAm at age 45



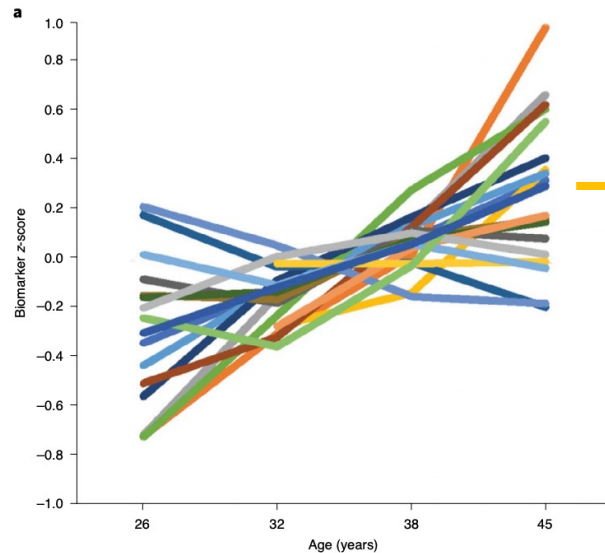
- Young Adulthood-Midlife follow-up avoids survival bias
- Same-age sample avoids cohort effects
- Repeated-measures longitudinal phenotyping identifies timing

A DNAm biomarker of Pace of Aging: DunedinPACE

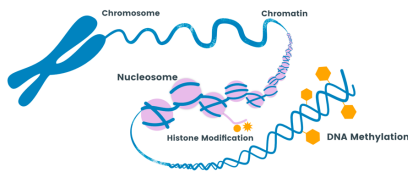
Dunedin Birth Cohort Follow-up



- BMI
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- Leptin
- Mean arterial pressure
- VO₂Max (rev)
- FEV₁/FVC (rev)
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- ApoB100/ApoA1
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- White blood cell count
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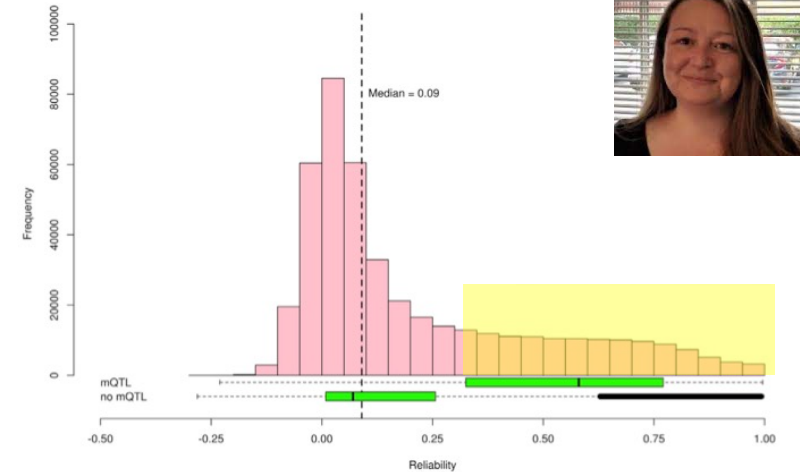


Blood DNAm at age 45



$$\alpha + \sum_j^{173} \beta_j \times CpG_{ij}$$

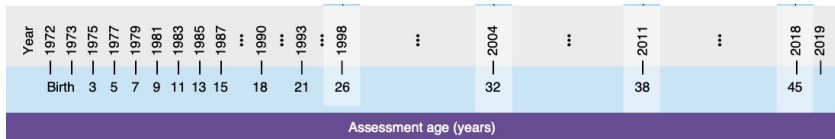
DunedinPACE is developed from CpG sites with (relatively) high measurement reliability in blood DNA



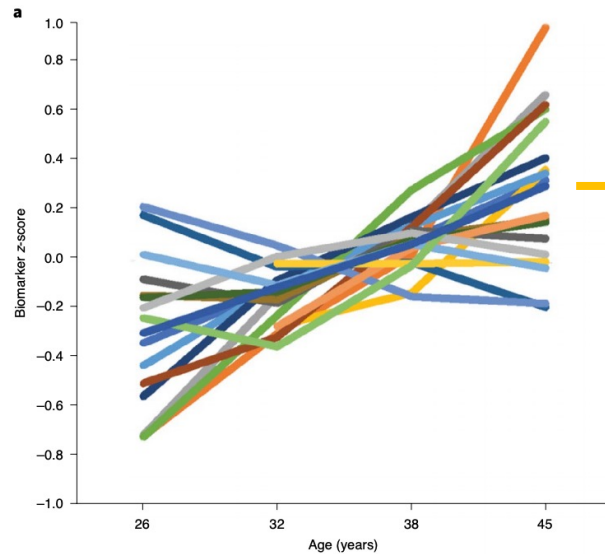
Sugden et al. 2020 Cell Patterns

A DNAm biomarker of Pace of Aging: DunedinPACE

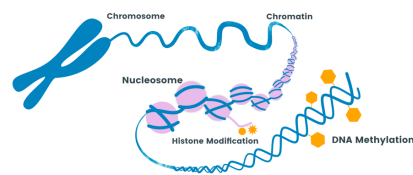
Dunedin Birth Cohort Follow-up



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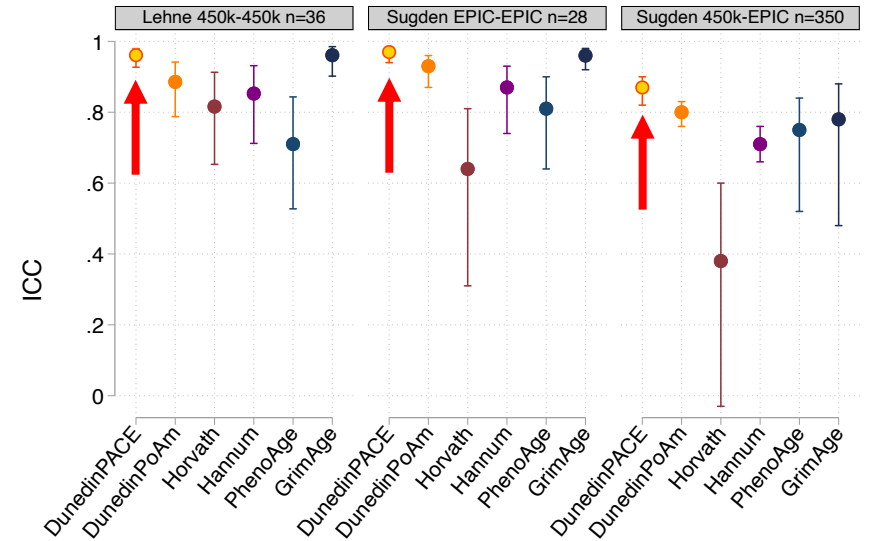


Blood DNAm at age 45



$$\alpha + \sum_j^{173} \beta_j \times CpG_{ij}$$

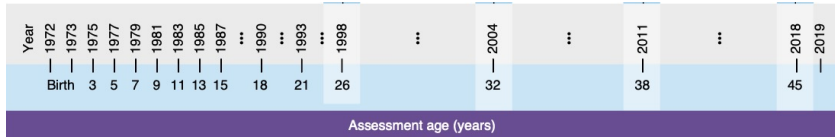
DunedinPACE has excellent test-retest reliability within array and good reliability across arrays



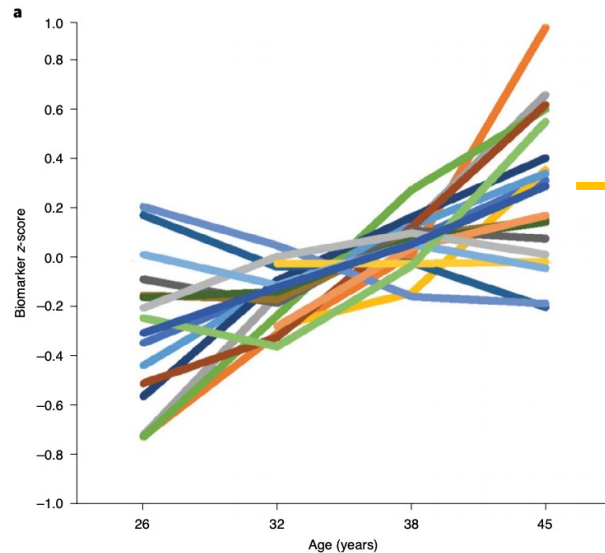
High Technical Reliability (“Repeatability”)

A DNAm biomarker of Pace of Aging: DunedinPACE

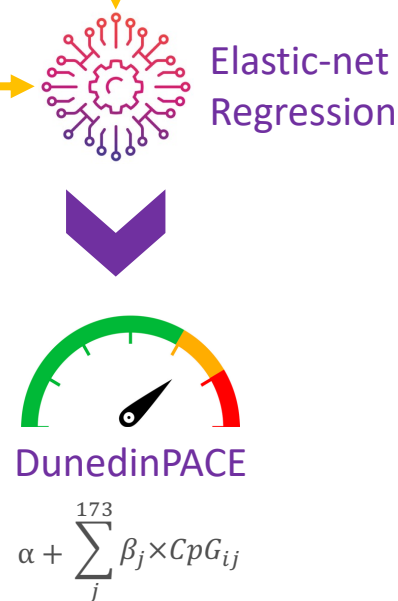
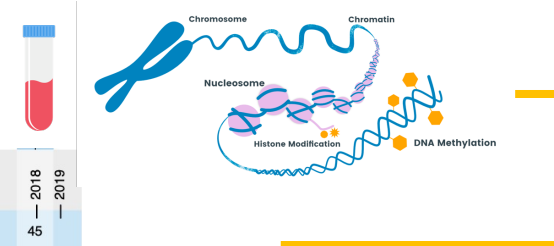
Dunedin Birth Cohort Follow-up



- BMI
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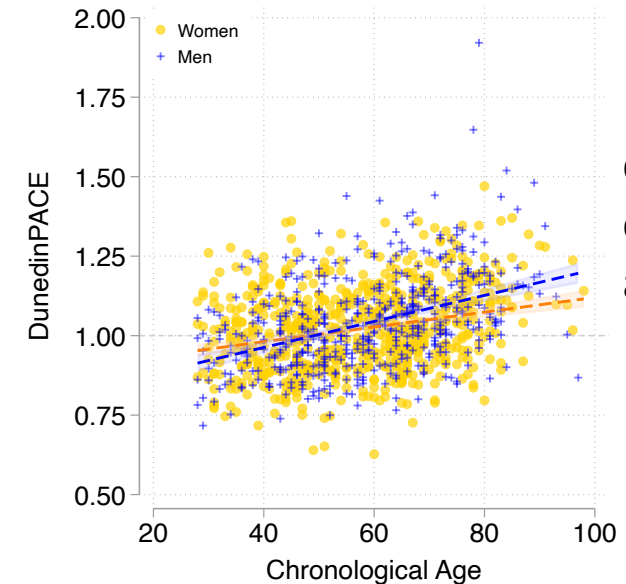


Blood DNAm at age 45



Interpretation:

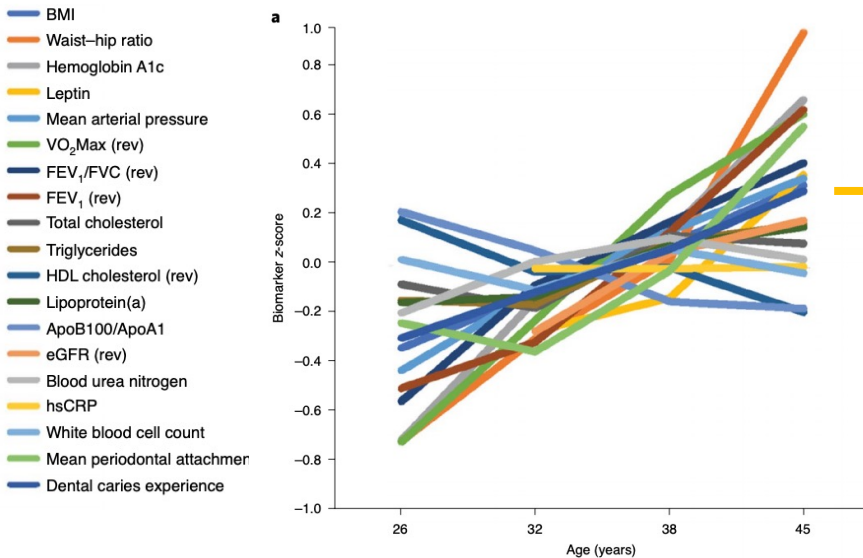
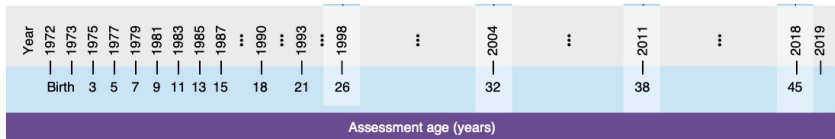
- DunedinPACE is a *RATE* measure
- NOT an age
- Values = years of biological aging per 12mo calendar time
- Expected value = 1 in midlife adults



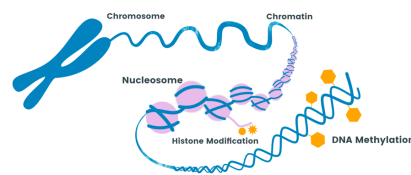
Moderate correlation w/ chronological age ($r \sim 0.2-0.4$)

A DNAm biomarker of Pace of Aging: DunedinPACE

Dunedin Birth Cohort Follow-up



Blood DNAm at age 45



$$\alpha + \sum_j^{173} \beta_j \times CpG_{ij}$$

Code freely available on GitHub

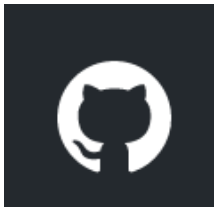
Available in many US & International Cohorts

- Child Health Study (PSU)
- Texas Twin Study (UT)
- HRS
- Framingham Heart Study
- MESA
- FACHS
- ADNI
- HANDLS
- Understanding Society (UK)
- ALSPAC (UK)
- TILDA (Ireland)
- CLHNS (Philippines)
- Taiwan Biobank
- Northern Finland Birth Cohort 1966
- MoBA (Norway)

Coming soon:

- Add Health
- Dutch Hunger Winter Families Study
- St. Jude's Lifetime Cohort
- DNHS
- G-SOEP (Germany)

Code to compute DunedinPACE from Illumina 450k and EPIC Array data is available on GitHub



Code to implement DunedinPACE in Illumina 450k or EPIC array data at <https://github.com/danbelsky/DunedinPACE>



main 1 branch 0 tags

Go to file

Code

About

Code to implement the DunedinPACE scoring algorithm in Illumina 450k or EPIC array data

Readme

GPL-3.0 license

5 stars

2 watching

2 forks

Report repository

Releases

No releases published

Packages

No packages published

Contributors 2

CPRyan Calen Patrick Ryan, PhD

danbelsky

	CPRyan Merge pull request #24 from CPRyan/main	a60a54e on Dec 5, 2022	50 commits
Folder	Data	reduced size of example betas.	4 months ago
Folder	R	Updated descriptions, added citation, explained getRequiredProbes ...	5 months ago
Folder	man	Changed name of help file from PoAmProjector to PACE projector	4 months ago
Folder	vignettes	reduced size of example betas.	4 months ago
File	.DS_Store	reduced size of example betas.	4 months ago
File	.Rbuildignore	Fixed authors, maintainer issues, added vignette, added bioCviews, ...	7 months ago
File	.gitignore	Fixed help documentation, added vignettes, etc.	7 months ago
File	DESCRIPTION	Changed name of help file from PoAmProjector to PACE projector	4 months ago
File	DunedinPACE.Rproj	Files uploaded from David Corcoran 1-5-2021	last year
File	LICENSE	Create LICENSE	last year
File	NAMESPACE	Files uploaded from David Corcoran 1-5-2021	last year
File	README.md	Updated descriptions, added citation, explained getRequiredProbes ...	5 months ago

README.md

DunedinPACE

Pace of Age calculator for Illumina methyl-array data (DunedinPACE)

DunedinPACE

Pace of Age calculator for Illumina methyl-array data (DunedinPACE)

PACEProjector.R -- 20220105

Given a set of methylation beta values, this tool will calculate the Dunedin Methylation Pace of Aging Methylation Score (DunedinPACE)

Installation (via devtools):

```
devtools::install_github("danbelsky/DunedinPACE")
```

Requirements (preprocessscore Bioconductor package):

```
if (!requireNamespace("BiocManager", quietly = TRUE))  
  install.packages("BiocManager")  
BiocManager::install("preprocessCore")
```

Load data and execute scoring

Usage:

```
library("DunedinPACE")  
PACEProjector(betas)
```

Your data here

There are two arguments needed for the package:

```
PACEProjector(betas=MyBetas, ProportionofProbesRequired=0.8)
```

Which can be simplified to

```
PACEProjector(MyBetas, .8)
```

Input:

betas:

Matrix or data.frame of beta values where rownames are probe ids and column names should correspond
Ensure beta values are numeric and that missing values should be coded as 'NA'

Example data from
[GSE55763](#)

(now included with the
DunedinPACE package)

```
##          7786915023_R02C02 7786915135_R04C02 7471147149_R06C01
## cg00000165      0.2277741      0.2473194      0.2440011
## cg00000363      0.3985622      0.4472925      0.4138226
## cg00001364      0.8911960      0.8489085      0.8350762
## cg00001446      0.8531862      0.8491986      0.8630675
## cg00001534      0.9386833      0.9244288      0.9481436
## cg00001593      0.8942515      0.9066900      0.9091480
##          7786915035_R05C01 7786923035_R01C01
## cg00000165      0.2009838      0.2402189
## cg00000363      0.3962381      0.3402043
## cg00001364      0.8881316      0.8727941
## cg00001446      0.8651739      0.8694210
## cg00001534      0.9142873      0.9470086
## cg00001593      0.9203527      0.9107432
```

proportionOfProbesRequired:

This is the proportion of probes to have a non-missing value for both the sample to have DunedinPACE calculated, as well as to determine if we can impute the mean from the current cohort. By default, this is set to 0.8.

Can set to any value. We recommend a minimum of 0.8.

What's under the hood?

List of CpG sites

To see list of probes necessary for each model:

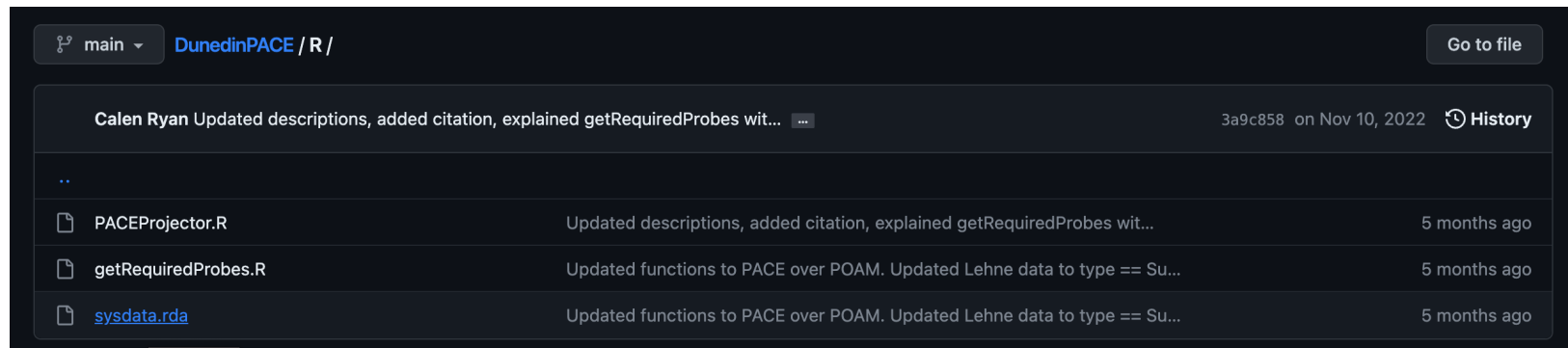
```
getRequiredProbes()
```

`getRequiredProbes(backgroundList = FALSE)` returns 173 probes used for calculating DunedinPACE directly.

`getRequiredProbes(backgroundList = TRUE)` returns 173 probes used for calculating DunedinPACE directly, as well as 19827 probes used in the normalization process.

We do not recommend excluding the 19827 probes used for normalization and calculating DunedinPACE using only the 173 DunedinPACE associated probes, as this could affect DunedinPACE estimates.

If you want the scoring coefficients, these are included in the `sysdata.rda` file



The screenshot shows a file history interface for the `DunedinPACE / R /` directory. The interface includes a search bar, a "Go to file" button, and a list of files with their respective update descriptions and timestamps.

File Name	Description	Timestamp
PACEProjector.R	Updated descriptions, added citation, explained getRequiredProbes wit...	5 months ago
getRequiredProbes.R	Updated functions to PACE over POAM. Updated Lehne data to type == Su...	5 months ago
sysdata.rda	Updated functions to PACE over POAM. Updated Lehne data to type == Su...	5 months ago

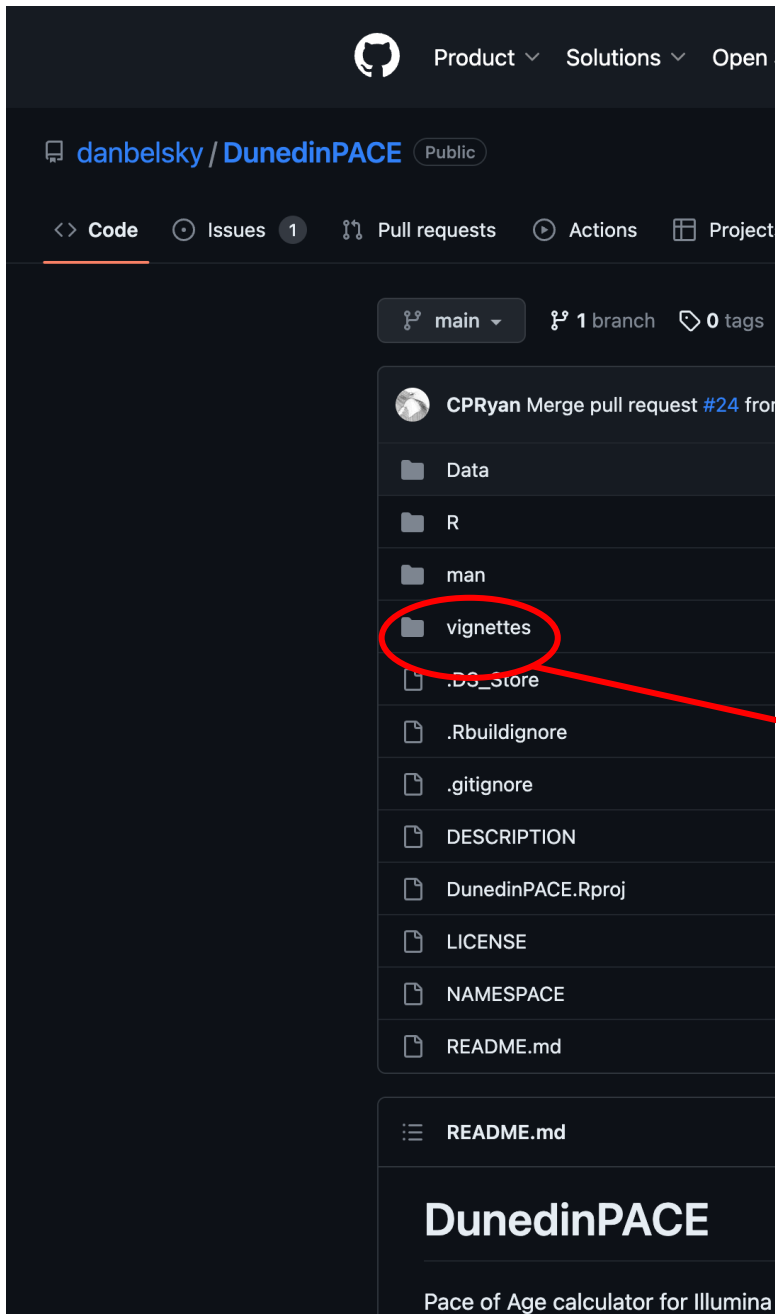
How should I prepare my data?

Noob (`preprocessNoob` in `mini`)
Functional Normalization (`funnorm` in `minif`)
Quantile normalization (`preprocessQuantile` in `minfi`)
BMIQ
ENMIX
Etc.

OK

DunedinPACE is designed to be run on already processed/normalized data.

The internal normalization is designed to ensure that values are comparable to the distribution in the original Dunedin Study training data



DunedinPACE: A DNA methylation biomarker of the pace of aging

Vignette created by - Calen P. Ryan, PhD

10 November 2022

Contents

- 1 Introduction to DunedinPACE
- 2 The `PACEProjector` function
- 3 The `getRequiredProbes()` function

1 Introduction to DunedinPACE

`DunedinPACE` is a novel blood biomarker of the pace of aging for gerontology and geroscience. It shows high test-retest reliability, is associated with morbidity, disability, and mortality, and indicated faster aging in young adults with childhood adversity. DunedinPACE effect-sizes are similar to GrimAge Clock effect-sizes. In analysis of incident morbidity, disability, and mortality, DunedinPACE and added incremental prediction beyond GrimAge.

Citation for the original paper describing `DunedinPACE()` in more detail is provided below:

- Belsky DW, Caspi A, Corcoran DL, Sugden K, Poulton R, Arseneault L, Baccarelli A, Chamarti K, Gao X, Hannon E, et al. 2022. DunedinPACE, a DNA methylation biomarker of the pace of aging. Deelen J, editor. eLife. 11:e73420. doi:10.7554/eLife.73420.

Measuring Pace of Aging: Theory

Aging is characterized by a gradual and progressive decline in system integrity

The rate of aging can be inferred from the rate of decline in integrity across multiple organ systems

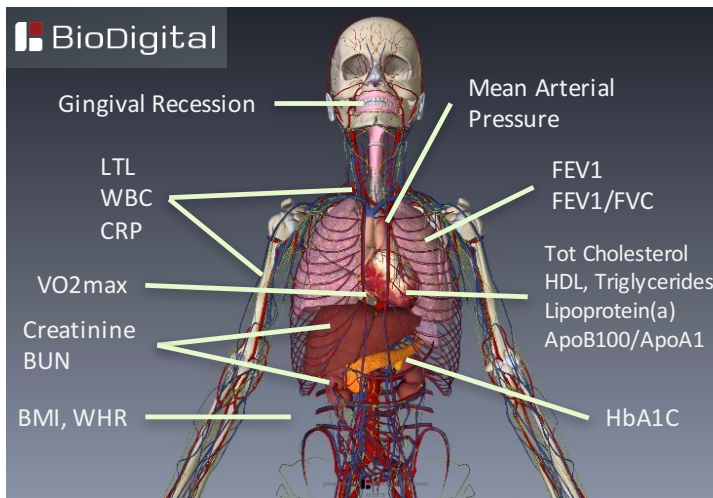
This decline should be observable already by young adulthood



Measuring Pace of Aging: Implementation

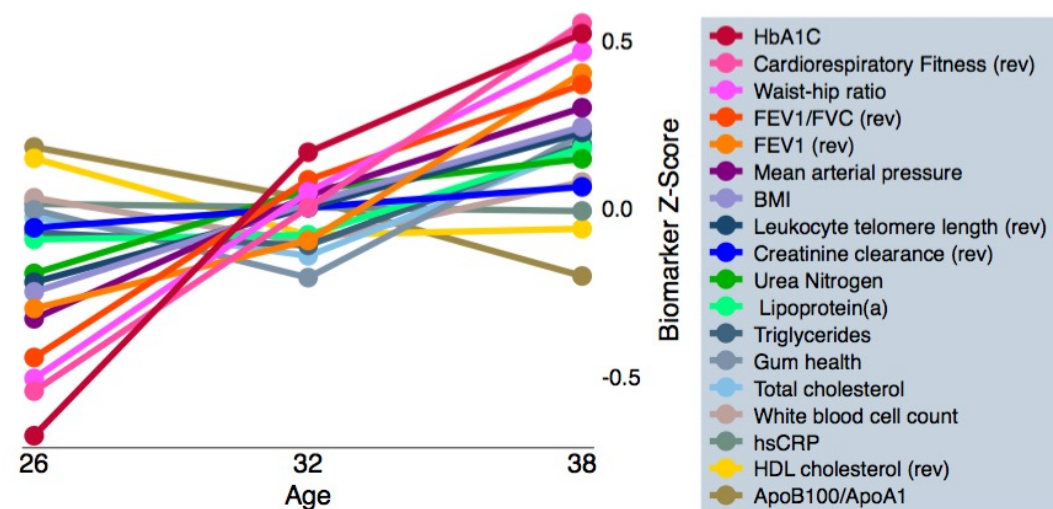
1

Measure 18 organ-system-integrity indicators at 3 time points



2

Model change over time: Do young, healthy bodies show signs of aging?



3

Build composite of slopes of change across 18 indicators: "The Pace of Aging"

