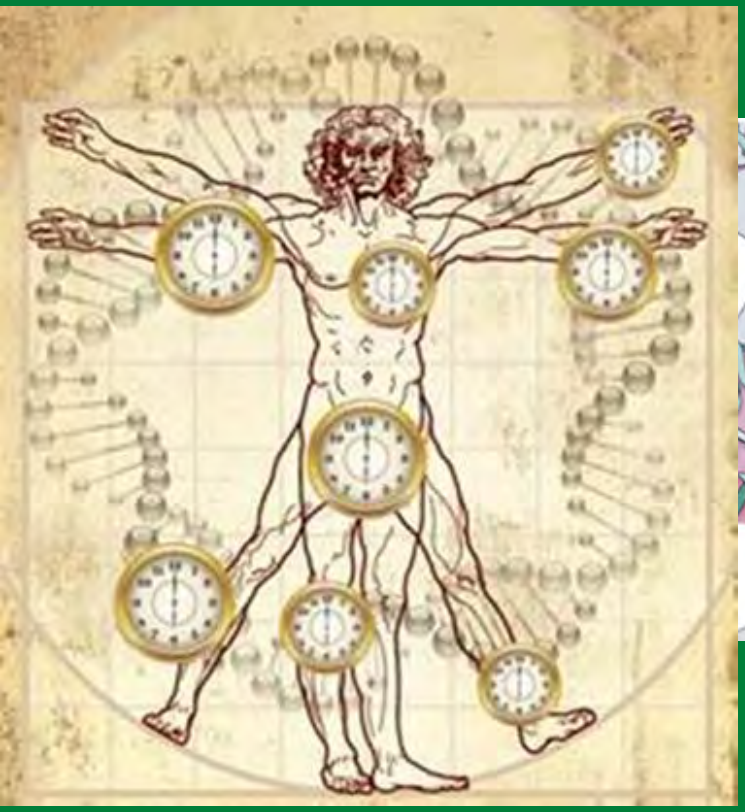
General Session I – Featured Presentation - Epigenetic Clock Studies of Centenarians

Epigenetic clocks

Steve Horvath

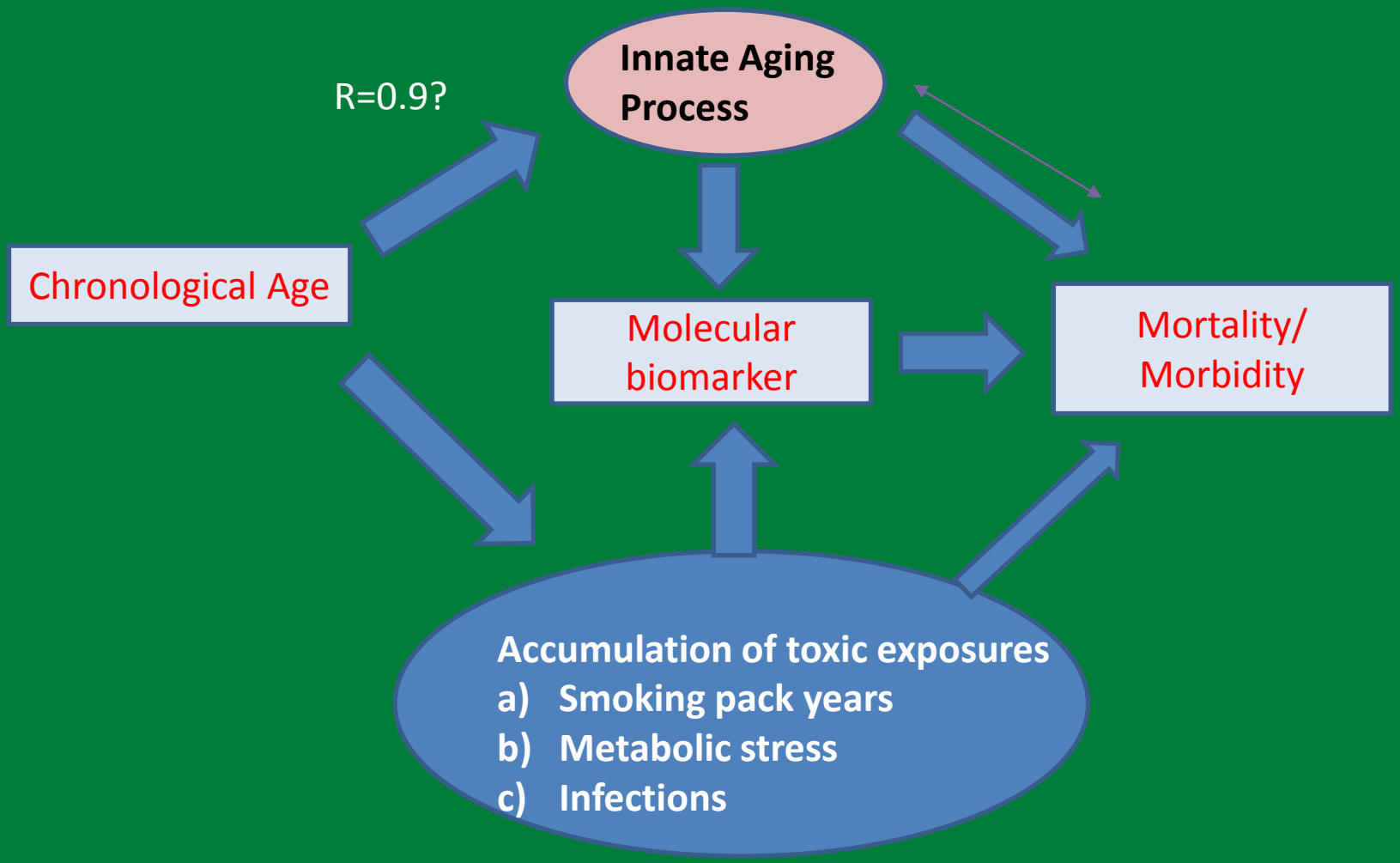


Disclosures: SAB of Life Biosciences, Intervene Immune, Patents

Fundamental questions

- **How do we measure aging?**
  - Epigenetic clocks and other biomarkers
- **Why do people age even if they follow the perfect lifestyle?**
  - Epigenetic changes and other hallmarks of aging
- **How do we measure the beneficial effects of an anti-aging strategy?**
  - Epigenetic clocks and other biomarkers
- **Why do some animals live long lives while others live short lives?**
  - Epigenetic changes explain 50% of the variation in maximum lifespan

Conceptual framework:
Molecular biomarkers relate to innate aging processes, confounders, and clinical phenotypes.

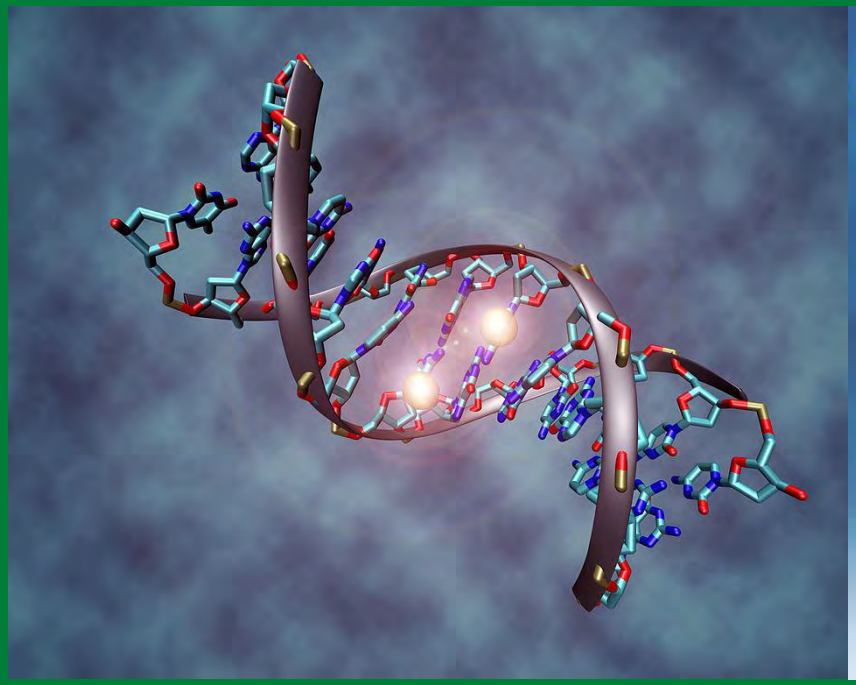


Basic introduction to epigenetic clocks

- Epigenetic changes= chemical modifications of the DNA molecule
- Epigenetic changes allow one to define
  - accurate measures of chronological age
  - Mortality risk estimators, predictors of lifespan
  - Measures of smoking history

Epigenetic aging effects are under genetic control (heritability of 40%) and reflect lifestyle/environmental stresses

DNA methylation: epigenetic modification of cytosine (CpG)



DNA molecule that is methylated at the two center cytosines.
DNA methylation plays an important role for epigenetic gene regulation in development and disease

DNA methylation measurement based on a chip/array

Ilumina methylation array

-measures about 860k locations (CpGs) in the genome

Each CpG specifies the amount of methylation that is present at this location.

- Number between 0 and 1

Methylation data

Rows=Cytosines (CpGs)

Columns: tissue samples from different people

Each entry lies between 0 and 1

Interpretation=proportion of chromosomes that are methylation at a location (CpG)

ProbeID	Person 1	Person 2	Person 3	Person 4	Person 5
cg00000292	0.931152	0.924445	0.825683	0.897291	0.917081
cg00002426	0.97761	0.953045	0.967067	0.94019	0.934625
cg00003994	0.015771	0.032869	0.033429	0.025322	0.018555
cg00004667	0.017812	0.028364	0.032527	0.045851	0.027674
cg00005847	0.076339	0.130129	0.077403	0.126975	0.08668
cg00006414	0.035001	0.025232	0.025502	0.030262	0.026784

Ordinary least squares regression

- y_i=Age, $\boldsymbol{x_i}$=vector of CpGs
- Find coefficient values $\boldsymbol{\beta}$ that minimize

$$argmin_{\beta} \sum_{i} (y_i - \boldsymbol{\beta}' \boldsymbol{x}_i)^2$$

- Problem: many more covariates (CpGs) than observations
- Solution: Penalized regression e.g. ridge regression or elastic net regression

Ridge regression penalizes the size of the regression coefficients based on their l^2 norm

$$argmin_{\beta} \sum_{i} (y_i - \boldsymbol{\beta}' \boldsymbol{x}_i)^2 + \lambda \sum_{k=1}^{K} \beta_k^2$$

- The tuning parameter serves λ to control the relative impact of these two terms on the regression coefficient estimates.
- cross-validation is used for selecting λ

Elastic Net penalize the size of the regression coefficients based on both their l^1 norm and their l^2 norm:

$$argmin_\beta \sum_i (y_i - \boldsymbol{\beta}' \boldsymbol{x}_i)^2 + \lambda_1 \sum_{k=1}^{K} |\beta_k| + \lambda_2 \sum_{k=1}^{K} \beta_k^2$$

- The l^1 norm penalty generates a sparse model.
- The l^2 norm penalty:
  - Removes the limitation on the number of selected variables.
  - Encourages variable group selection: automatically include whole groups of predictors into the model if one predictor amongst them is selected.

Construction of the human pan tissue epigenetic clock

- Combined publicly available individual data sets measured on the Illumina 27K or Illumina 450K array platform.
- Training+test data involved n=7844 non-cancer samples
  - 82 individual data sets
  - 51 different tissues and cell types
- Elastic net regression of Age (dependent variable) on roughly 21k CpGs
  - It automatically selected 353 CpGs

Pan tissue epigenetic clock

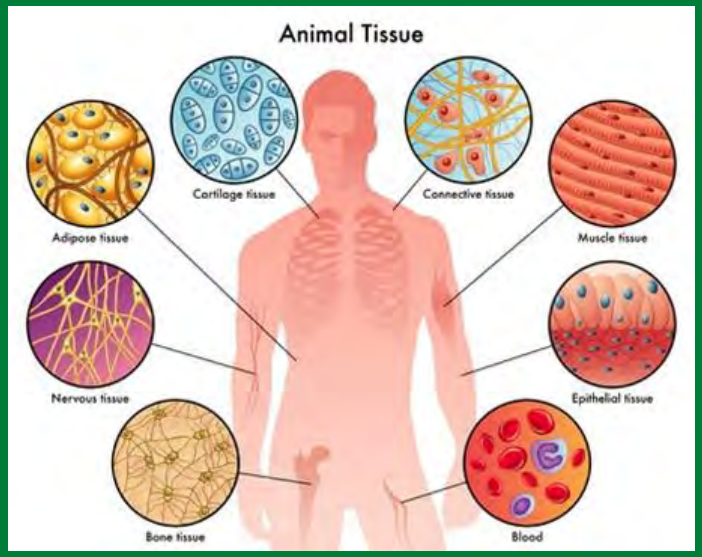
- Step 1: Measure the DNA methylation levels of 353 CpGs.
- Step 2: Form a weighted average
- Step 3: Transform the average so it is in units of “years”

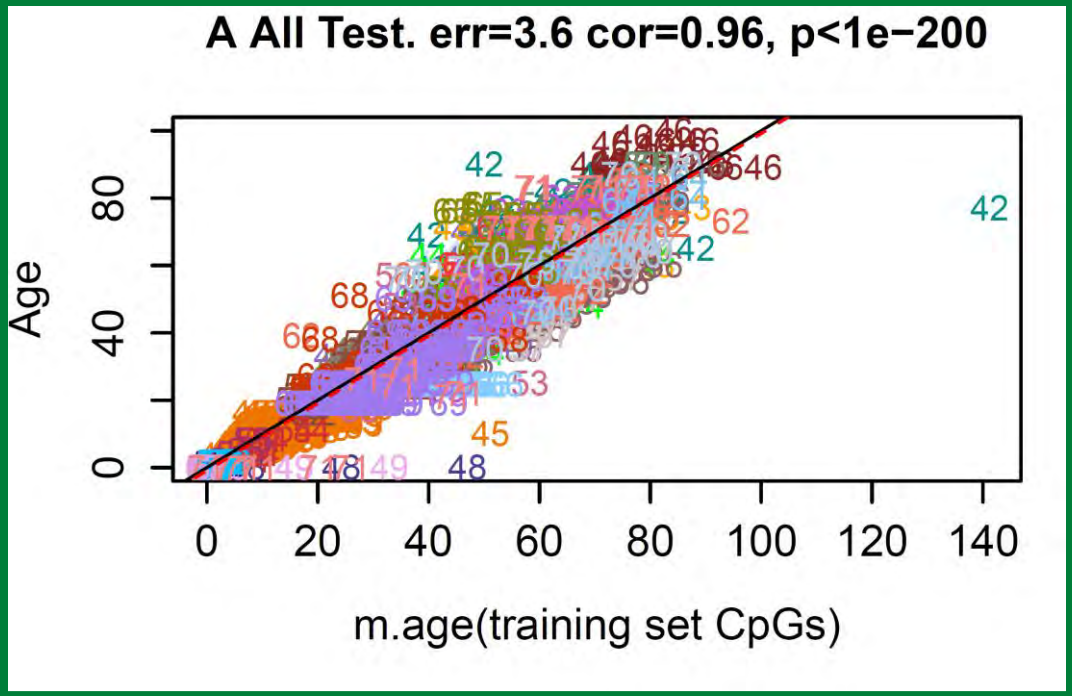
Result: age estimate (a number) that is known as “epigenetic age” or “DNA methylation age”

Comment: same definition for every tissue and cell type.

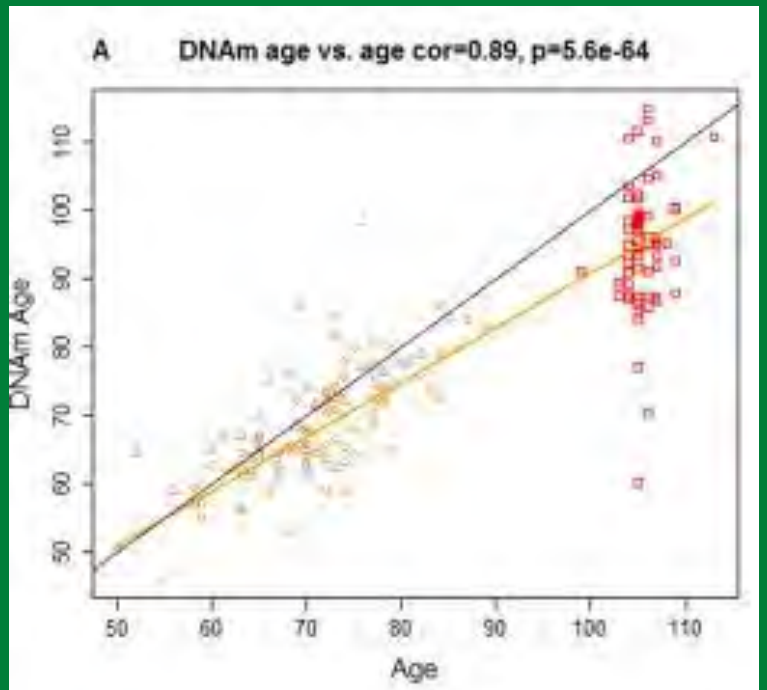
Horvath 2013

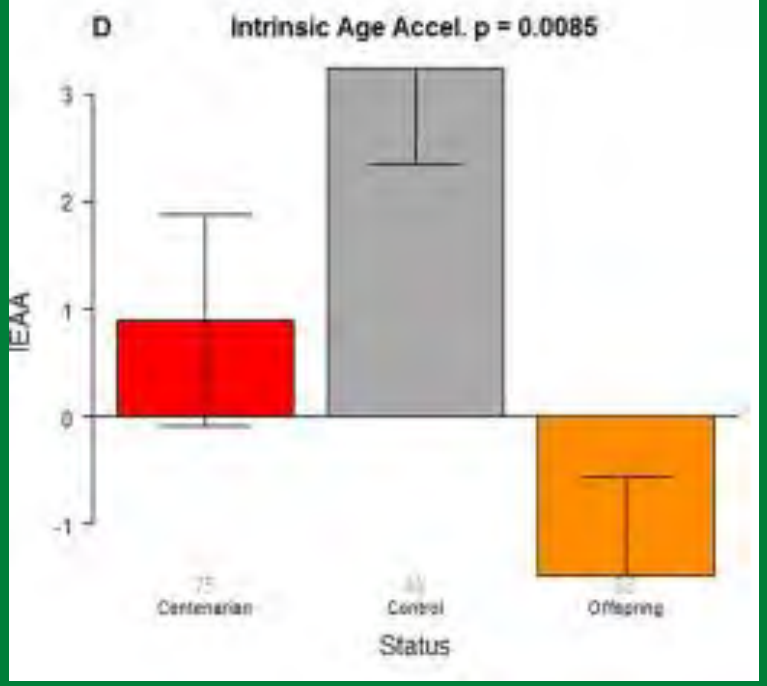
The human pan-tissue DNAm age estimator is the most accurate molecular biomarker of age across tissues. Hence the name “epigenetic clock”.

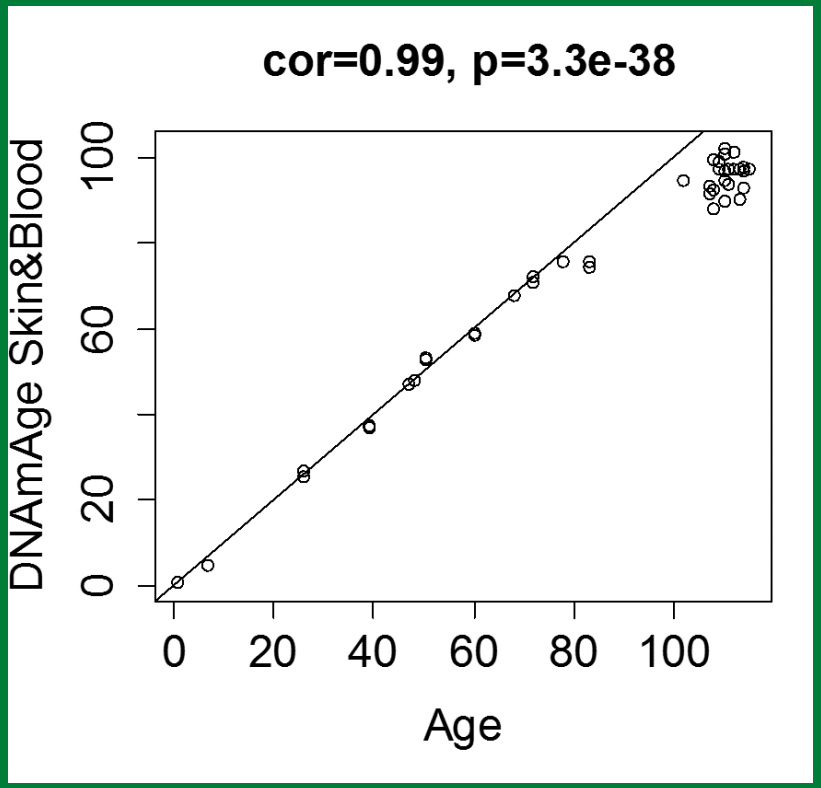




Analysis of centenarians and their offspring







www.impactaging.com AGING, May 2015, Vol. 7, No 5

Research Paper

The cerebellum ages slowly according to the epigenetic clock

Steve Horvath[1,2], Vei Mah[3], Ake T. Lu[1], Jennifer S. Woo[3], Oi-Wa Choi[4], Anna J. Jasinska[4], José A. Riancho[5], Spencer Tung[3], Natalie S. Coles[6], Jonathan Braun[3], Harry V. Vinters[3], and L. Stephen Coles[6,*]

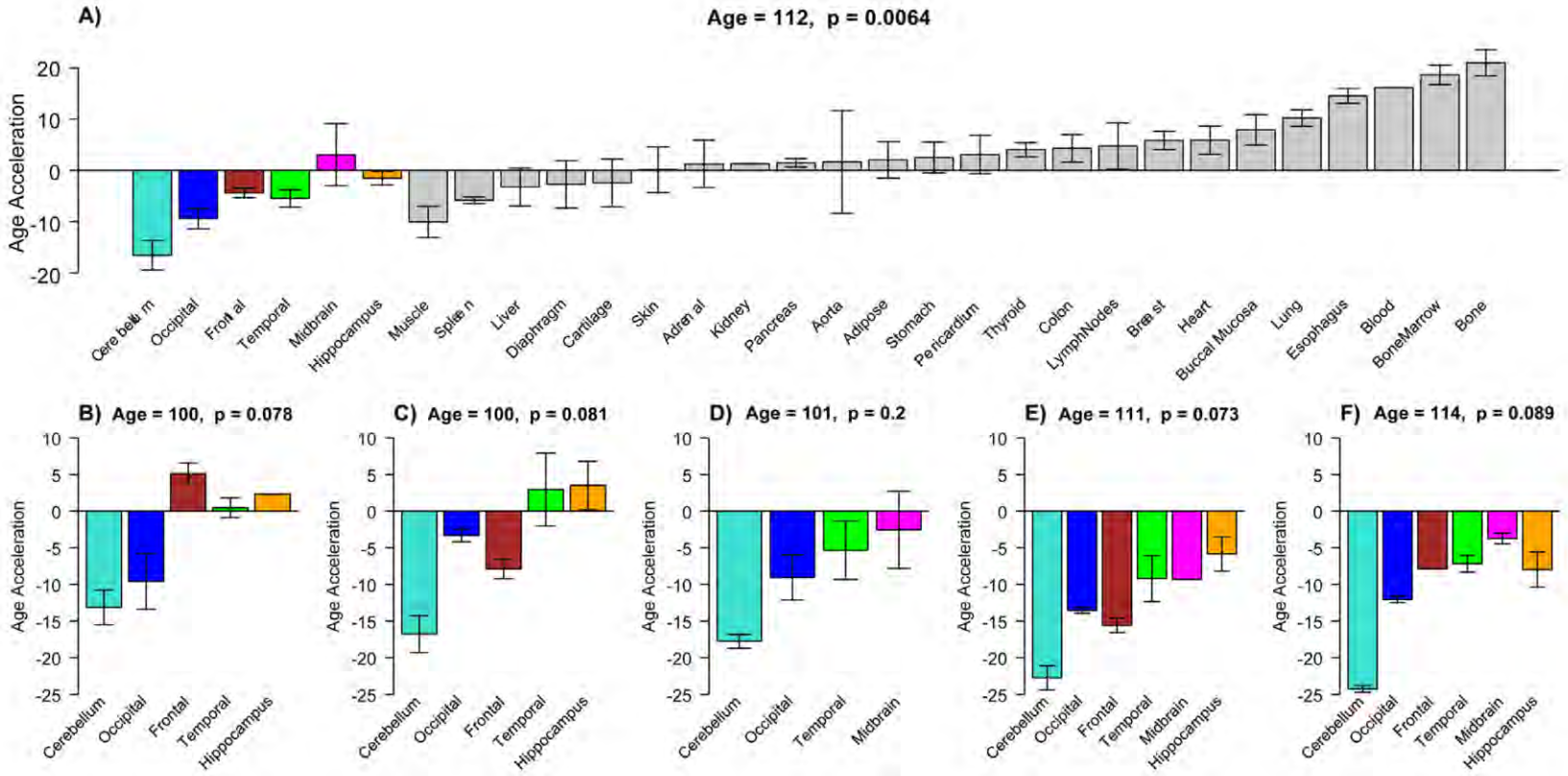
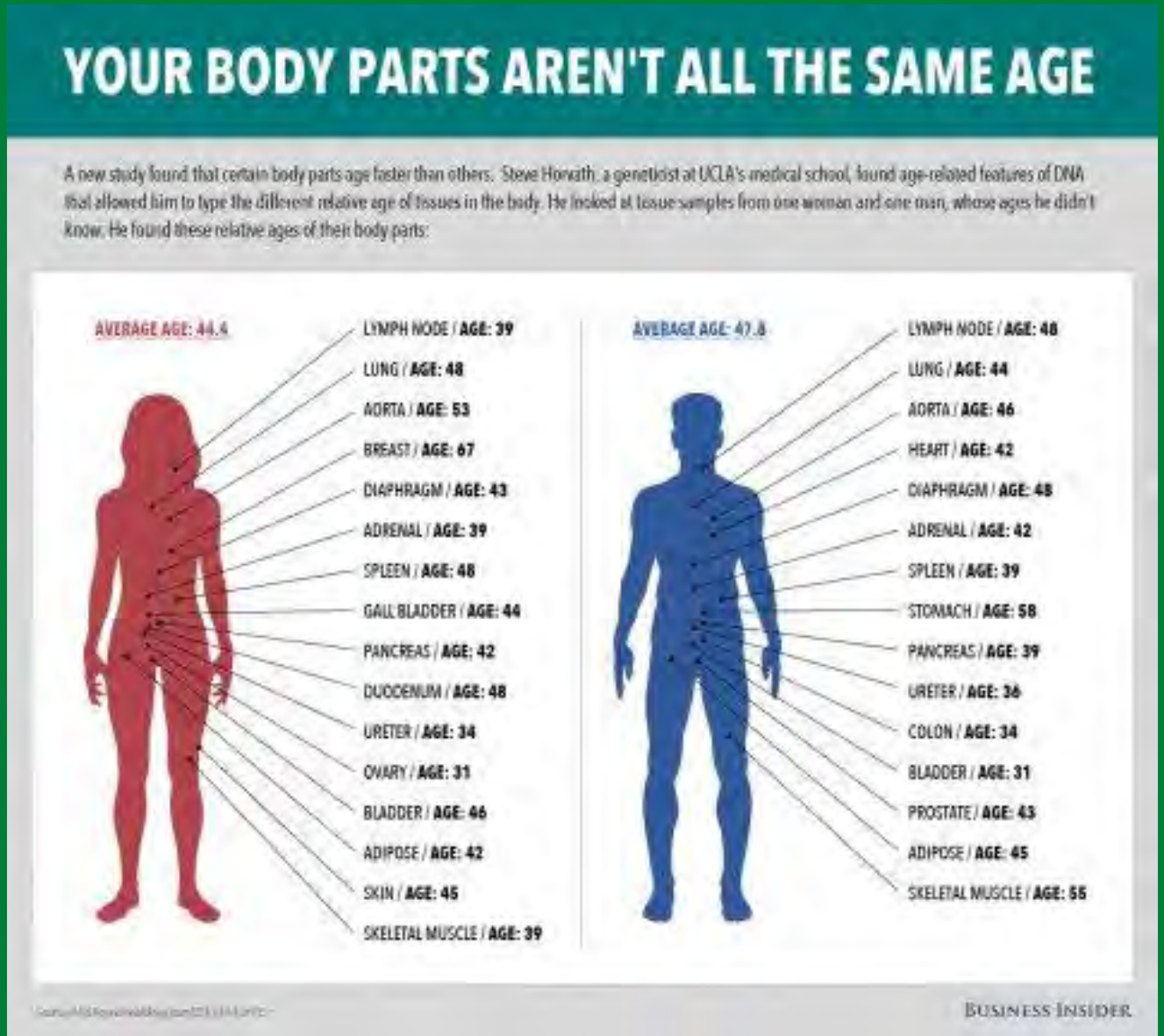


Figure 3. Epigenetic age acceleration in tissues from individual centenarians. (a) Mean DNAm age

Using the clock for measuring the age of different parts of the body

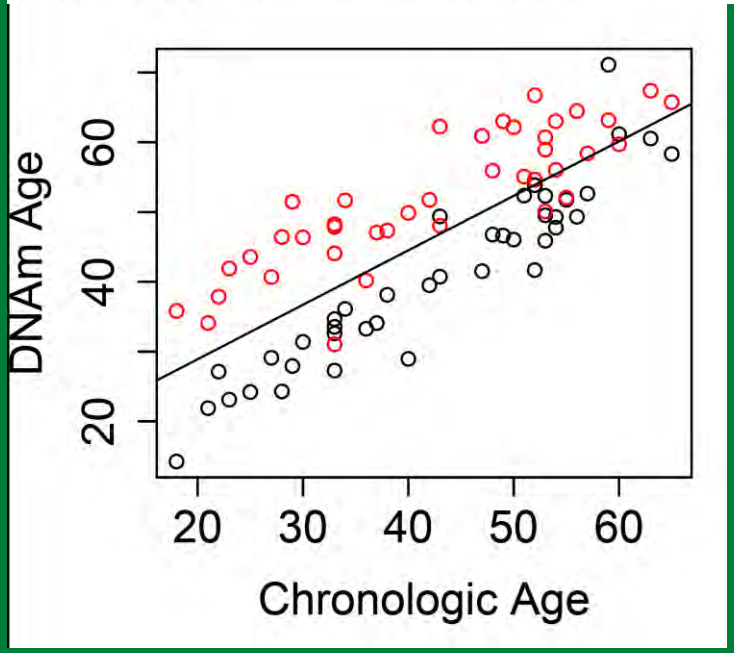


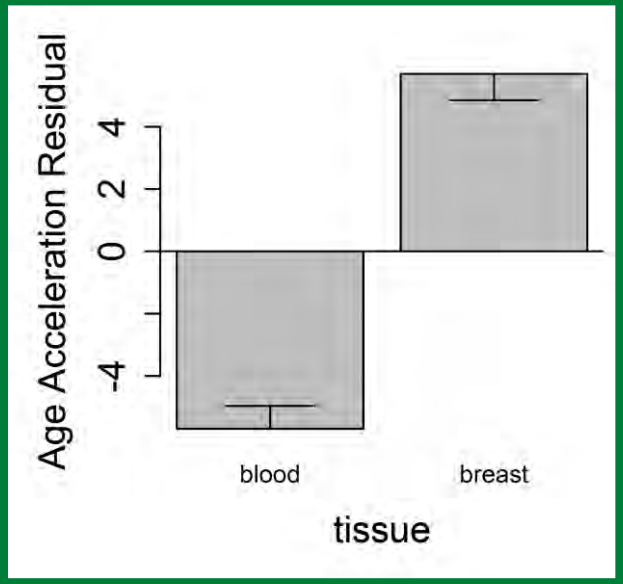
Breast Cancer Res Treat
DOI 10.1007/s10549-017-4218-4

BRIEF REPORT

DNA methylation age is elevated in breast tissue of healthy women

Mary E. Sehl[1,2] · Jill E. Henry[3] · Anna Maria Storniolo[3] · Patricia A. Ganz[1,4] · Steve Horvath[5,6]

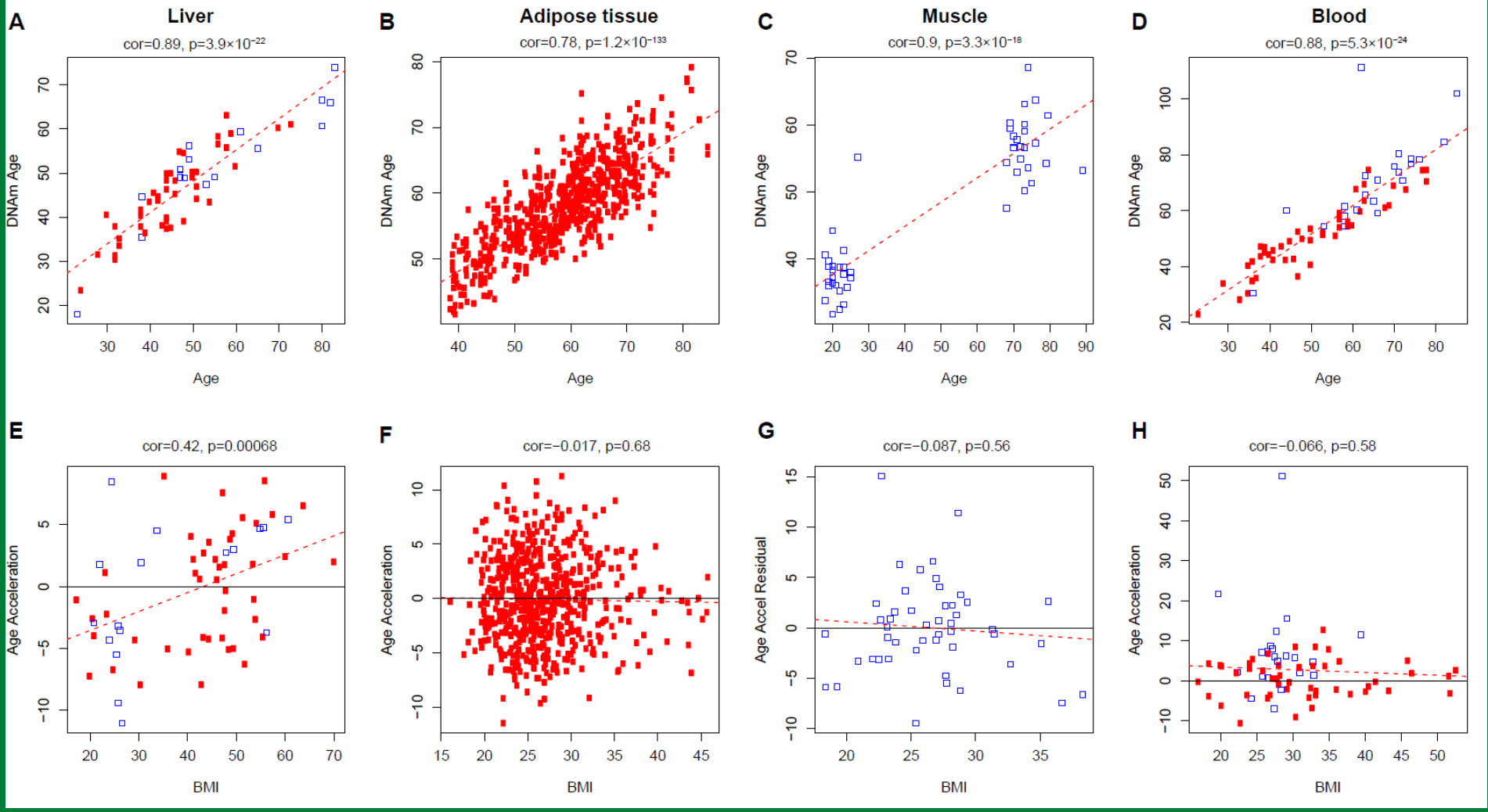




Red=breast
Black=blood collected at the same time

Obesity accelerates epigenetic aging of human liver

Steve Horvath[a,b,1], Wiebke Erhart[c], Mario Brosch[d], Ole Ammerpohl[e], Witigo von Schönfels[f], Markus Ahrens[f], Nils Heits[f], Jordana T. Bell[g], Pei-Chien Tsai[g], Tim D. Spector[g], Panos Deloukas[h,i,j], Reiner Siebert[e], Bence Sipos[k], Thomas Becker[f], Christoph Röcken[l], Clemens Schafmayer[f,2], and Jochen Hampe[d,2]



Epigenetic clocks judged by the criteria for biomarkers of aging

- It must predict a person's physiological, cognitive, and physical function in an age-related way. In other words, it must predict the future onset of age-related conditions and diseases, and do so independently of chronological age.

Marioni et al. Genome Biology (2015) 16:25
DOI 10.1186/s13059-015-0584-6

Genome Biology

RESEARCH Open Access

DNA methylation age of blood predicts all-cause mortality in later life

Riccardo E Marioni[1,2,3†], Sonia Shah[3,4†], Allan F McRae[3,4†], Brian H Chen[5,6†], Elena Colicino[7†], Sarah E Harris[1,2], Jude Gibson[8], Anjali K Henders[9], Paul Redmond[10], Simon R Cox[1,10], Alison Pattie[10], Janie Corley[10], Lee Murphy[8], Nicholas G Martin[9], Grant W Montgomery[9], Andrew P Feinberg[11,12], M Daniele Fallin[11,13], Michael L Multhaup[11], Andrew E Jaffe[13,14], Roby Joehanes[5,15,16], Joel Schwartz[7,17], Allan C Just[7], Kathryn L Lunetta[5,18], Joanne M Murabito[5,19], John M Starr[1,20], Steve Horvath[21,22†], Andrea A Baccarelli[7,17†], Daniel Levy[5,6†], Peter M Visscher[1,3,4†], Naomi R Wray[3*†] and Ian J Deary[1,10*†]

www.aging-us.com AGING 2016, Vol. 8, Advance

Priority Research Paper

DNA methylation-based measures of biological age: meta-analysis predicting time to death

Brian H. Chen[1,2,3*], Riccardo E. Marioni[4,5,6*], Elena Colicino[7*], Marjolein J. Peters[8], Cavin K. Ward-Caviness[9], Pei-Chien Tsai[10], Nicholas S. Roetker[11], Allan C. Just[7], Ellen W. Demerath[11], Weihua Guan[12], Jan Bressler[13], Myriam Fornage[13,14], Stephanie Studenski[1], Amy R. Vandiver[15], Ann Zenobia Moore[1], Toshiko Tanaka[1], Douglas P. Kiel[16,17], Liming Liang[18,19], Pantel Vokonas[18], Joel Schwartz[18], Kathryn L. Lunetta[20,2], Joanne M. Murabito[2,21], Stefania Bandinelli[22], Dena G. Hernandez[23], David Melzer[24], Michael Nalls[23], Luke C. Pilling[24], Timothy R. Price[23], Andrew B. Singleton[23], Christian Gieger[9,25], Rolf Holle[26], Anja Kretschmer[9,25], Florian Kronenberg[27], Sonja Kunze[9,25], Jakob Linseisen[9], Christine Meisinger[9], Wolfgang Rathmann[28], Melanie Waldenberger[9,25], Peter M. Visscher[4,6,29], Sonia Shah[6,29], Naomi R. Wray[6], Allan F. McRae[6,29], G. Uitterlinden[8,30], Devin Absher[31], Themistocles ilip S. Tsao[32,34], Lifang Hou[35,36], JoAnn E. Manson[37], nder P. Reiner[40,41], Tim D. Spector[10], Andrew P. arelli[7,44*], Joyce van Meurs[8*], Jordana T. Bell[10*], nkow[11*], Luigi Ferrucci[1*], Steve Horvath[33,46*]

Aging Cell (2016) **15**, pp149–154

DNA methylation age is associated with mortality in a longitudinal Danish twin study

Lene Christiansen,[1] Adam Lenart,[2] Qihua Tan,[1,3] James W. Vaupel,[2,4] Abraham Aviv,[5] Matt McGue[1,6] and Kaare Christensen[1,3,7]

Due to the advent of array technologies, HumanMethylation27 and HumanMethylation methylation levels of CG dinucleotides (CpGs) new easily accessible markers. Such array based

RESEARCH Open Access

CrossMark

Epigenetic age acceleration predicts cancer, cardiovascular, and all-cause mortality in a German case cohort

Laura Perna[1*], Yan Zhang[1], Ute Mons[1], Bernd Holleczek[2], Kai-Uwe Saum[1] and Hermann Brenner[1,3]

Two types of mortality risk predictors

- One-step models: Regress time-to-death on CpGs directly
- Two-step models: Regress time-to-death on DNA methylation based biomarkers i.e. based on aggregated measures of CpGs
  - Example of aggregated measure: DNA methylation based estimator of smoking history

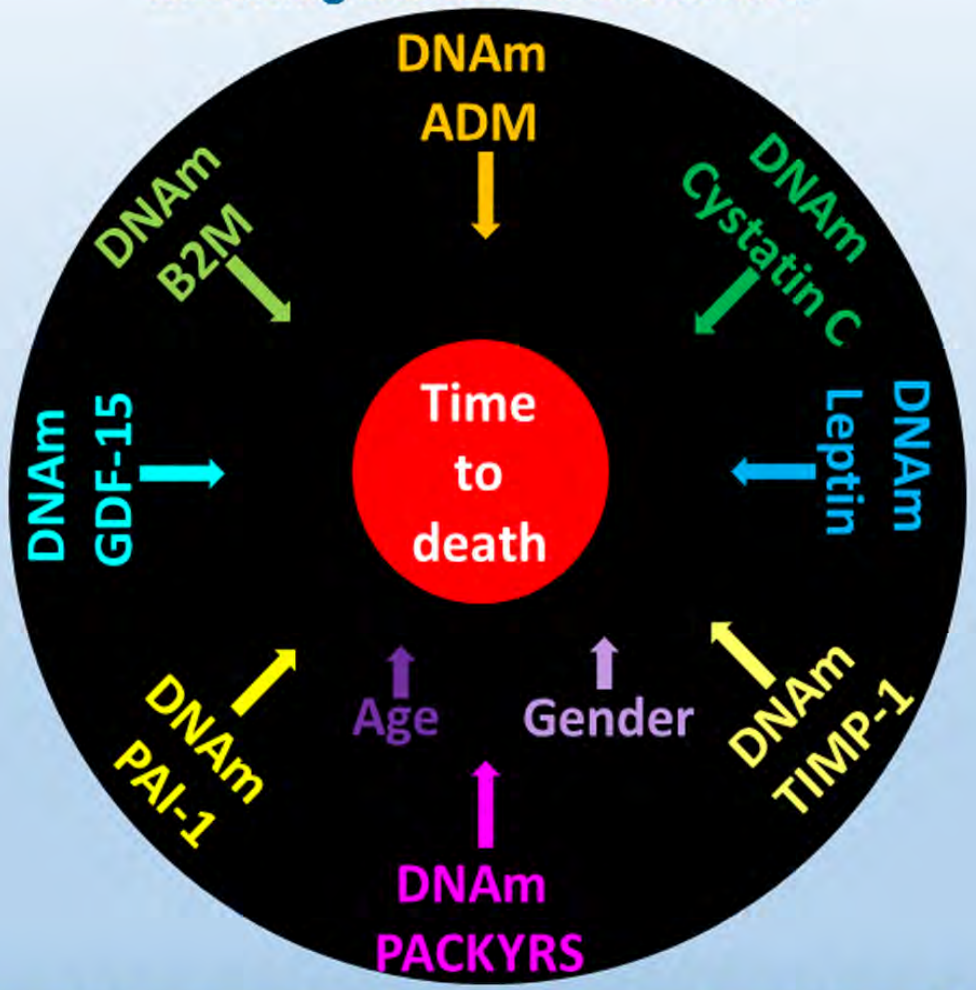
DNA methylation GrimAge strongly predicts lifespan and healthspan

(2019) Aging

Ake T. Lu, Austin Quach, James G. Wilson, Alex P. Reiner, Abraham Aviv, Kenneth Raj, Lifang Hou, Andrea A. Baccarelli, Yun Li, James D. Stewart, Eric A. Whitsel, Themistocles L. Assimes, Luigi Ferrucci, Steve Horvath

Stage 2: Regress time-to-death on DNAm based biomarkers (from step1) , age & gender

Resulting ElasticNet Cox model



DNAm GrimAge=$-50.28483 + 8.3268 * X^T\beta$

Cox regression model

- Mortality rate=number of new deaths per population at risk per unit time
- Cox regression models the effect of covariates on the mortality rate but leaves the baseline mortality rate unspecified
- **Hazard ratio=ratio of mortality rates**
- Estimates *relative* rather than *absolute* mortality risk

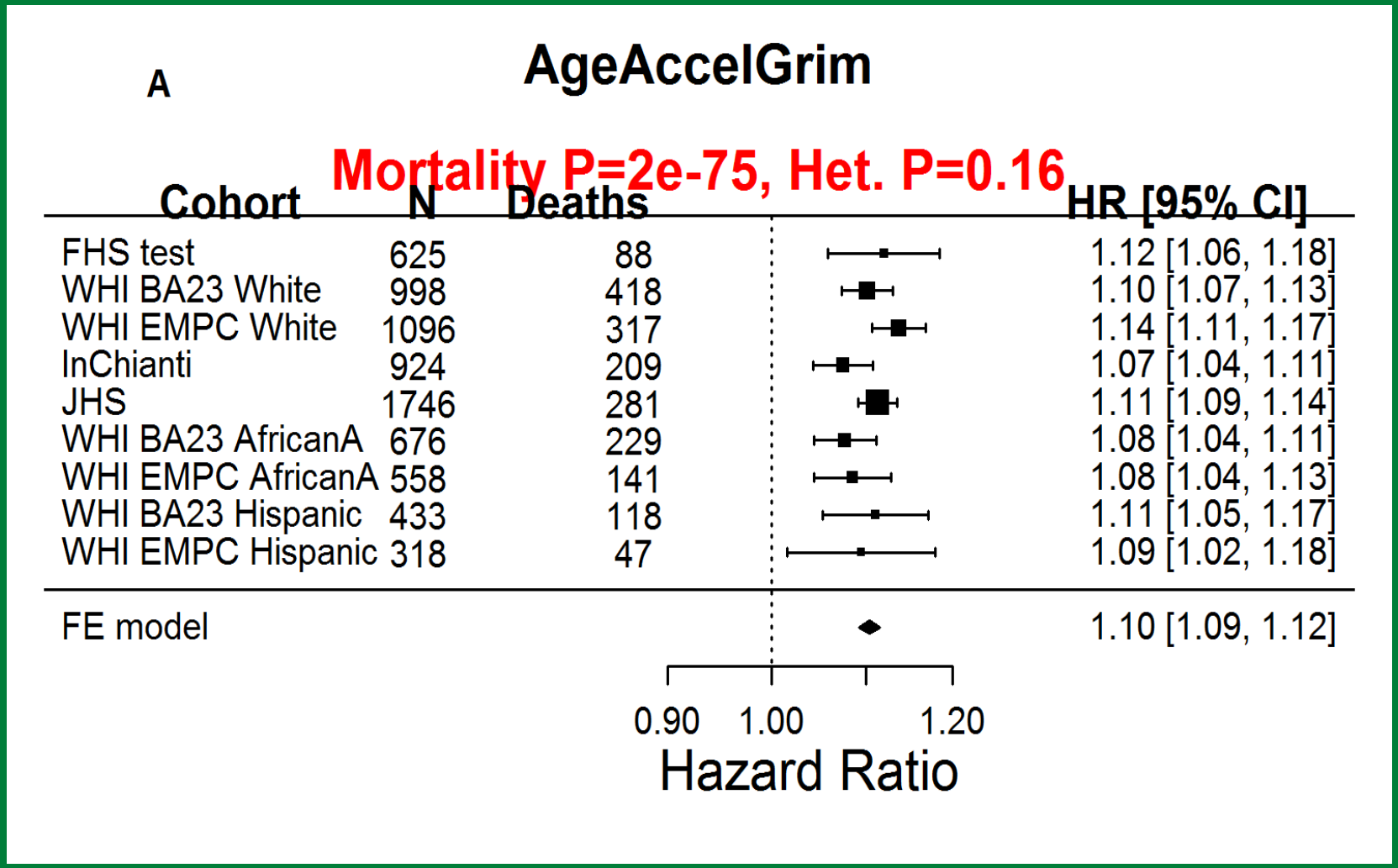
Interpreting the hazard ratio from a Cox regression model of GrimAge

Hazard Ratio=$e^{coefficient}$=1.10

– Interpretation: 10% increase in mortality rate for every 1 year increase in GrimAge

- Hazard Ratio=1.10^8=2.14 associated with an 8 year old increase in GrimAge

Meta analysis for the hazard ratio associated with all-cause mortality



Measures of age acceleration adjust DNAm age for Age and possibly Sex

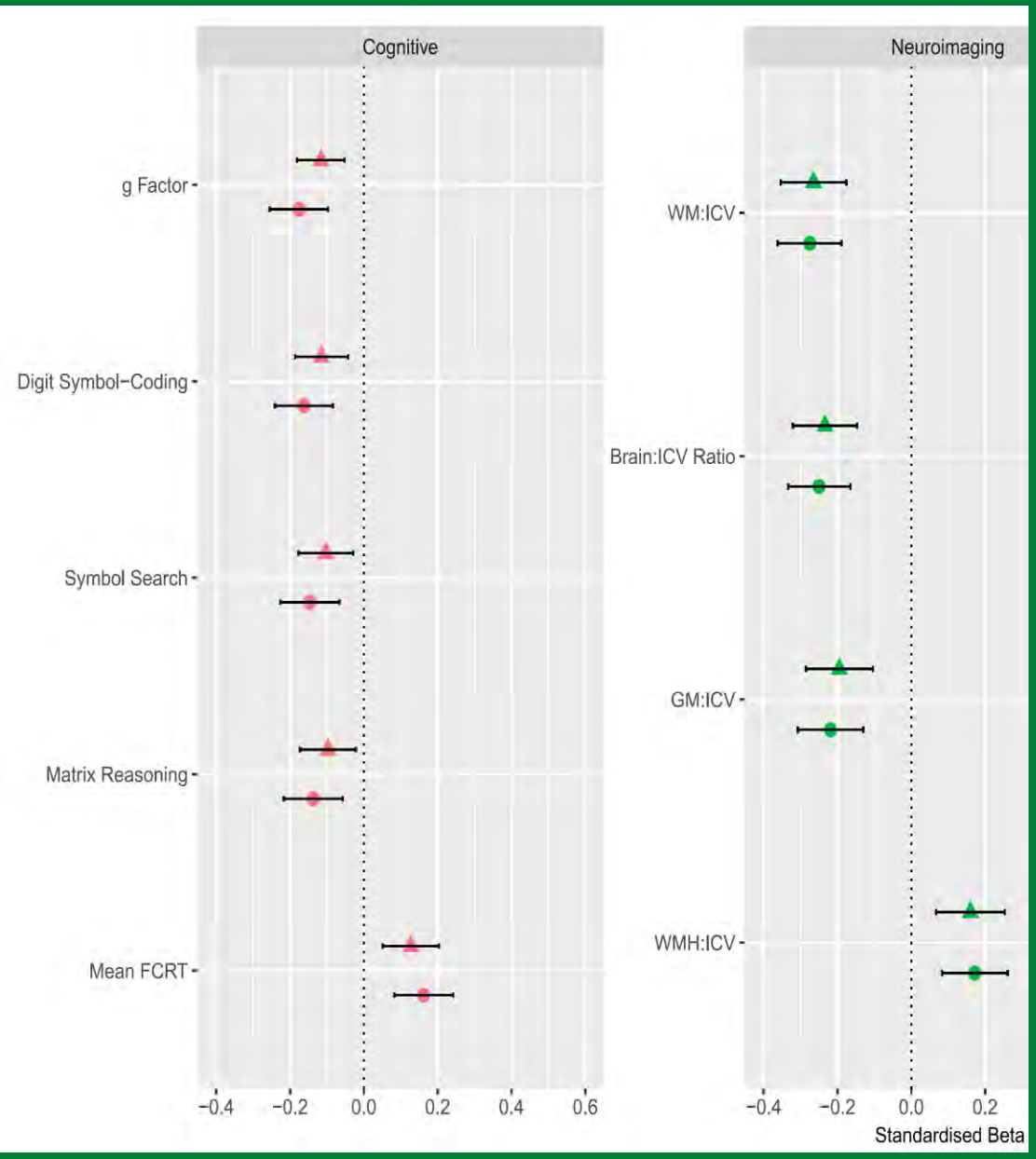
- Age=age at the time of the blood draw
- AgeAccelerationResidual=raw residual resulting from regressing DNAmAge on chronological age
- AgeAccel=residuals(lm(DNAmAge~Age))
- In case of GrimAge also include Sex
- AgeAccelGrim=residuals(lm(DNAmGrimAge~Age+Sex))

Healthy lifestyle is associated with lower AgeAccelGrim

		N	cor	P
Dietary biomarkers	Mean carotenoids	2266	-0.26	9E-39
	Lycopene	2267	-0.07	6E-4
	log2(alpha-Carotene)	2267	-0.28	4E-44
	log2(beta-Carotene)	2266	-0.22	5E-28
	log2(Lutein+Zeaxanthin)	2267	-0.14	9E-12
	log2(beta-Cryptoxanthin)	2267	-0.22	2E-26
	log2(alpha-Tocopherol)	2267	-0.06	3E-3
	log2(gamma-Tocopherol)	2267	0.14	2E-11
Measurements	log2(C-reactive protein)	2809	0.28	2E-52
	log2(Insulin)	4042	0.16	2E-26
	log2(Glucose)	4144	0.12	2E-14
	log2(Triglyceride)	4148	0.11	5E-13
	Total cholesterol	4148	0.01	0.65
	LDL cholesterol	4084	0.00	0.83
	HDL cholesterol	4145	-0.10	1E-10
	log2(Creatinine)	2748	0.03	0.07
	Systolic blood pressure	4177	0.07	9E-7
	Diastolic blood pressure	4178	-0.01	0.36
	BMI	4145	0.14	1E-20
	log2(Waist / hip ratio)	4037	0.19	4E-34
Life style	Education	4143	-0.09	2E-9
	Income	4054	-0.07	2E-6
	log2(1+Exercise)	3914	-0.10	3E-10
	Current smoker	2321	0.44	5E-113
	log2(1+Alcohol)	3700	-0.04	0.02

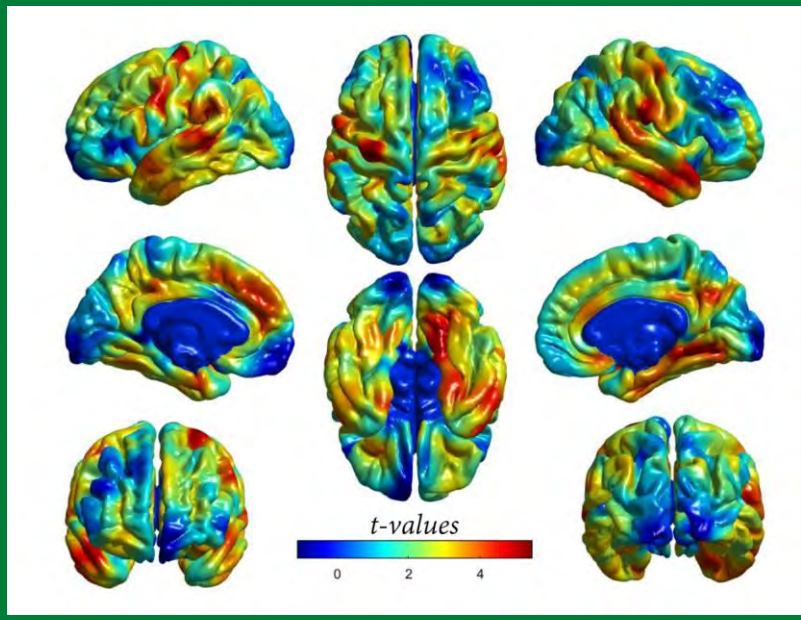
Computed tomography data of fat content in organs

			BMI		AgeAccelGrim		adj.DNAm ADM		adj.DNAm B2M		adj.DNAm Cystatin C		adj.DNAm GDF-15		adj.DNAm Leptin		adj.DNAm PAI-1	
		N	bicor	P	bicor	P	bicor	P	bicor	P	bicor	P	bicor	P	bicor	P	bicor	P
All	LIVER	1177	-0.55	1.0E-101	-0.24	1.8E-10	-0.21	1.2E-10	-0.06	3.3E-01	-0.11	9.6E-04	-0.12	2.2E-02	-0.28	1.1E-14	-0.41	2.9E-37
	SPLEEN	1055	-0.62	3.1E-157	-0.19	2.4E-09	-0.17	1.4E-09	-0.03	2.0E-01	-0.09	1.1E-03	-0.09	6.5E-03	-0.18	1.2E-04	-0.23	1.9E-15
	MUSCLE	1172	-0.34	7.3E-42	-0.18	6.6E-07	-0.14	1.6E-08	-0.07	2.2E-02	-0.11	3.2E-04	-0.10	1.0E-05	-0.13	1.4E-04	-0.19	4.4E-09
	SAT (CM^3)	1160	0.82	<1.0E-280	0.18	8.2E-10	0.21	5.9E-17	0.06	1.6E-03	0.11	7.1E-09	0.07	3.2E-02	0.29	1.0E-21	0.28	6.1E-25
	SAT	1160	-0.42	2.1E-49	-0.09	8.4E-03	-0.10	3.9E-02	-0.02	2.7E-01	-0.07	3.5E-03	-0.04	7.0E-01	-0.14	3.9E-04	-0.15	6.5E-08
	VAT (CM^3)	1171	0.69	3.0E-195	0.23	1.8E-12	0.21	7.5E-13	0.04	1.4E-01	0.13	5.2E-06	0.09	1.1E-03	0.30	1.8E-11	0.42	1.5E-41
	VAT	1171	-0.60	1.0E-126	-0.17	4.9E-08	-0.16	5.0E-08	-0.02	3.8E-01	-0.13	2.0E-05	-0.05	1.8E-01	-0.26	4.9E-09	-0.37	2.4E-34



DNAmGrimAge relates to cognitive and neuroimaging traits in the Lothian Birth Cohort 1936.

(Robert Hillary, R. Marioni 2019)



Discussion of DNAm GrimAge

- AgeAccelGrim stands out among pre-existing epigenetic clocks in terms of its predictive ability for
  - time-to-death,
  - time-to-coronary heart disease,
  - time-to-cancer,
  - early age at menopause.
- Surprising finding that DNAm pack-years outperforms self-reported pack-years in predicting lifespan
- DNAm PAI-1 stands out when it comes to associations with type 2 diabetes status, glucose-, insulin-, triglyceride levels, anthropometric measures of adiposity (body mass index and waist-to-hip ratio), and computed tomography data on fatty liver and excess adipose tissue.
- Our DNAm-based surrogate biomarkers of plasma protein levels may be leveraged by researchers who rely on bio-banked DNA samples without the availability of plasma samples.

Epigenetic clocks are useful for identifying and validating anti-aging targets

- Reality check: epigenetic clocks do not stand out in terms of lifespan prediction.
  - Many alternatives: blood pressure, smoking, frailty indices, lipid levels, glucose levels
  - But epigenetic clocks *enhance* standard lifespan predictors
- Advantage of epigenetic clocks
  - Clocks relate to at least one root cause of aging
  - proximal to an innate aging process
  - they can be applied to cells in a dish (in vitro studies)

What do epigenetic clocks teach us about anti-aging strategies?

Strategy:
Using a cocktail of drugs that were intended to regenerate the thymus

ORIGINAL ARTICLE

Aging Cell

Reversal of epigenetic aging and immunosenescent trends in humans

Gregory M. Fahy[1] | Robert T. Brooke[1] | James P. Watson[2] | Zinaida Good[3] | Shreyas S. Vasanawala[4] | Holden Maecker[5] | Michael D. Leipold[5] | David T. S. Lin[6] | Michael S. Kobor[6] | Steve Horvath[7]

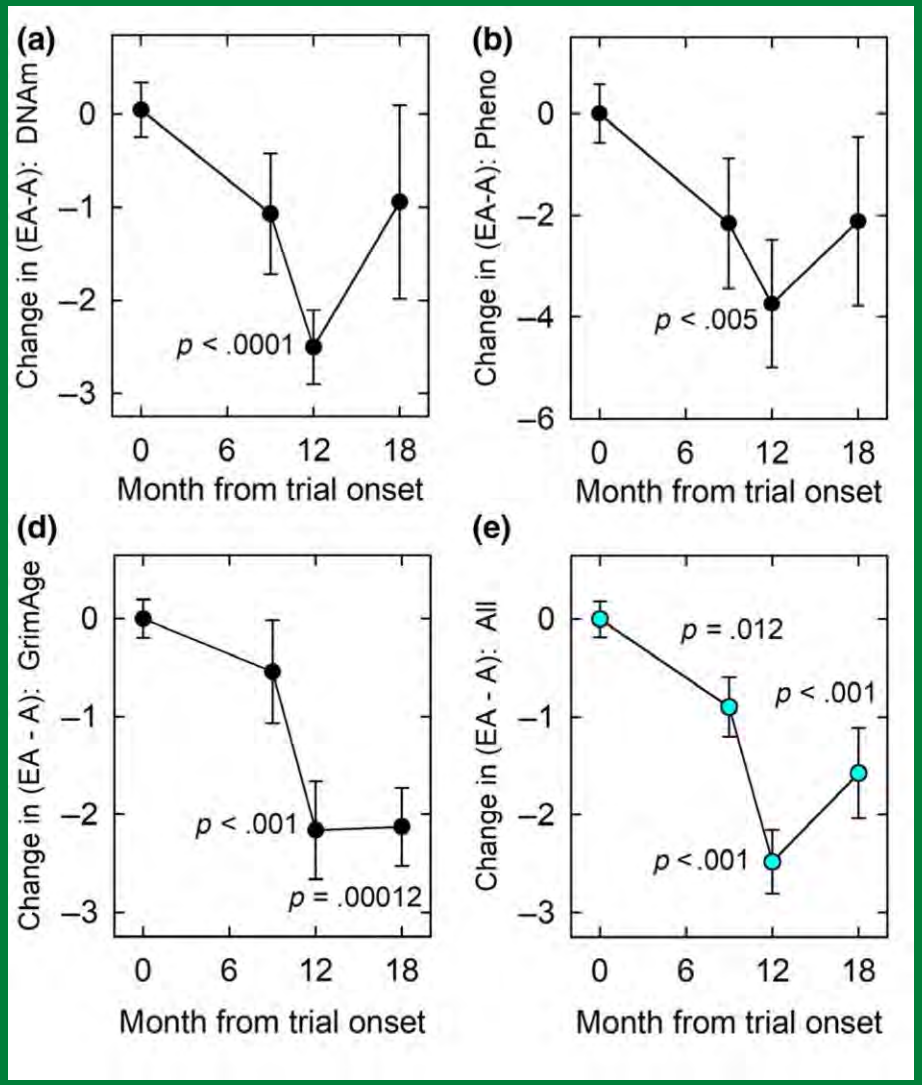
TRIIM treatment
by Greg Fahy and R. Brooke

- Original intention: regenerate the thymus
- Side effect: epigenetic rejuvenation

Cocktail of substances

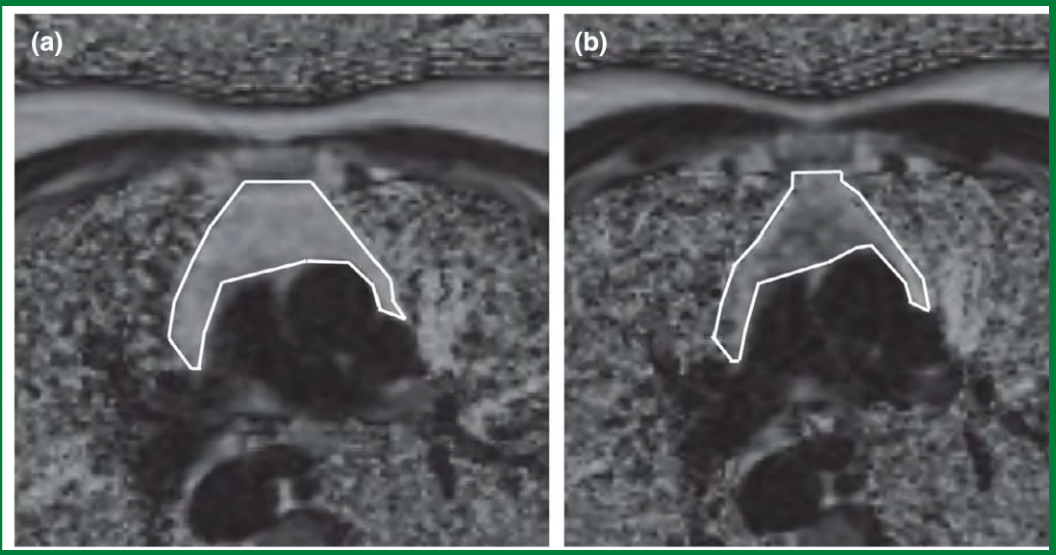
1. **growth hormone** (rhGH)
   - Purpose: regrow thymus
2. **DHEA** and **metformin**
   - Purpose: limit the “diabetogenic” effect of GH
3. Supplements: vitamin D and zinc
   - Purpose: protect bone, etc

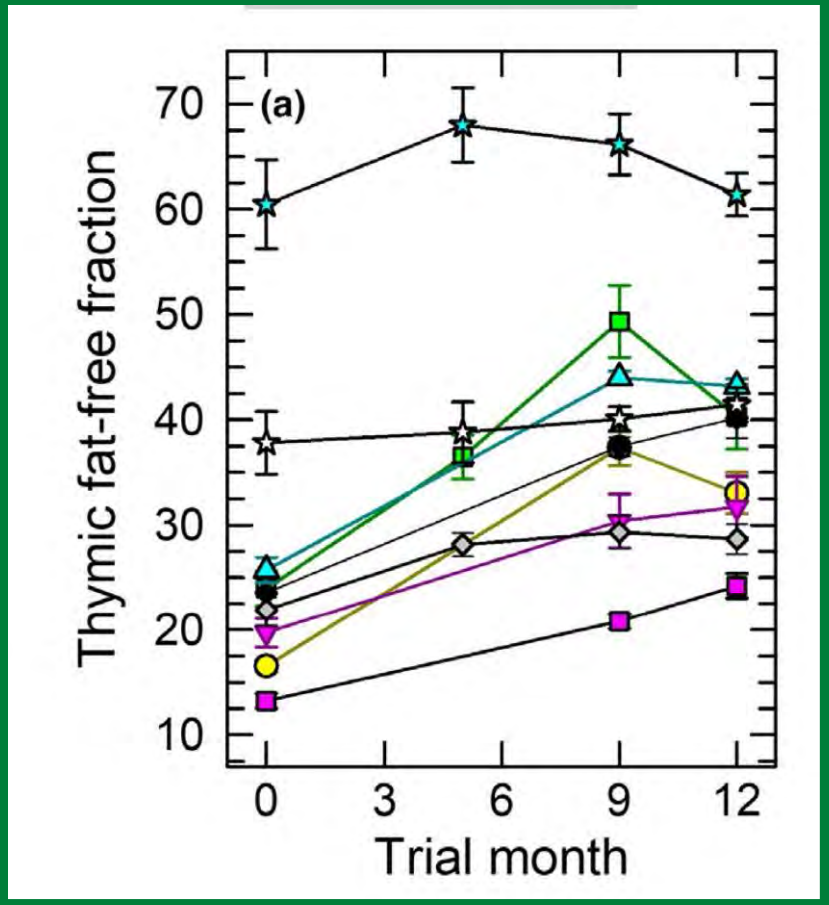
Treatment induced changes in epigenetic age (several epigenetic clocks)



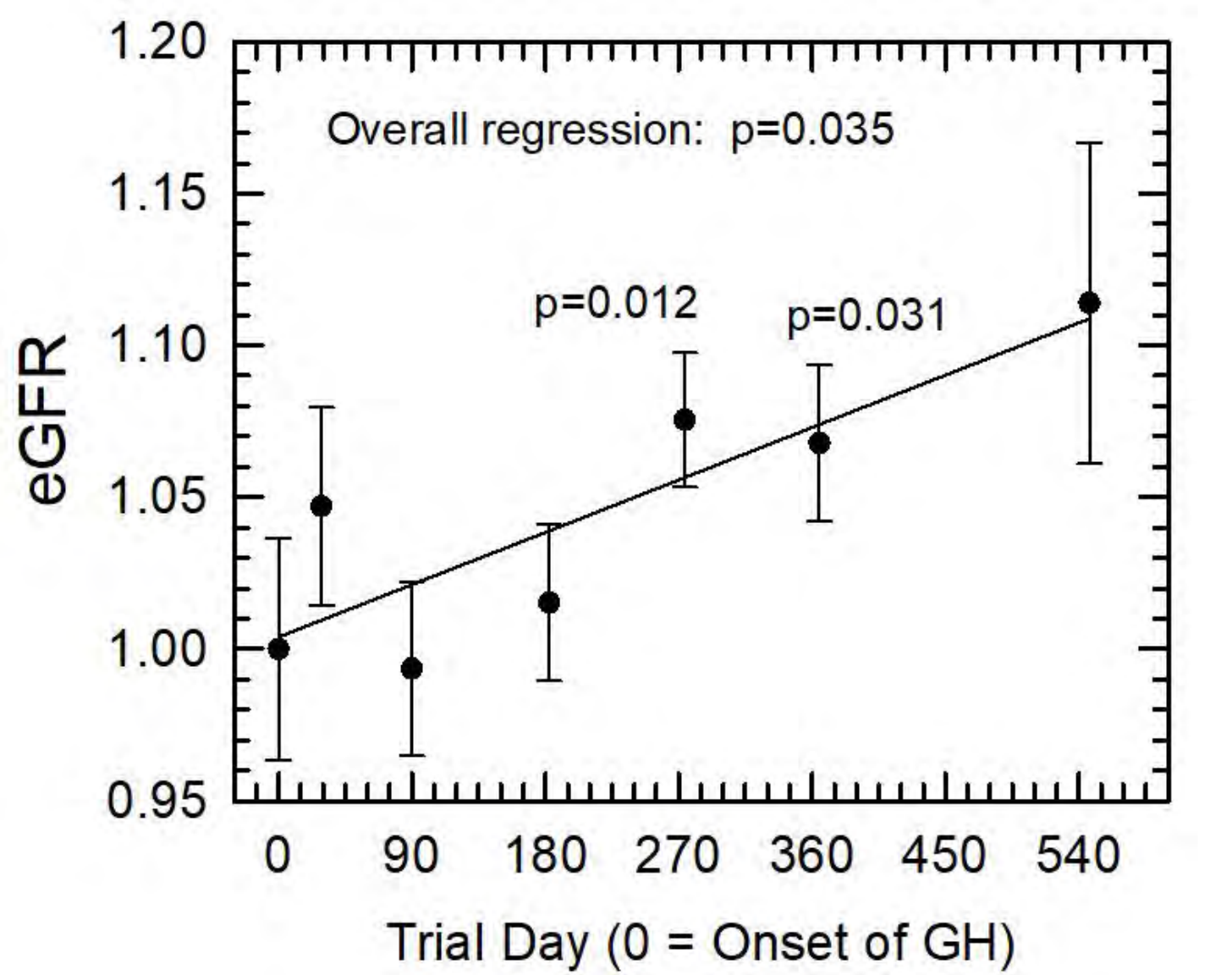
- Mean epigenetic age approximately 1.5 years less than baseline after 1 year of treatment
- GrimAge showed a 2-year decrease in epigenetic vs. chronological age that persisted six months after discontinuing treatment.
- These effects are probably independent of changes in blood composition

Treatment induced changes in thymic MRI

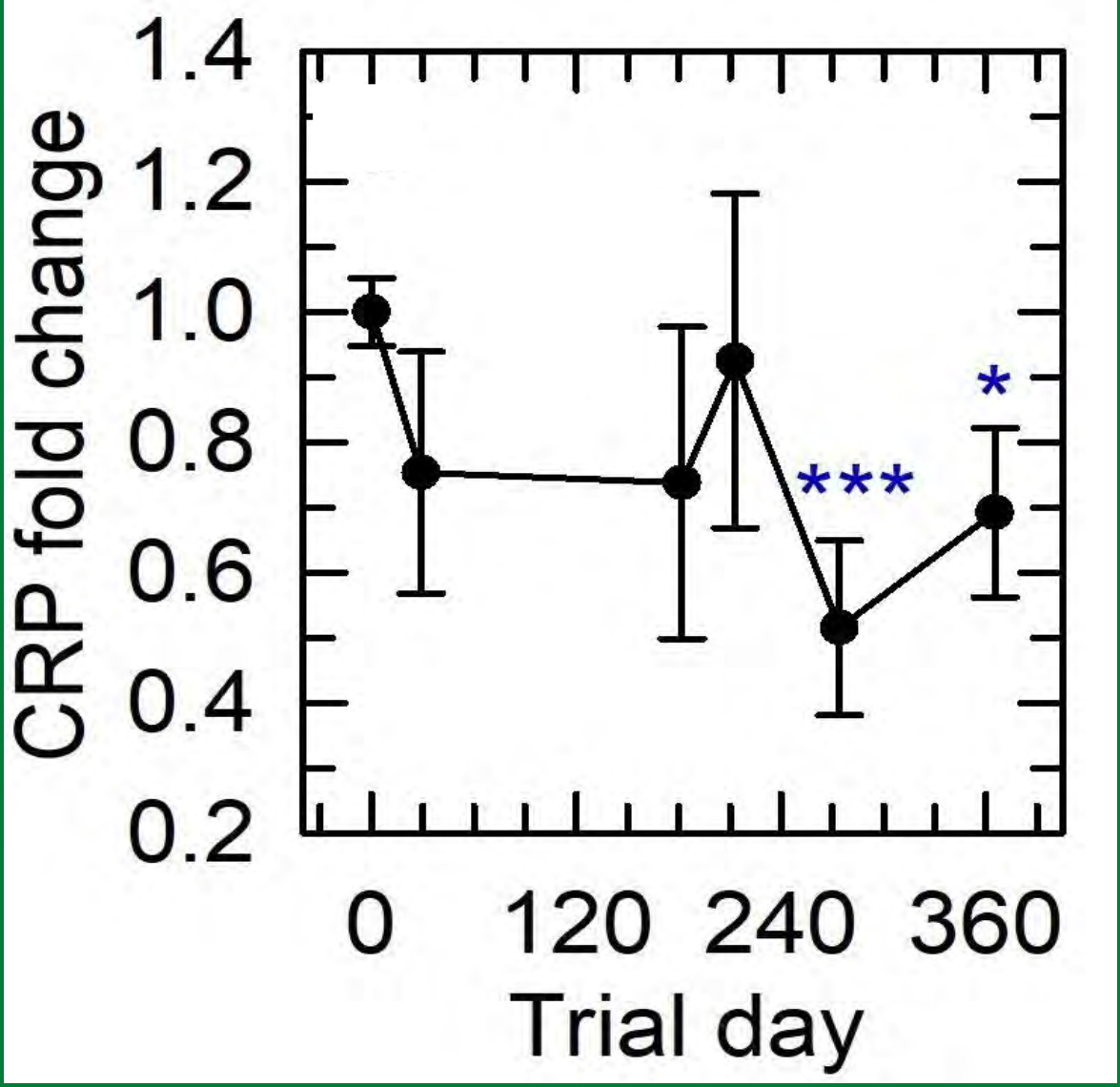




Improved Kidney Function



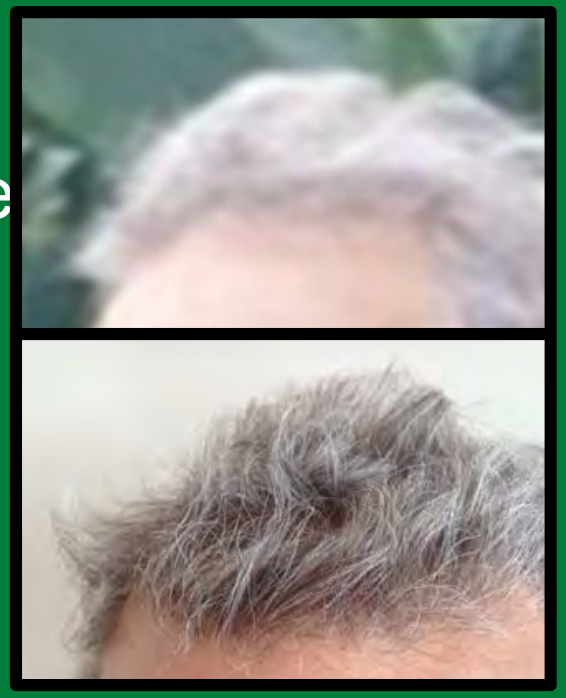
C-reactive protein was reversed “Inflammaging”

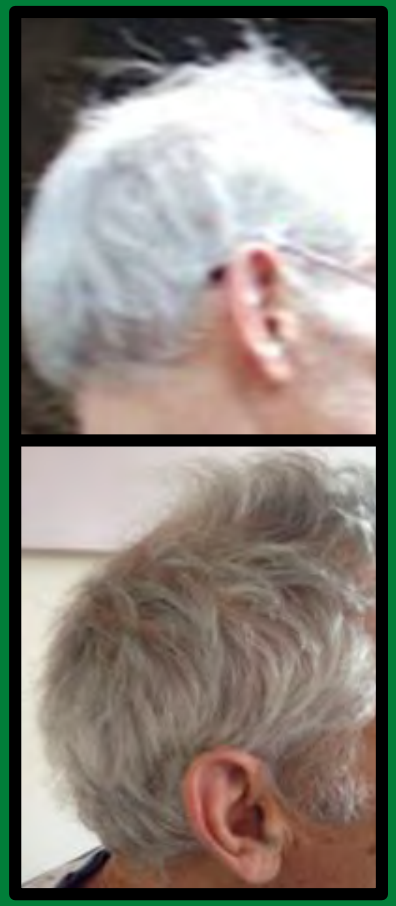


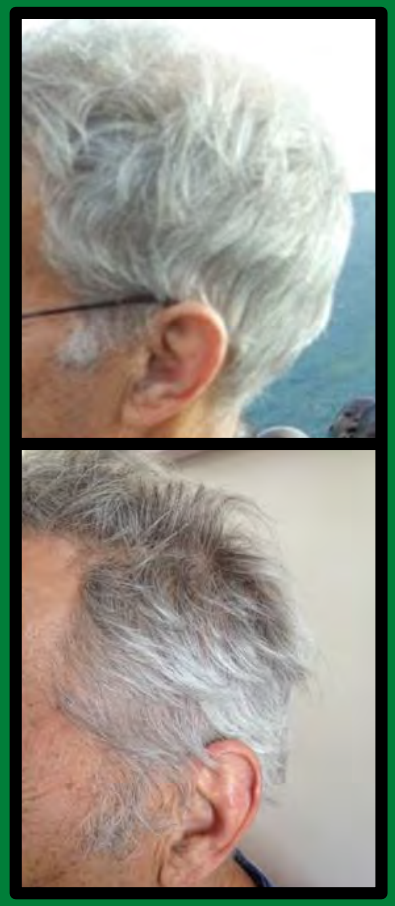
Another Sign: Hair Rejuvenation?

Before

After







Discussion of TRIIM results

- Cons:
  - Limited sample size: n=9 individuals
  - No placebo arm (phase 1 trial)
- Pros
  - Deep phenotyping: Methylation, Blood counts, MRI
  - All biomarkers indicate rejuvenation
  - Human treatment that can be applied NOW.
  - Rejuvenation effect is very strong (detectable in 9 people)
  - 5 blood draws per person. 2 blood draws before treatment.
  - Persistent rejuvenation of DNAm GrimAge which tracks multiple organ dysfunction and is the best epigenetic predictor of lifespan/healthspan

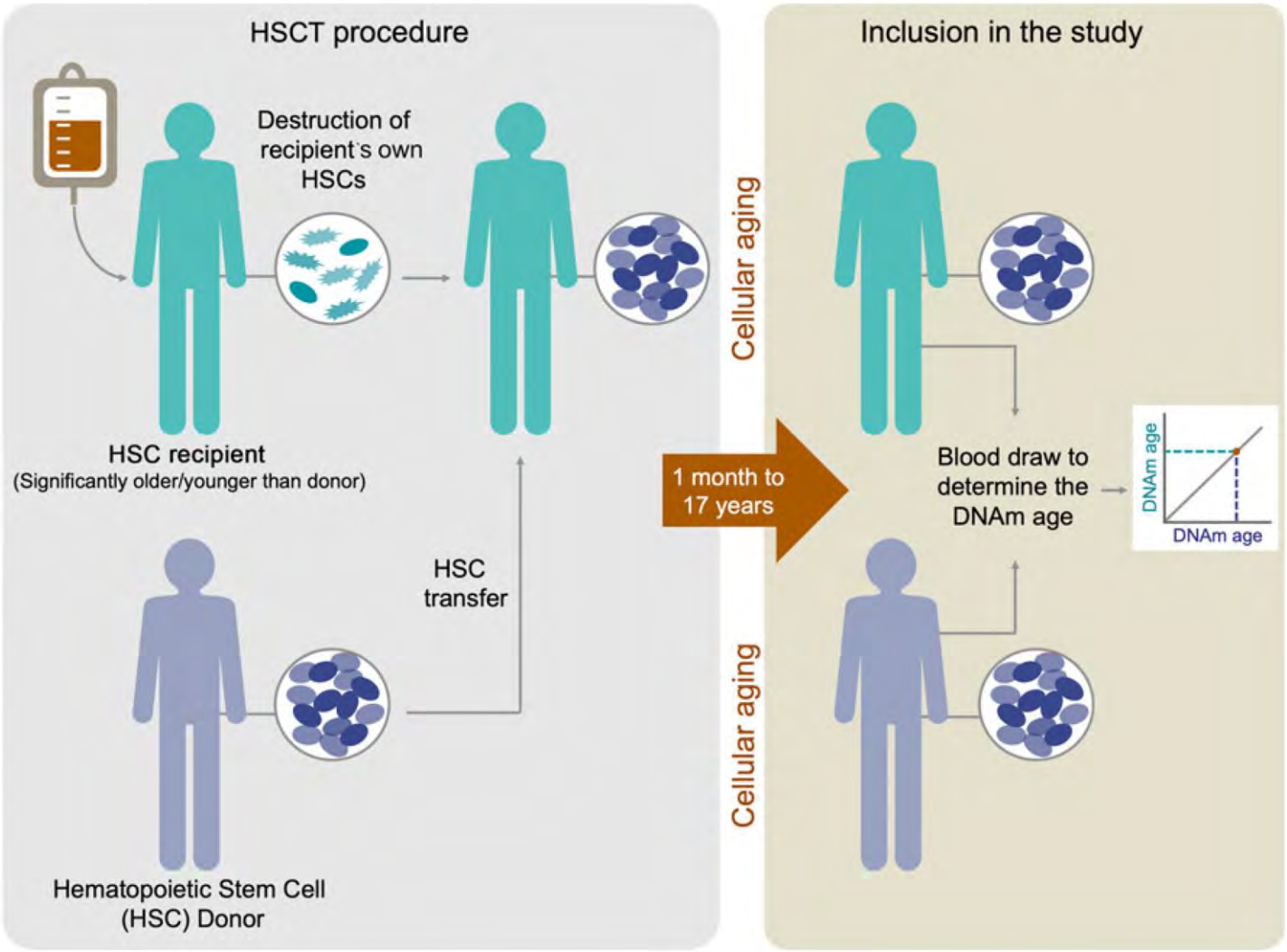
Strategy: Rejuvenation by hematopoietic stem cell transplantation

ORIGINAL PAPER

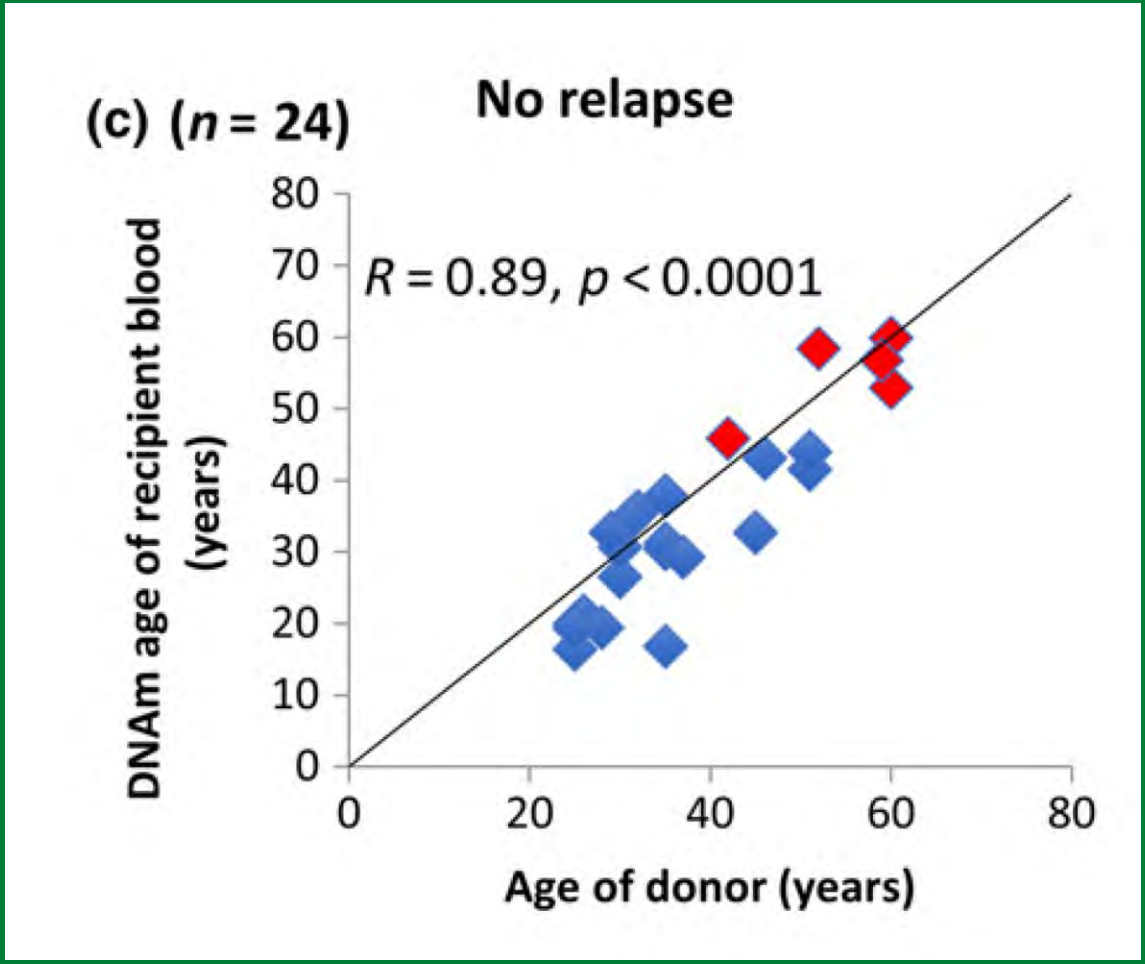
WILEY Aging Cell

Epigenetic age is a cell-intrinsic property in transplanted human hematopoietic cells

Arne Søraas[1*] | Mieko Matsuyama[2*] | Marcos de Lima[2,3] | David Wald[4] | Søraas[8] | Brian Chen[9] | | Shigemi Matsuyama[2,12]

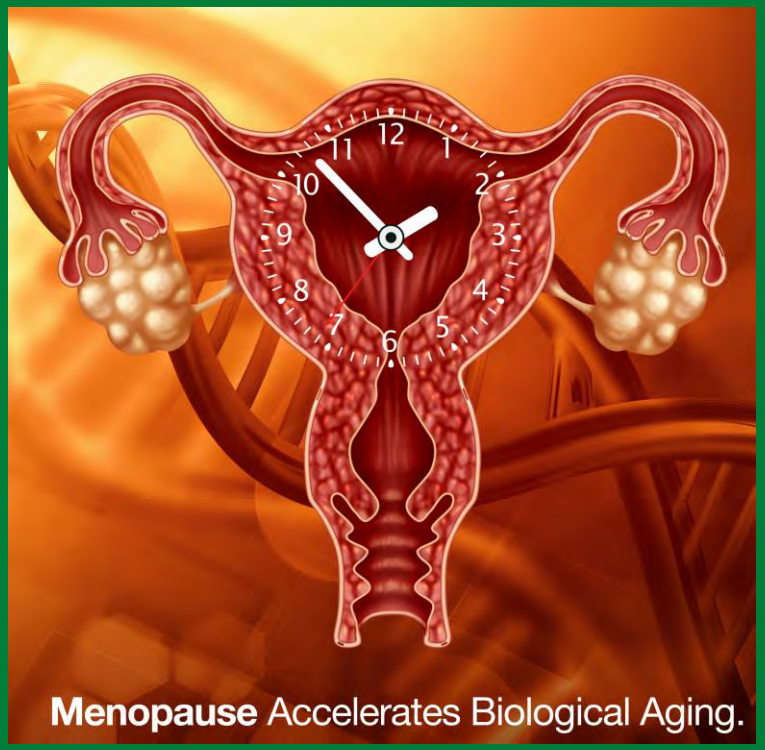


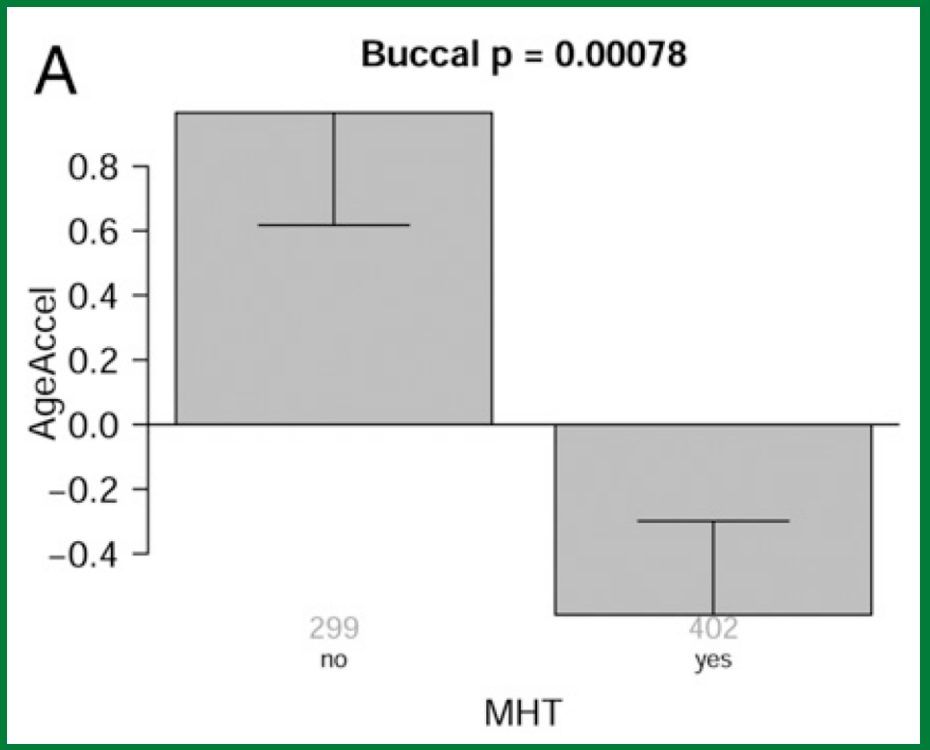
Age of the reconstituted blood in the recipient equals the age of the donor even after long followup



Strategy: Slow aging using hormone treatments

Menopausal hormone therapy keeps buccal cells young but not blood cells.

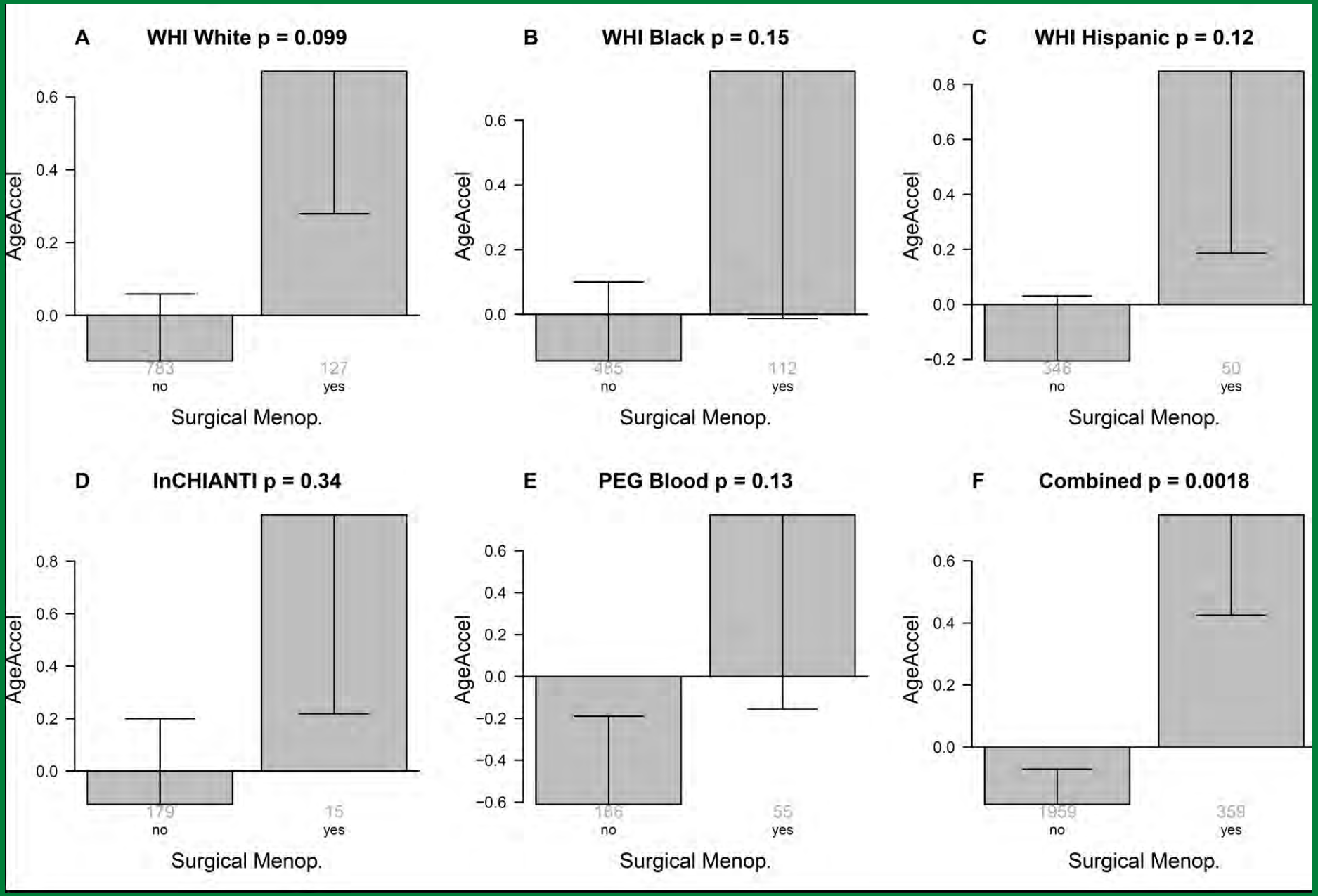




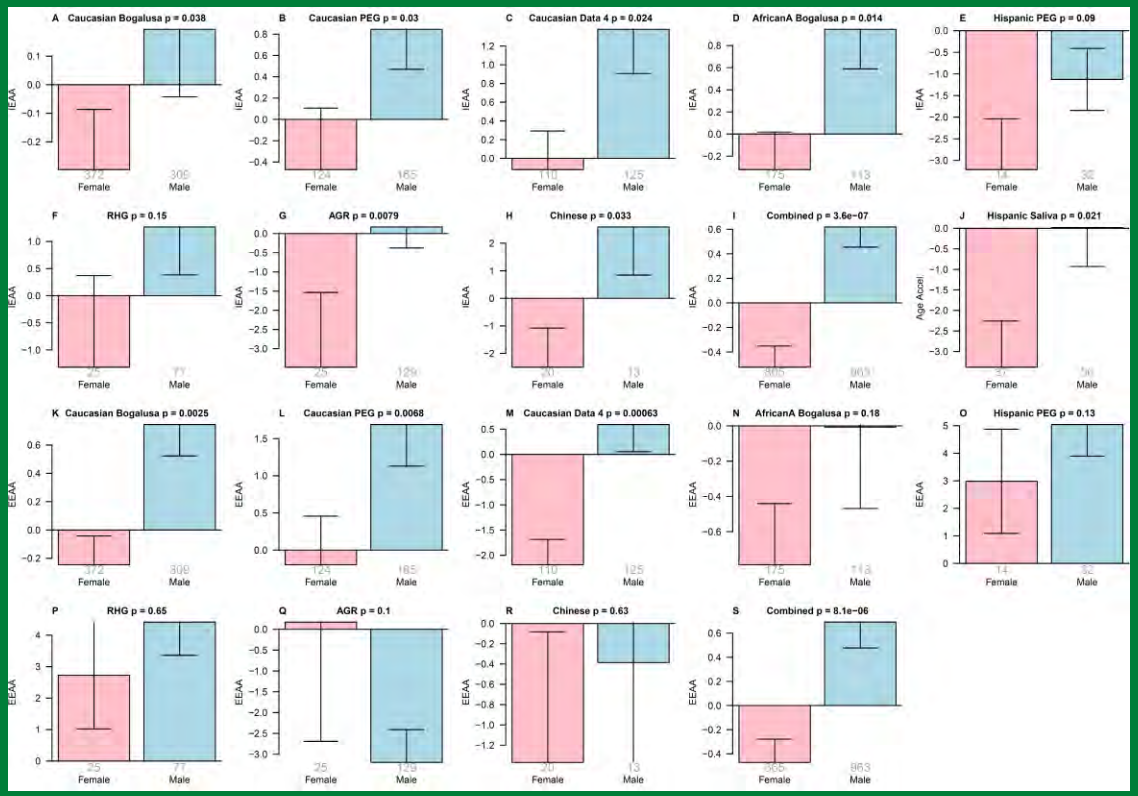
Menopause accelerates biological aging

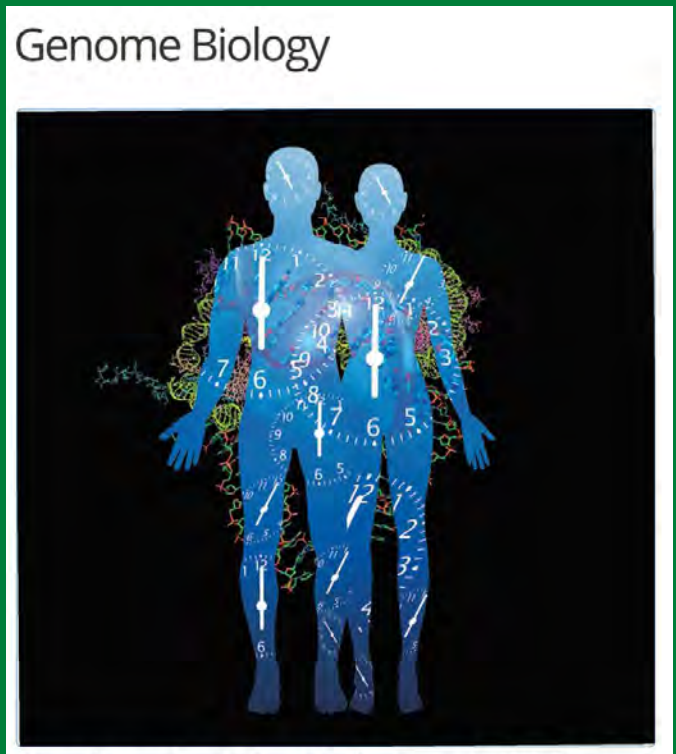
Morgan E. Levine[a,b], Ake T. Lu[a], Brian H. Chen[c], Dena G. Hernandez[d], Andrew B. Singleton[d], Luigi Ferrucci[c], Stefania Bandinelli[e], Elias Salfati[f], JoAnn E. Manson[g], Austin Quach[a], Cynthia D. J. Kusters[h], Diana Kuh[i], Andrew Wong[i], Andrew E. Teschendorff[j,k,l,m], Martin Widschwendter[j], Beate R. Ritz[h], Devin Absher[n], Themistocles L. Assimes[f], and Steve Horvath[a,o,1]

Effect of surgical menopause



Women age more slowly than men according to the epigenetic clock (blood, brain, liver). All ethnic groups.



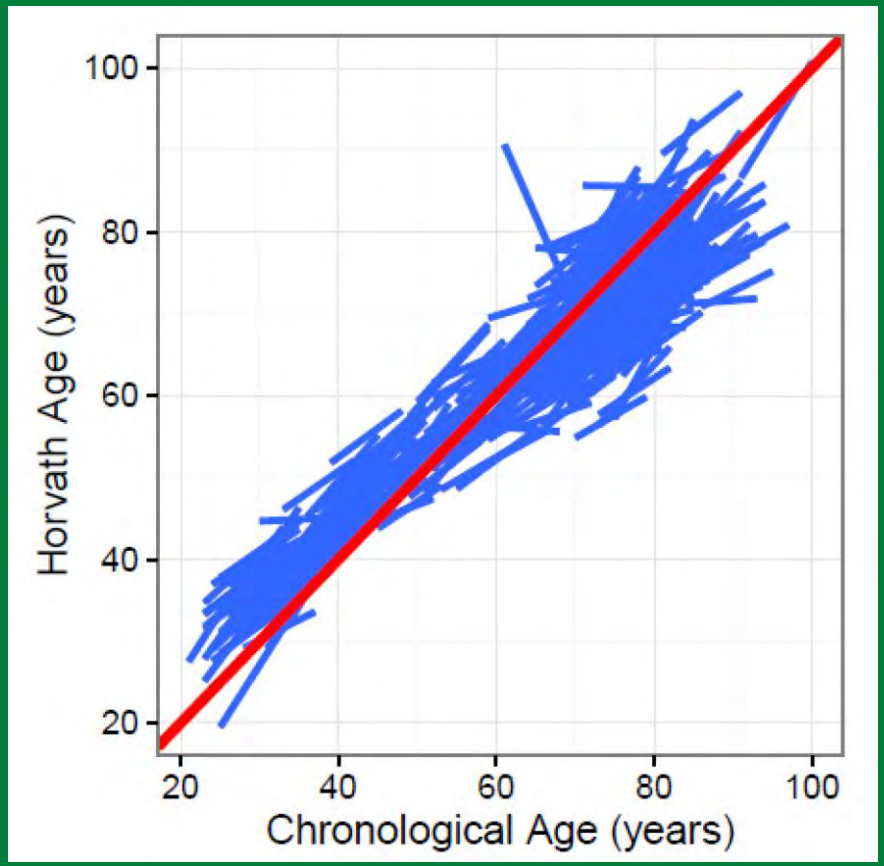


An epigenetic clock analysis of race/ethnicity, sex, and coronary heart disease

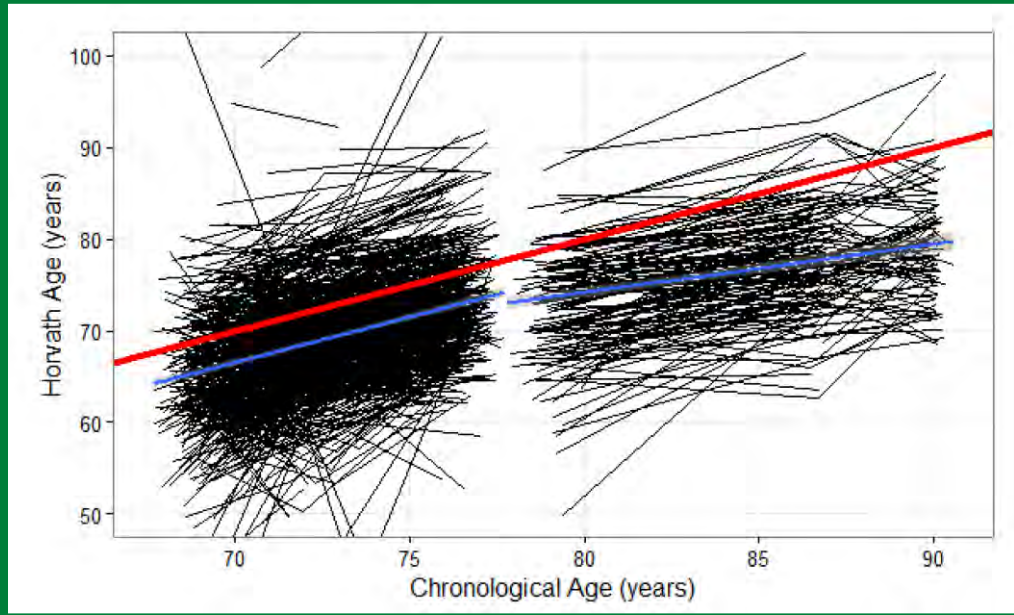
Tracking the epigenetic clock across the human life-course

R. Marioni, S. Hagg (2018)

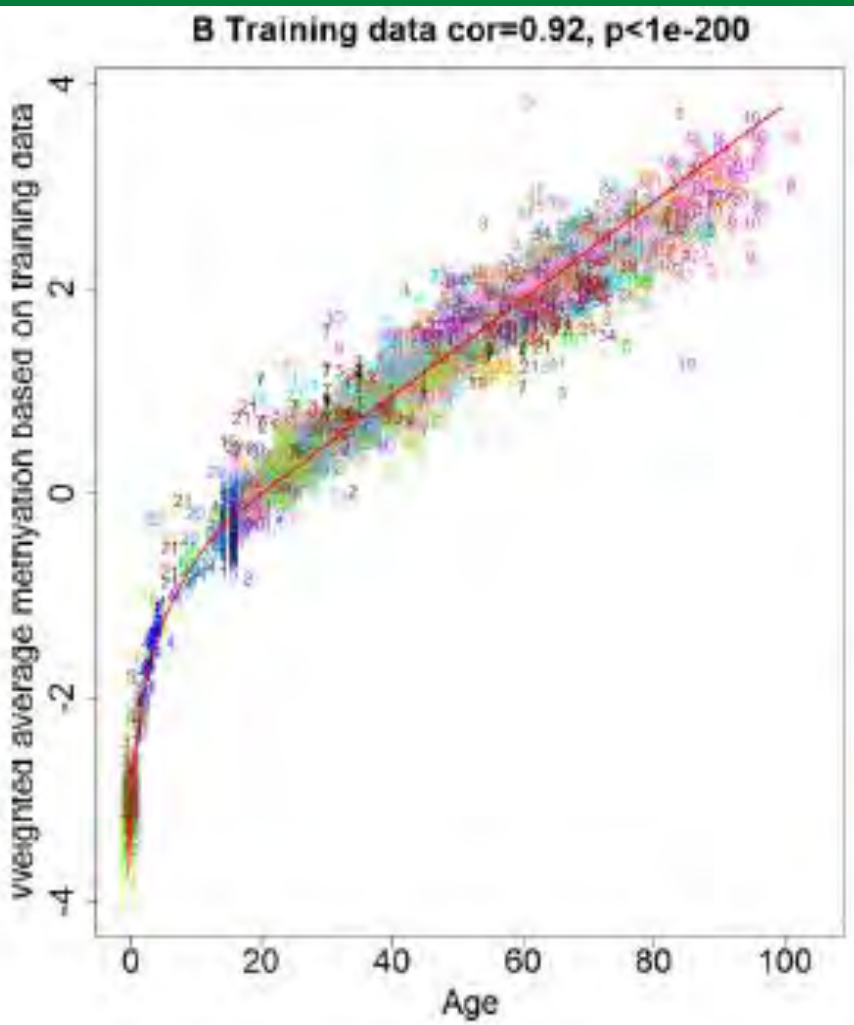
InCHIANTI cohort

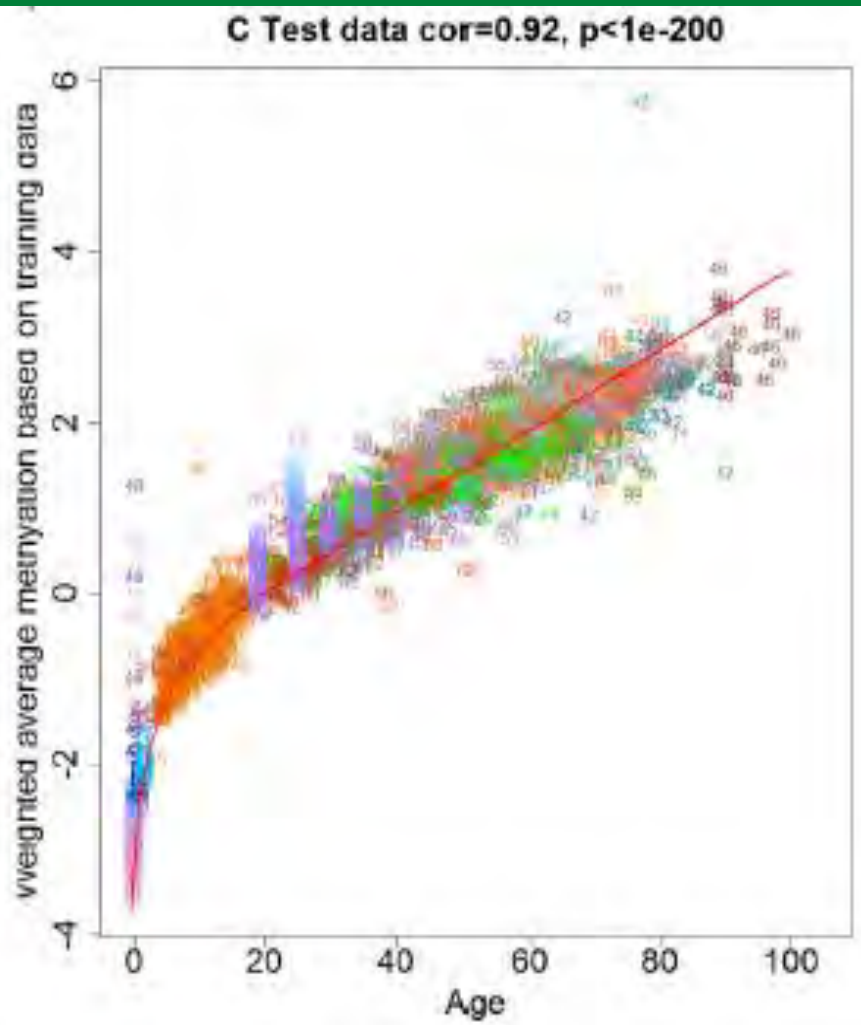


Lothian Birth Cohorts

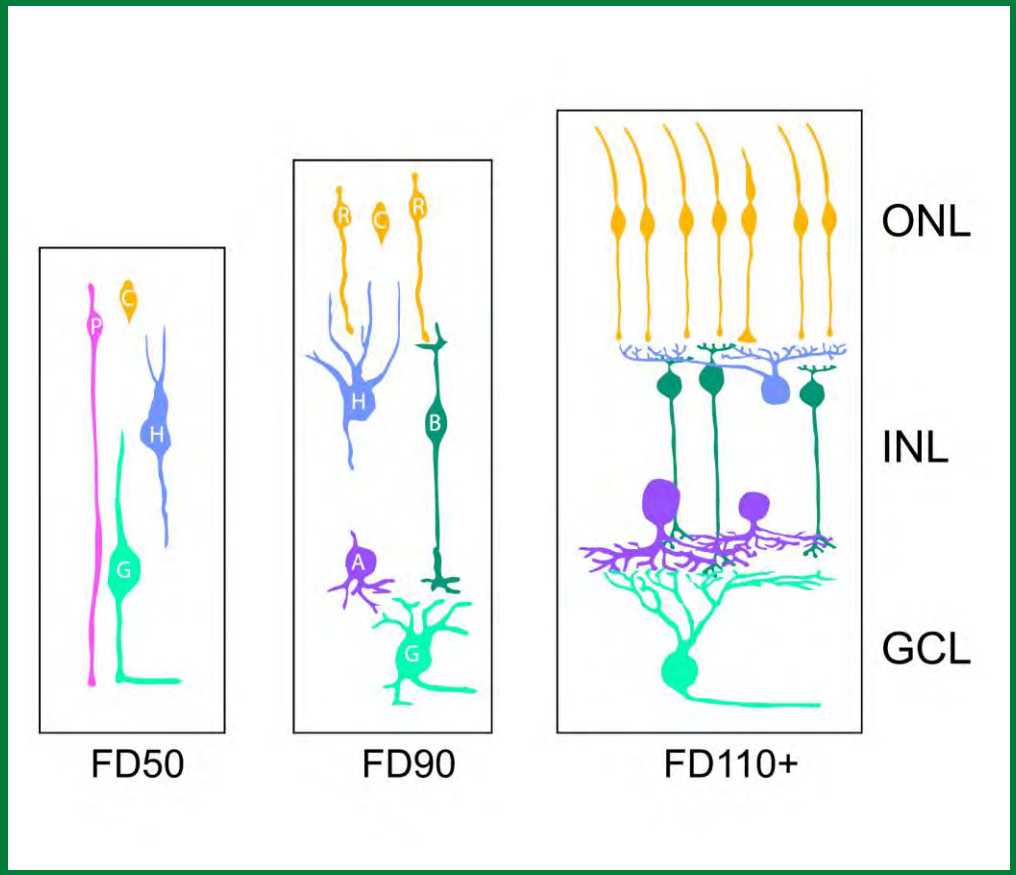


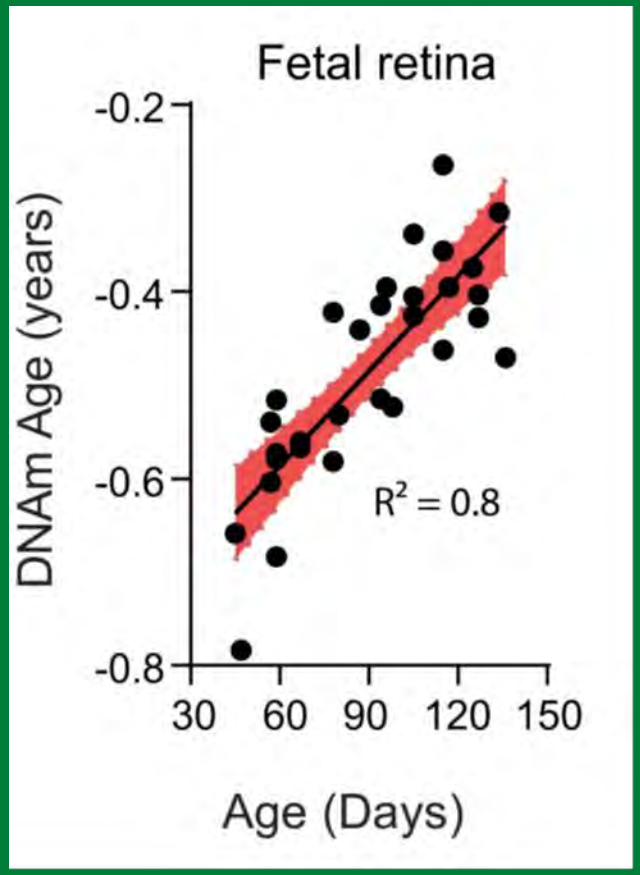
Multi-tissue DNAm age estimator (353 CpGs) applies to all tissues/cell types across the entire life course



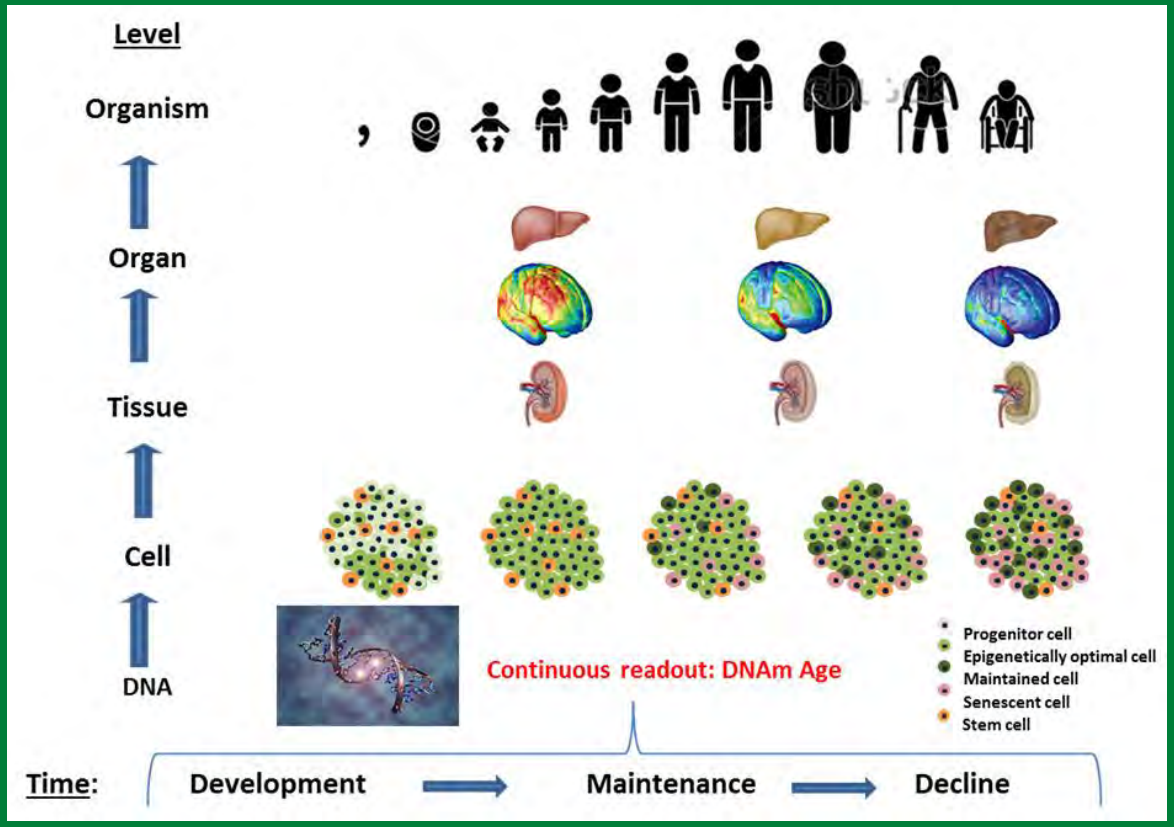


Pan tissue clock also applies to early development: highly accurate on fetal retina samples (A. Hoshino, Thomas Reh 2019)





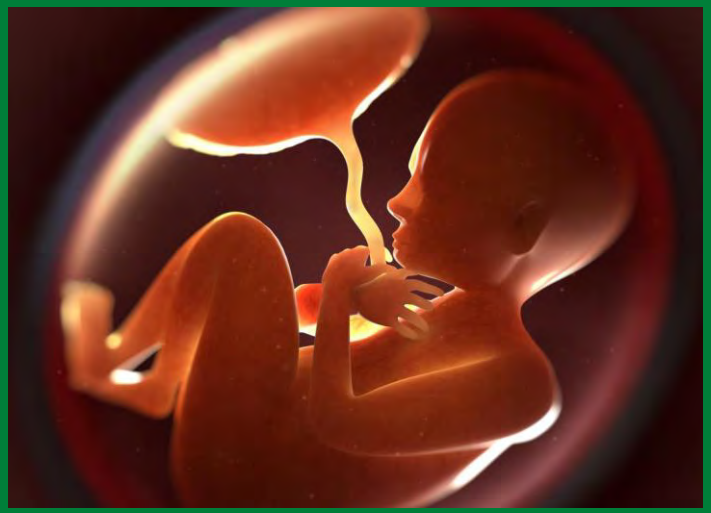
Epigenetic clock theory of aging: DNAm age is a continuous read-out that links processes that play a role in development, maintenance, and aging



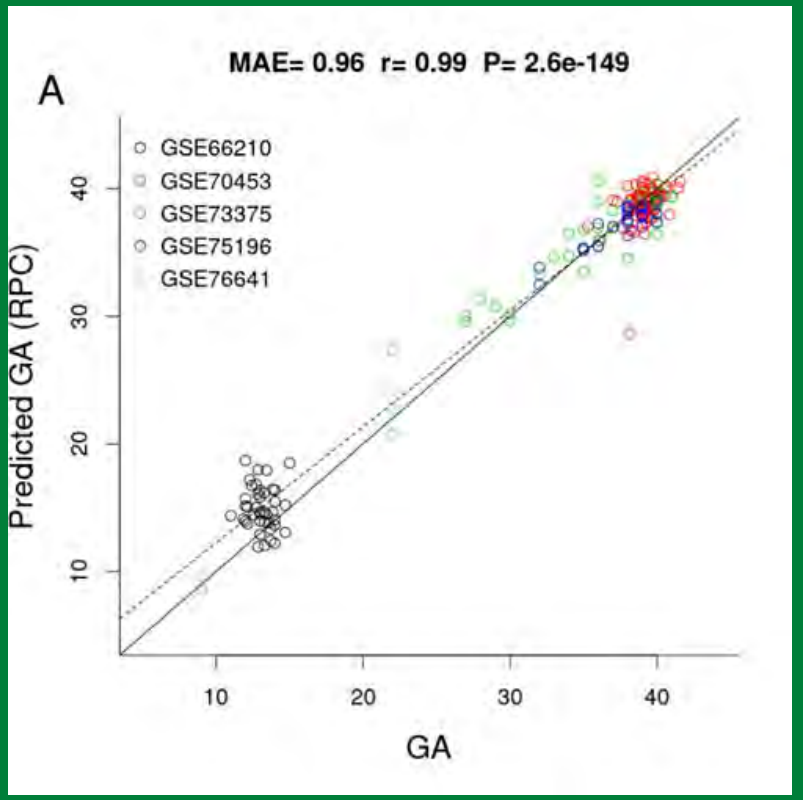
Epigenetic clock links purposeful molecular processes to un-intended adverse consequences later in life (antagonistic pleiotropy).

Horvath and Raj, Nat Rev Genet 2018

Placental epigenetic clocks: estimating gestational age using placental DNA methylation levels (Yunsung Lee, Aging 2019)



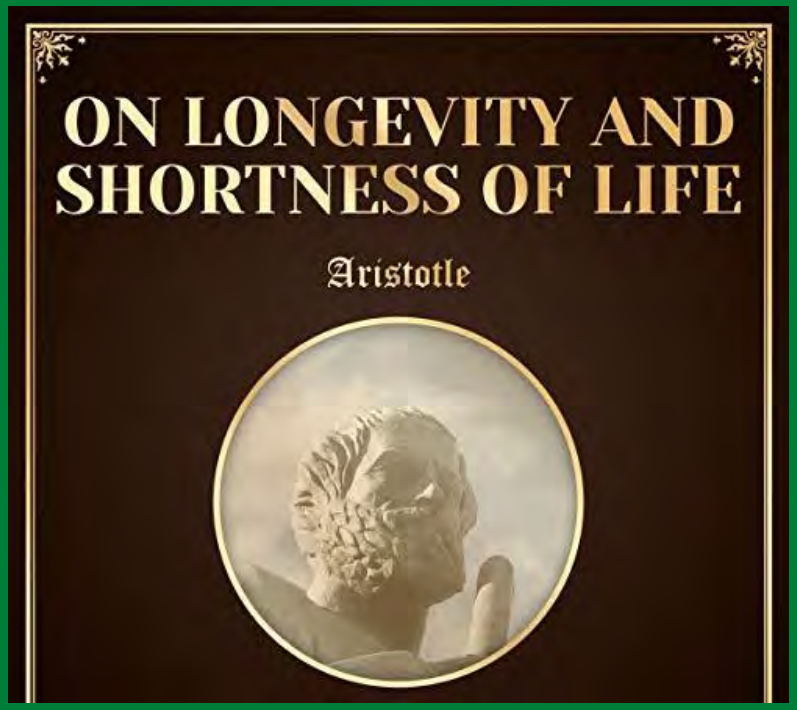
Gestational Age In Test Data



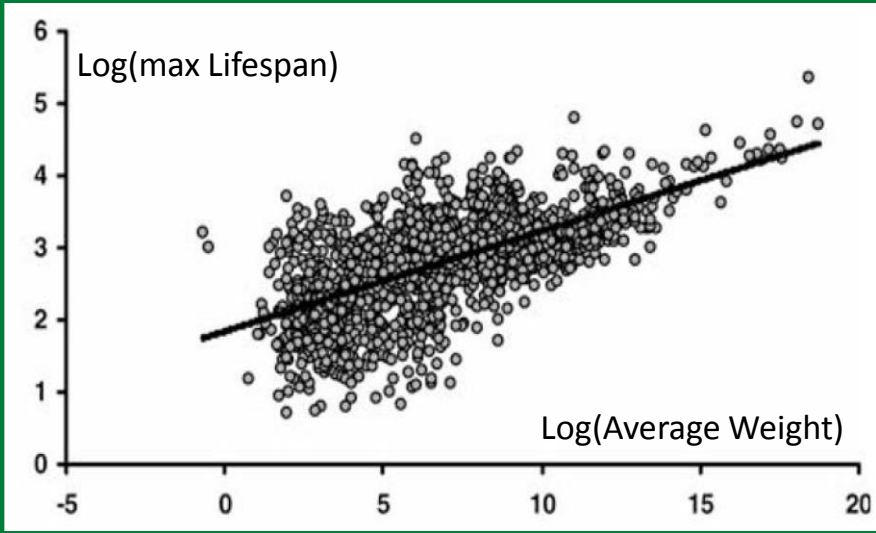
Studying epigenetic aging in mammals

Central question of biology:
Why do similar species, such as mammals, have markedly different maximum lifespans?

Substantial literature:
Schmidt-Nielsen 1984, Finch 1990, Charnov 1993, Austad 2001, de Magalhaes 2007, Healy 2014,…



de Magalhães et al (2007) developed an online database (AnAge) with over 3000 animal species.



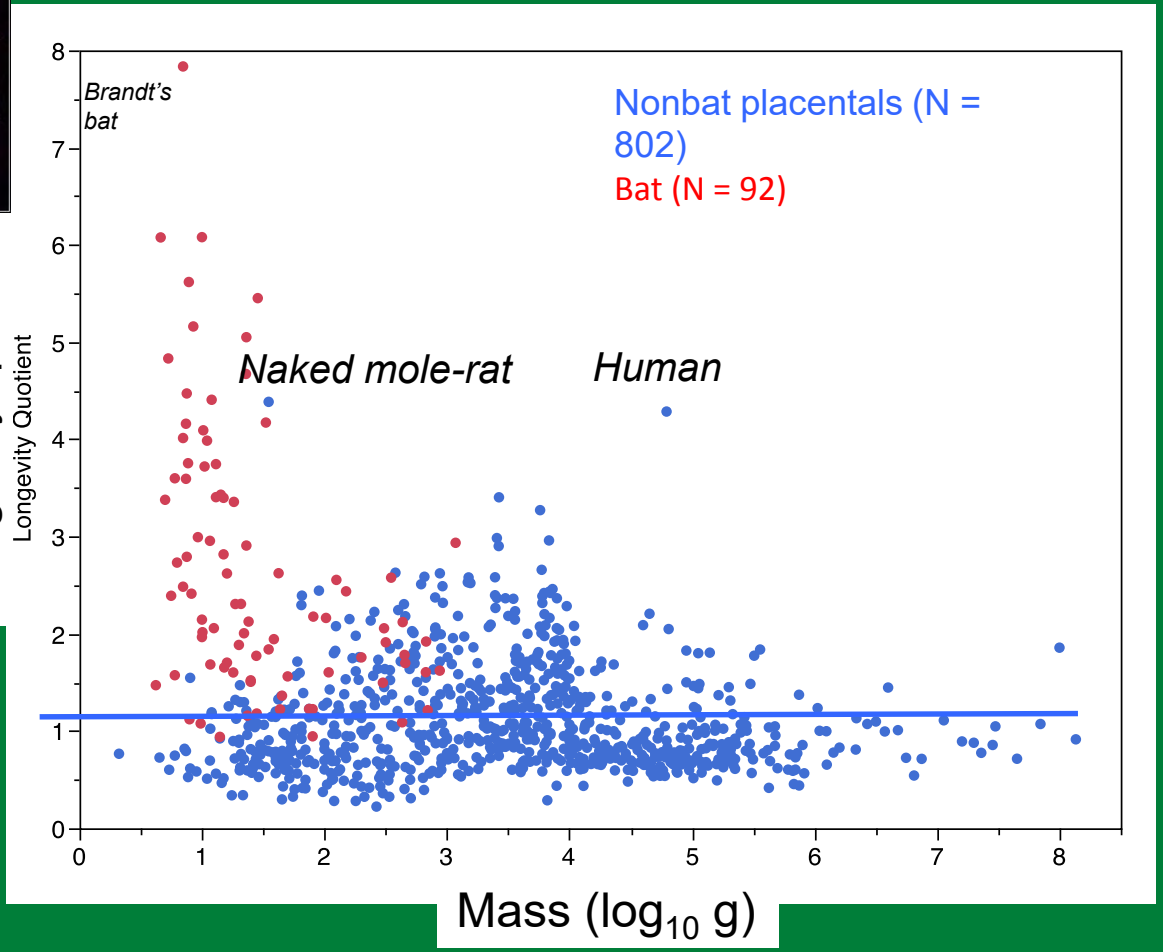
Body weight and the ability to avoid predators (e.g flying) predict lifespan

J Gerontol A Biol Sci Med Sci. 2007 February ; 62(2): 149–160.

An Analysis of the Relationship Between Metabolism, Developmental Schedules, and Longevity Using Phylogenetic Independent Contrasts

João Pedro de Magalhães[1], **Joana Costa**[2], and **George M. Church**[1]

Bats, naked mole rate, and humans live longer than equal sized mammals



Naked mole rat

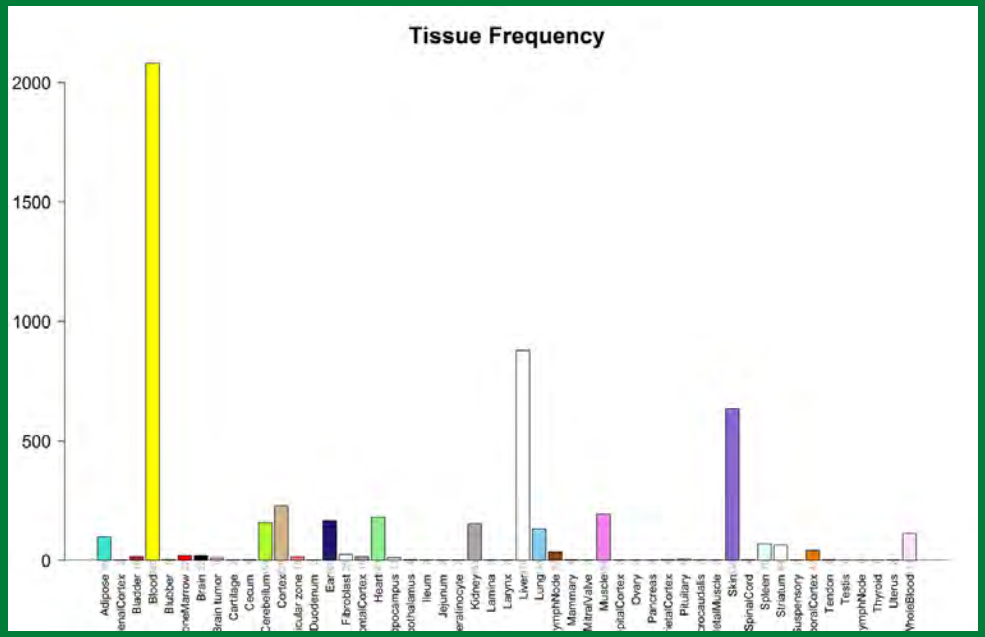
J. Wilkinson

Incomplete molecular understanding of maximum lifespan

- Molecular theories include
  - Various epigenetic theories, e.g. DNA methylation
  - DNA repair mechanisms (SIRT6)
  - ….
- Need for large data involving MANY species

Our mammalian methylation data

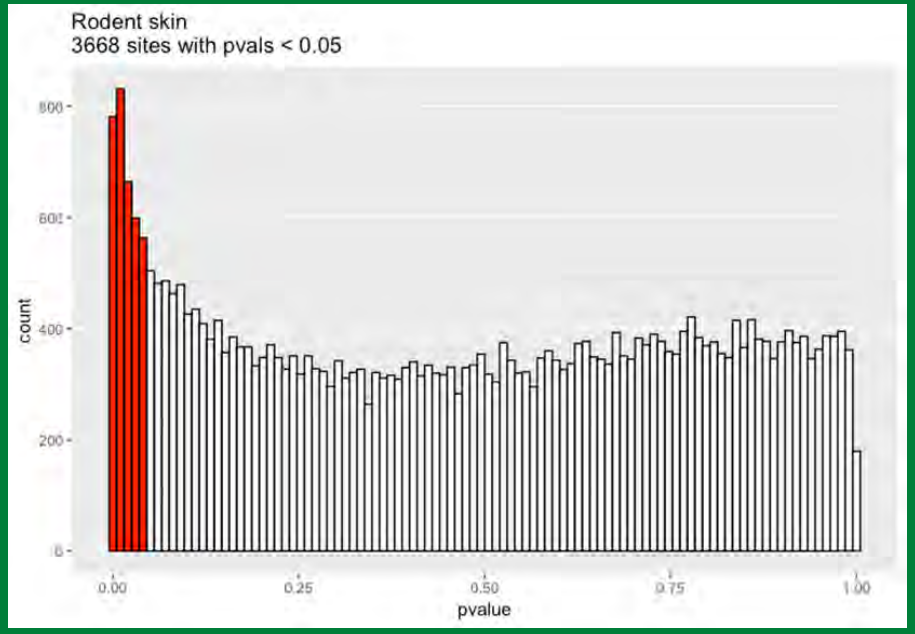
- Over 100 different mammalian species
- Current status: n=10k samples



THE PAUL G. ALLEN FRONTIERS GROUP

Tissues: blood, liver, skin, brain/cortex, Muscle,…

Epigenomewide association studies for maximum lifespan reveal thousands of CpGs even after controlling for phylogeny
(Caesar Li, Vera Gorbunova, Diego Villar, Todd Robeck)

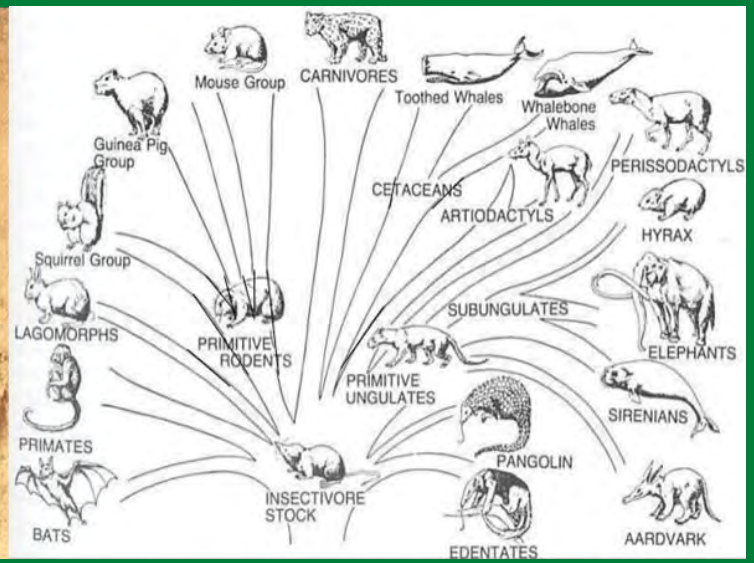


Insights

DNA methylation levels relate strongly to maximum lifespan across mammals

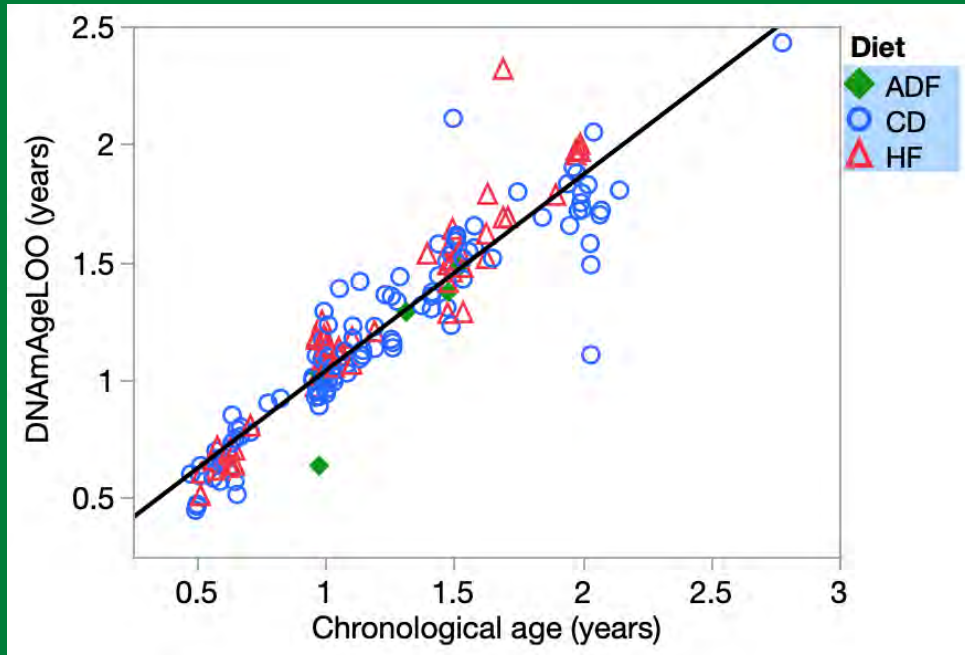
Insight: One can develop highly accurate estimators of chronological age (epigenetic clocks) in all mammals

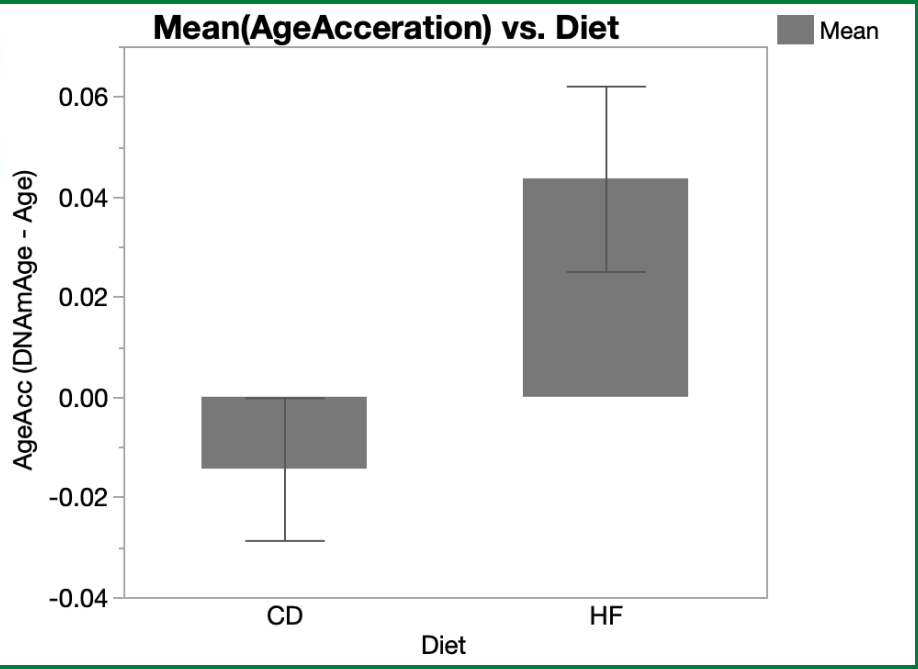
- Now we focus on age of a specific animal as opposed to the maximum lifespan of a species



Mouse epigenetic clocks reveal faster aging due to high fat diet

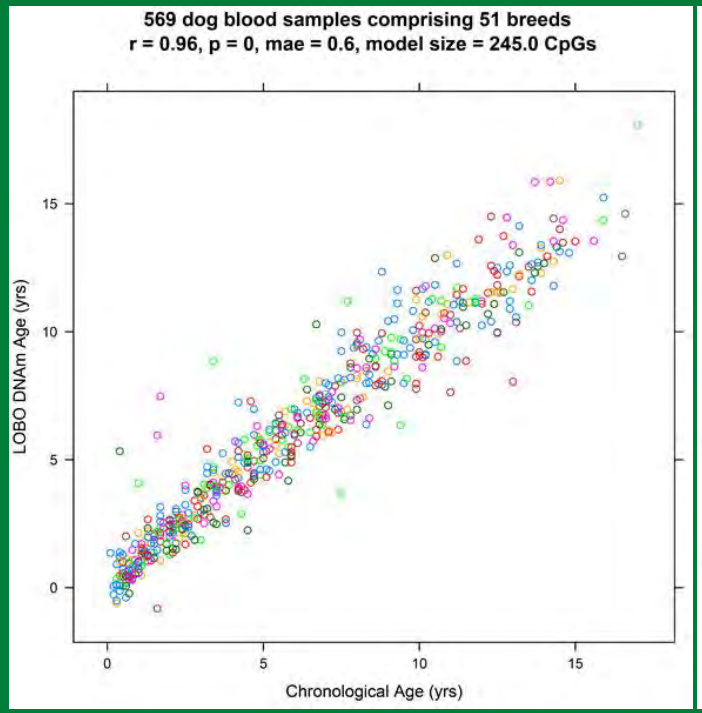
(Beni Mozhui, Nan Wang, William Yang)

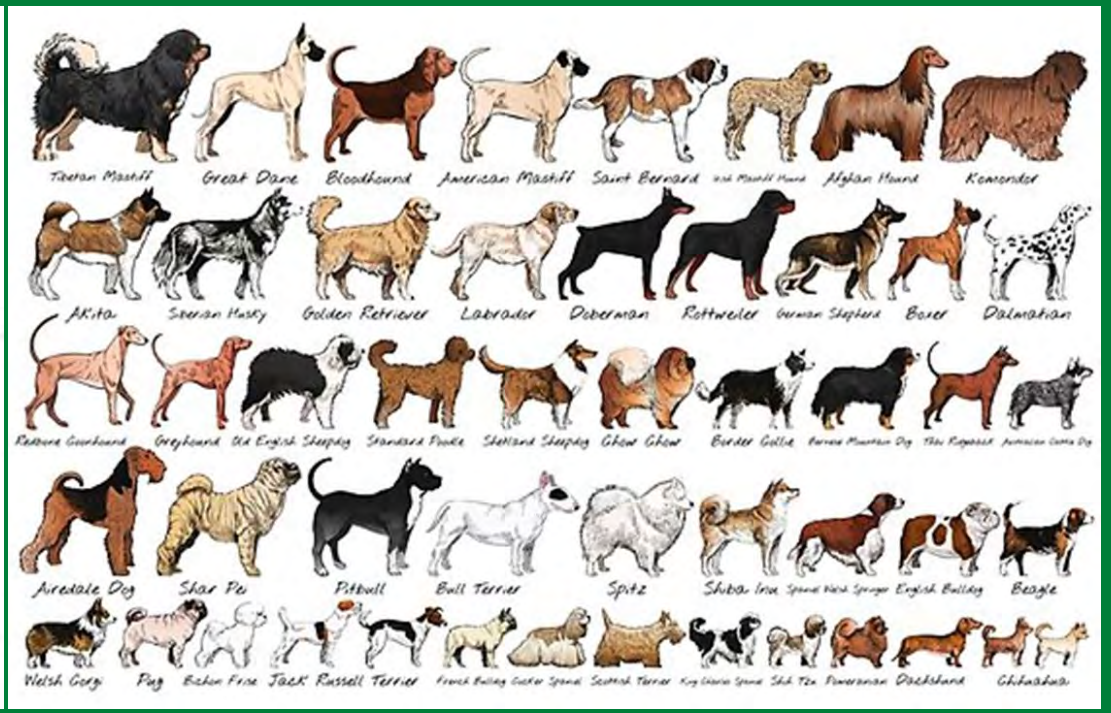




Highly accurate epigenetic clocks in pure dog breeds

(Elaine Ostrander, Andrew Hogan)

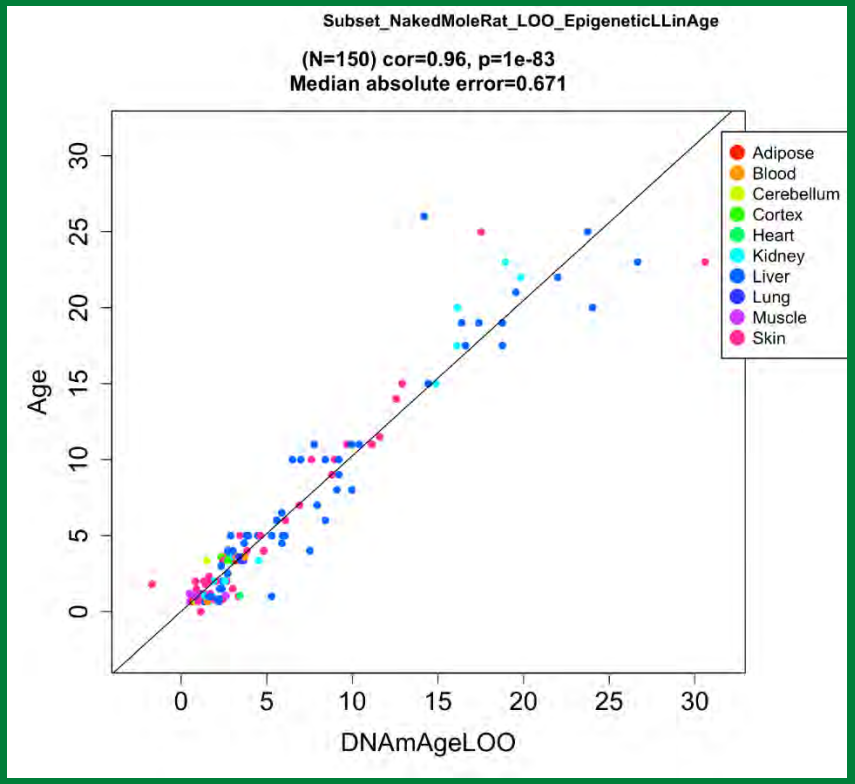




Dog epigenetic clock based on 245 CpGs

Naked mole rat

Vera Gorbunova, Chris Faulkes, Joseph Zoller, Masaki Takasugi, Julia Ablaeva

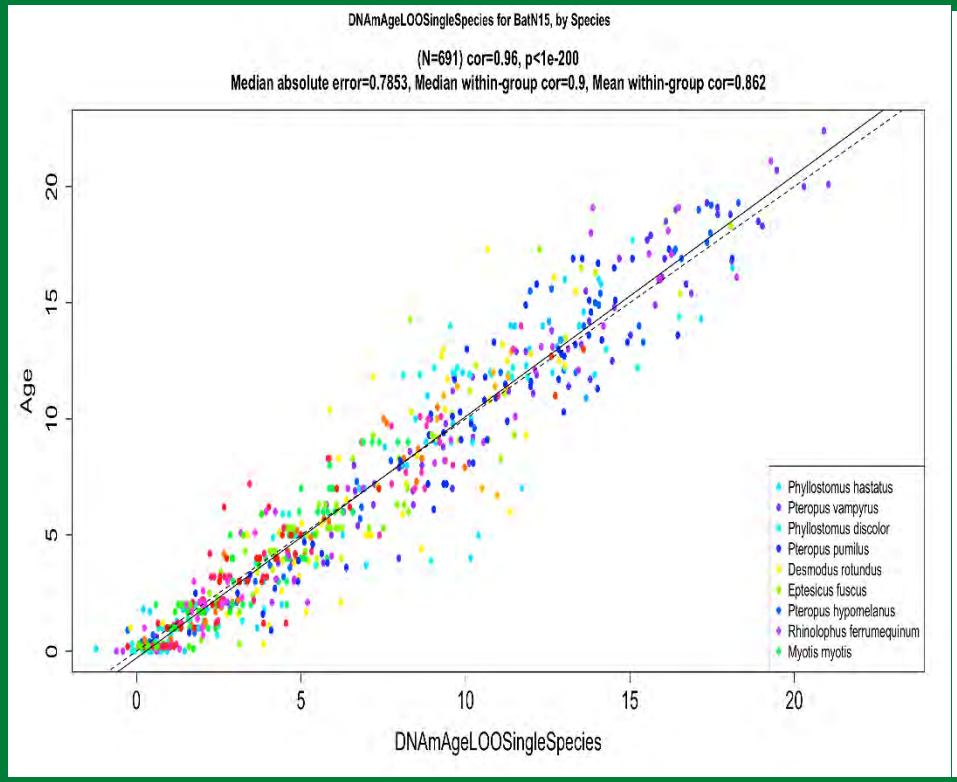


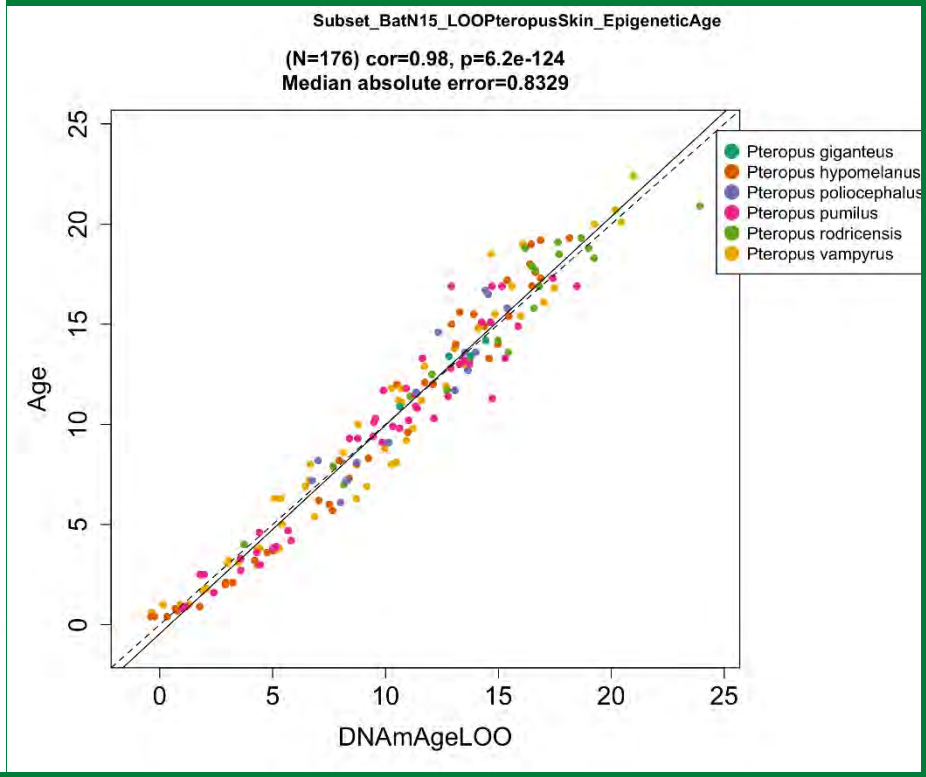
Methylation explains in part why some bat species live longer than others

Jerry Wilkinson, Sonja Vernes, Emma Teeling

Highly accurate epigenetic clocks across bat species (Jerry Wilkinson)

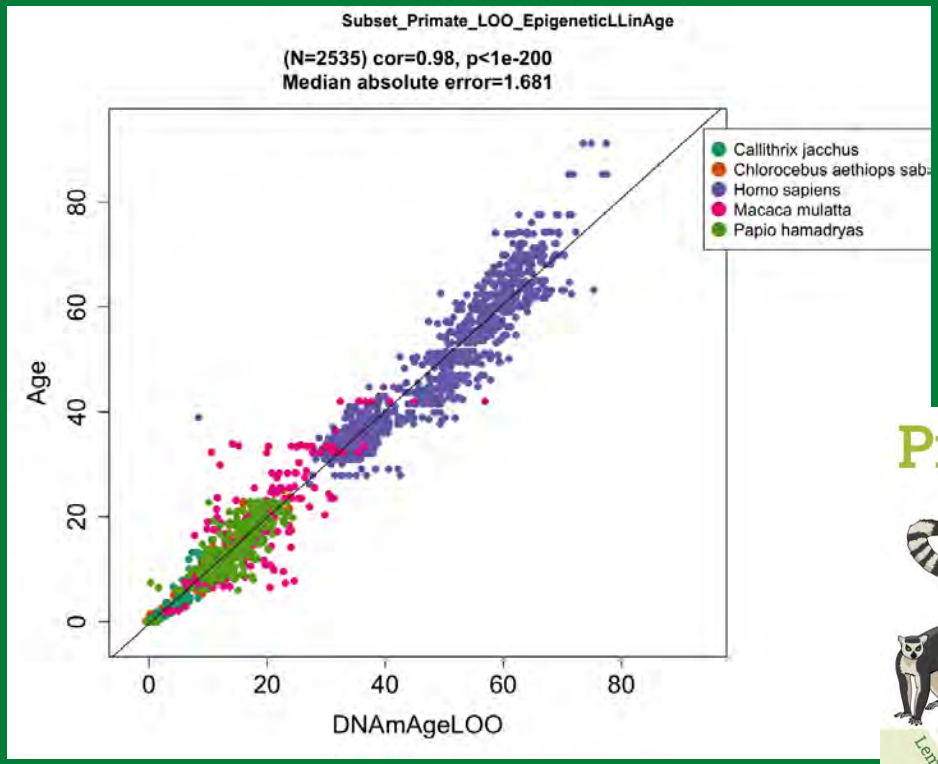
800 DNA samples
From 30 bat species

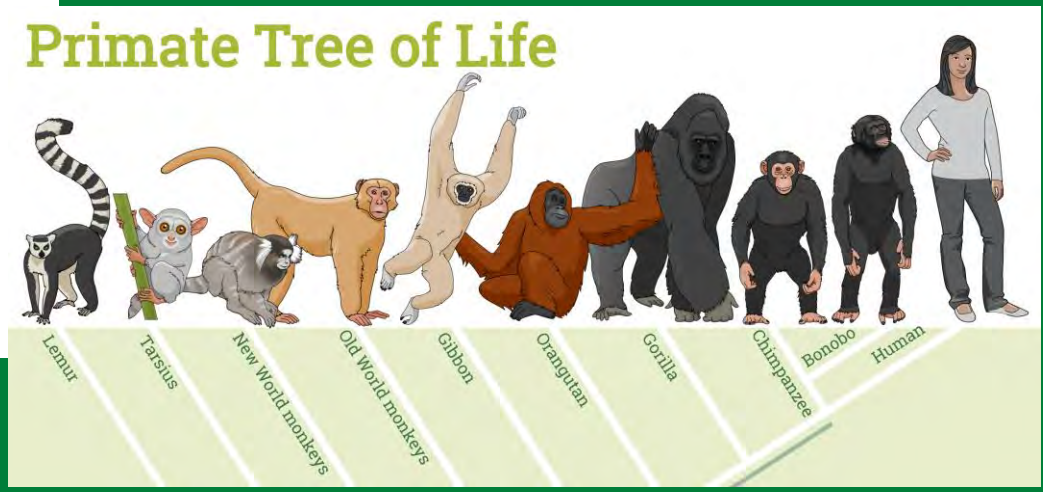




Epigenetic clock for primates

Ania Jasinska, Cun Li, Peter Nathanielsz, Adam Salmon, Julie Mattison, Rafa de Cabo, Joseph Zoller





Conclusions

- Several epigenetic clocks
  - All correlate strongly with age
  - Clocks differ in predictive accuracy for mortality
- DNA methylation is predictive of mortality risk even after adjusting for many risk factors
- DNAm age will not replace standard clinical measures (blood pressure, lipid levels, glucose measures)
- DNA methylation often have a cell type specific effect
  - Judicious choice of source of DNA: blood, saliva, buccal, urine, fat tissue, muscle

Acknowledgement

- Current/former lab members: Ake Lu, Morgan Levine, Austin Quach, Caesar Li, Joseph Zoller, Joshua Zhang
- Mammalian array:
  - UCLA: Adriana Sperlea, Jason Ernst, Michael Thompson, M. Pellegrini
- Collaborators: Ken Raj, Riccardo Marioni, James G Wilson, Luigi Ferrucci, many more
- NIH/NIA U34+U01
- Paul G. Allen Frontiers Group

NIH National Institute on Aging

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