Estimating and interpreting Biological Age

Peter Joshi

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Disclosures

Until 2021, Peter Joshi was a tenured member of faculty, and is now an Honorary Fellow, at University of Edinburgh

He is now founder of a genomic advisory business - Geromica

He currently advises Humanity Inc and Global Gene Corp, on genetics and healthy aging

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Global Gene Corp

Summary

Biological Age (BA)

- is a potential actionable marker of health
- to be meaningful, BA must beat your birth certificate
- we can to associate -omics assays with
  - chronological age (accurately) and
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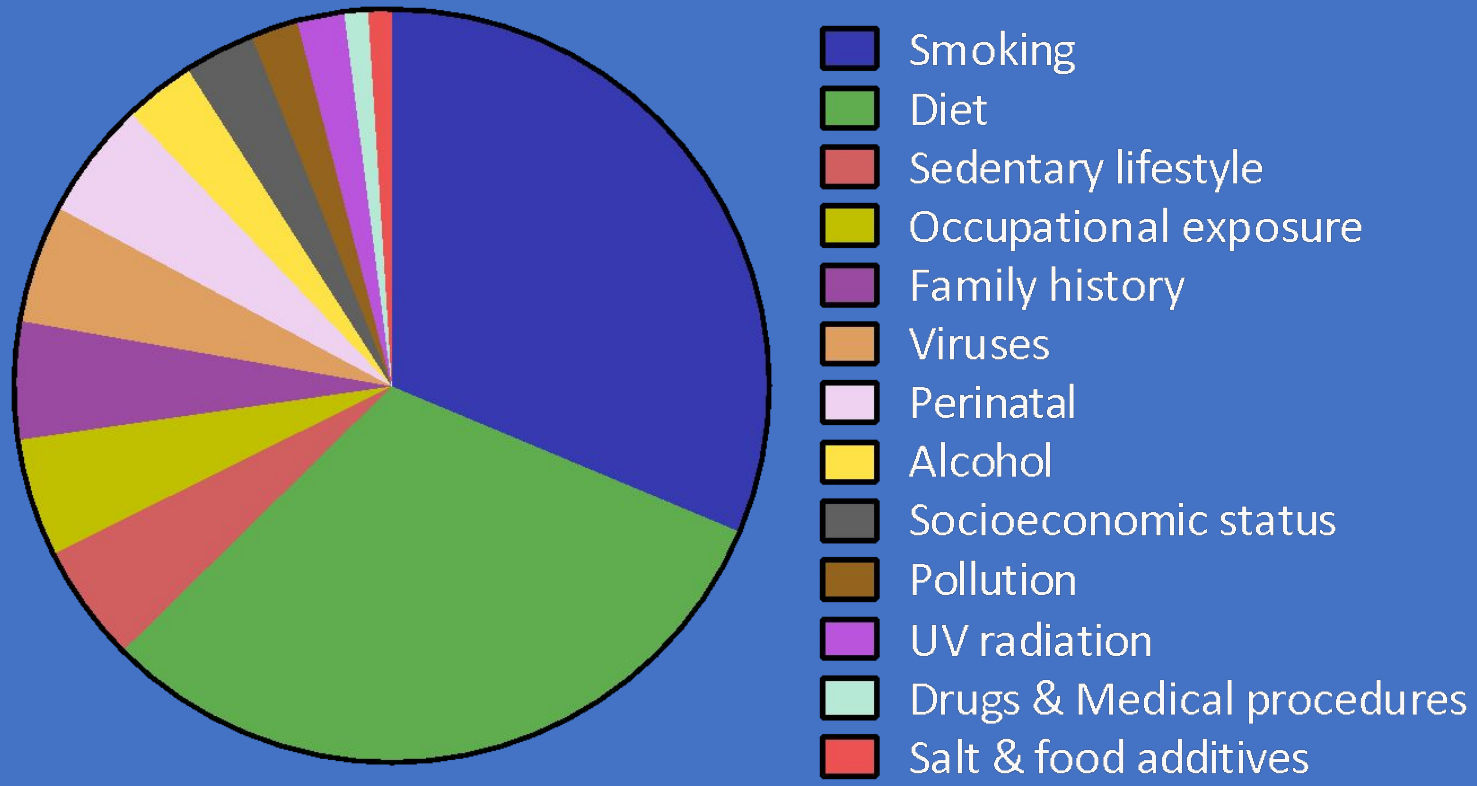
Risk Factors for Cancer



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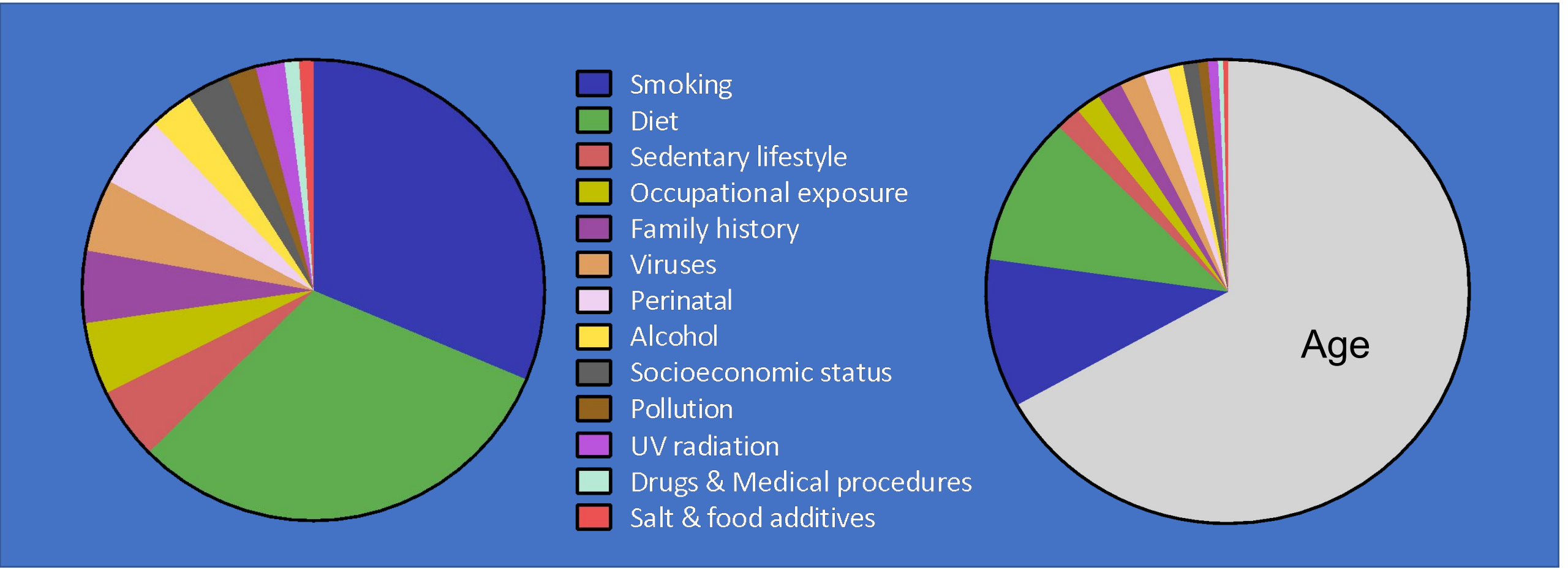
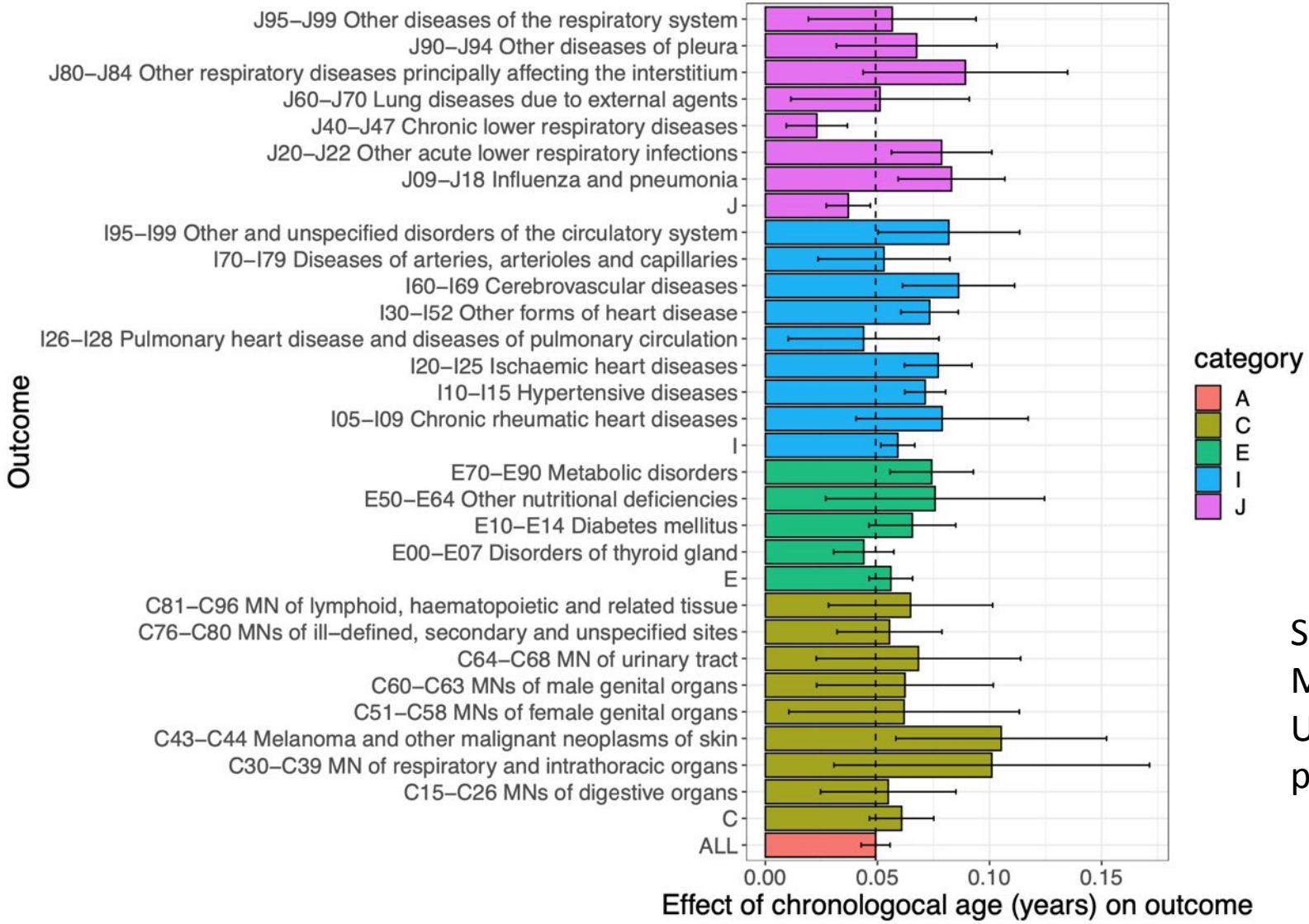


The effect of age on disease



Source: Erin Macdonald-Dunlop, University of Edinburgh, in preparation

What is Aging?

Passage of time

Molecular changes

shortening of telomeres, genomic instability, DNA methylation pattern, deregulated nutrient sensing, mitochondrial dysfunction, cellular senescence, stem cell exhaustion, loss of proteostasis and altered intercellular communication

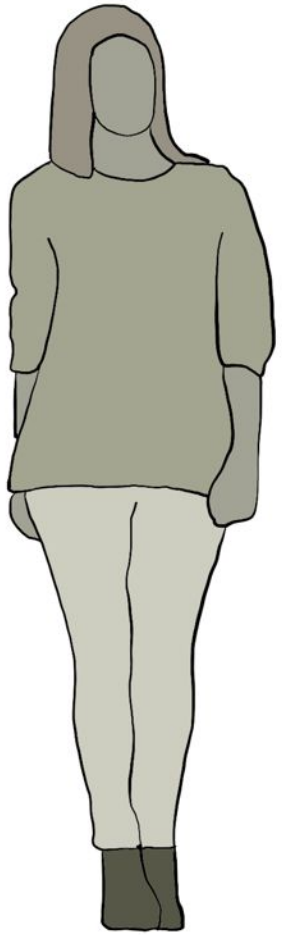
López-Otín, C., Blasco, M. A., Partridge, L., Serrano, M. & Kroemer, G. The Hallmarks of Aging. *Cell* **153**, 1194–1217 (2013)

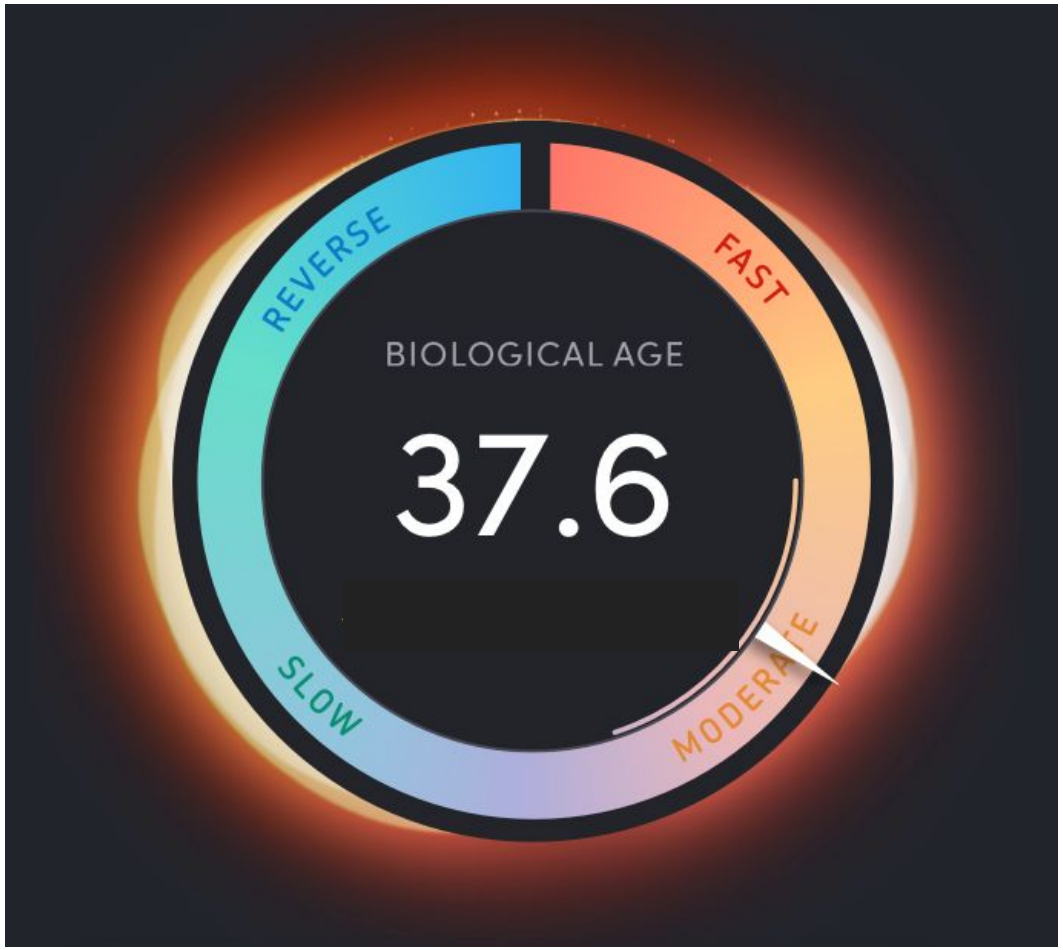
Phenotypic characteristics

greying hair, baldness, loss of skin elasticity and worsening of posture

decline in eyesight and hearing and hypertension

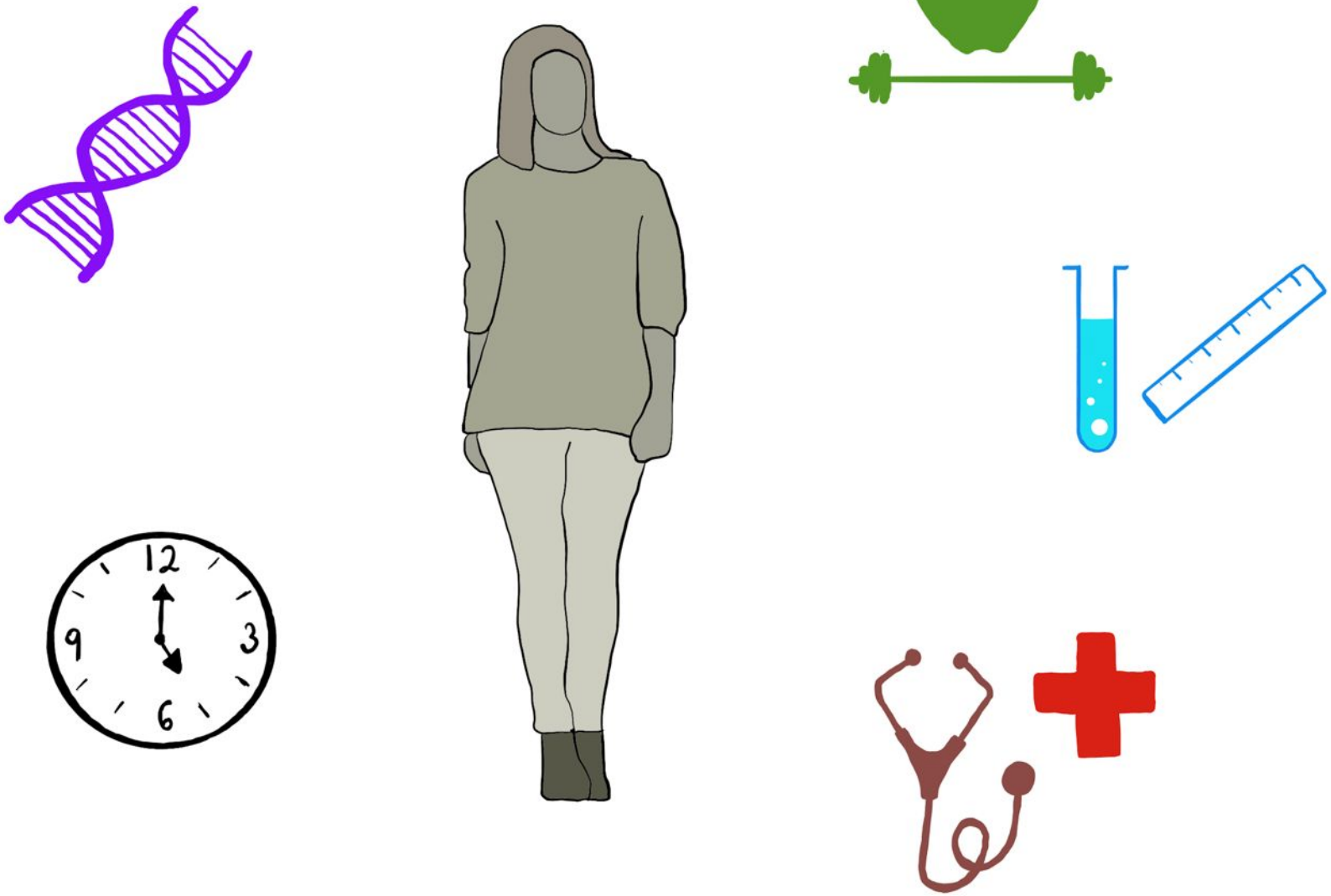
Biological Age



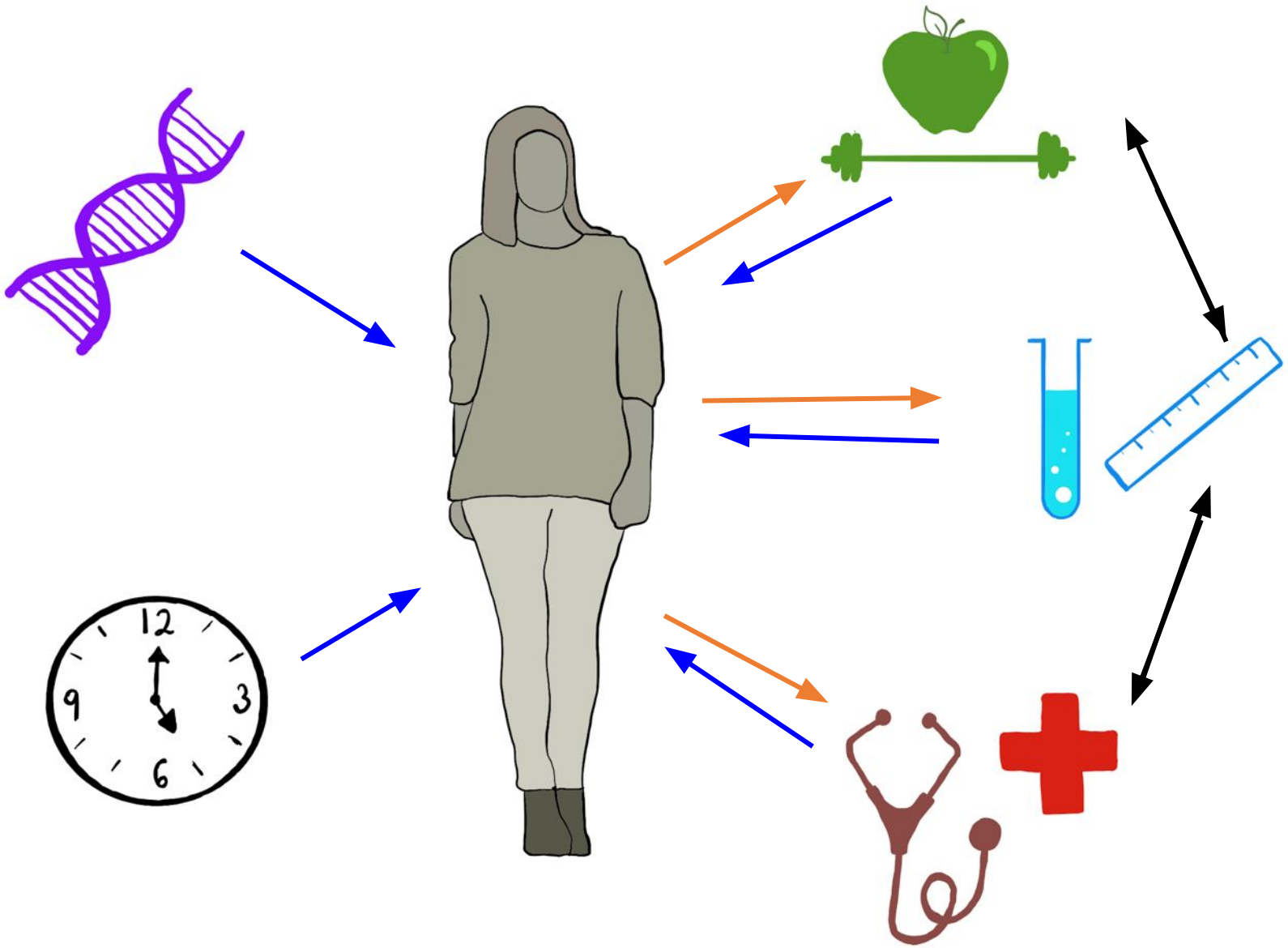


HUMANITY

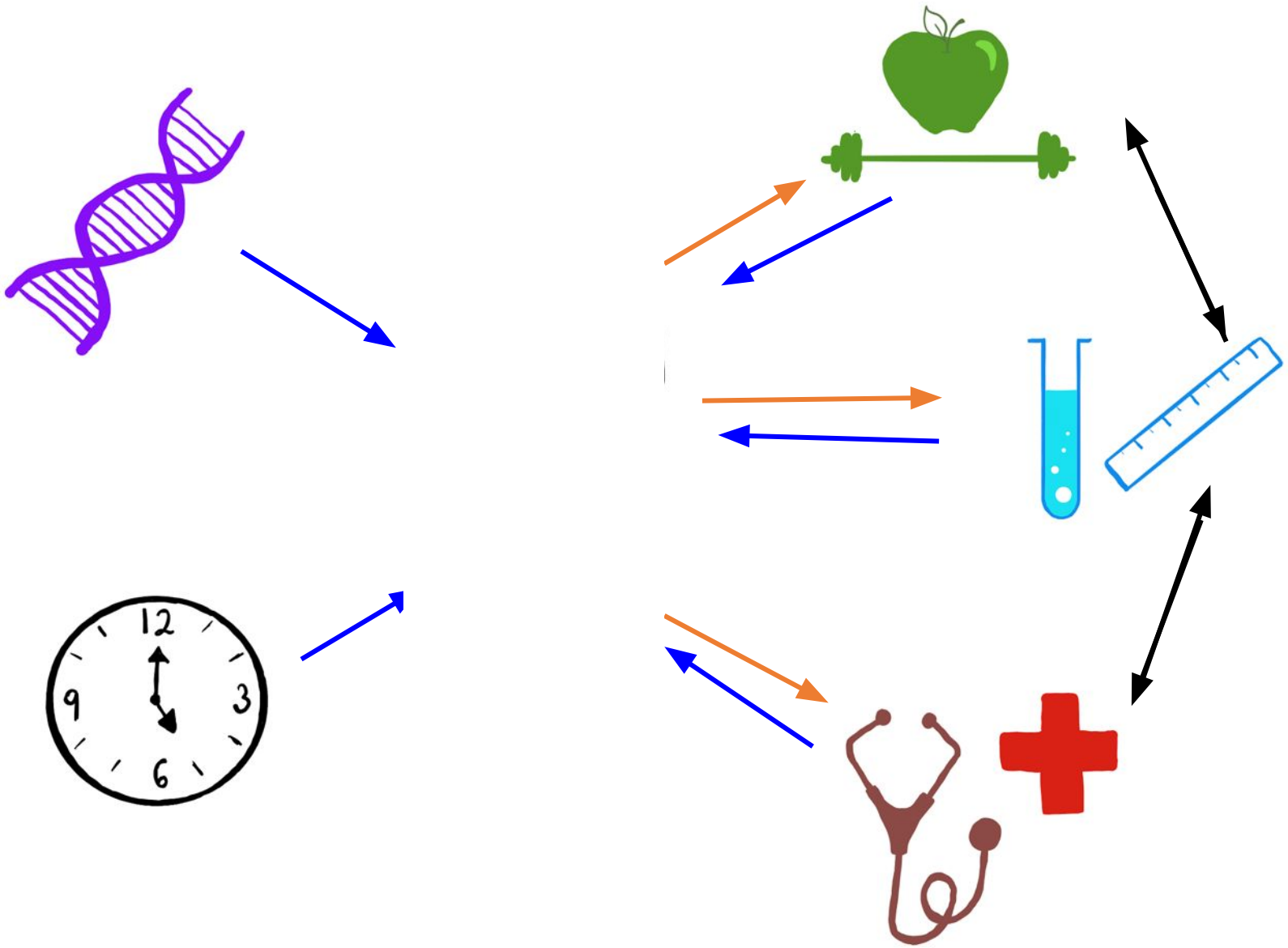
Biological Age associates with



Biological Age causation



Biological Age is hidden



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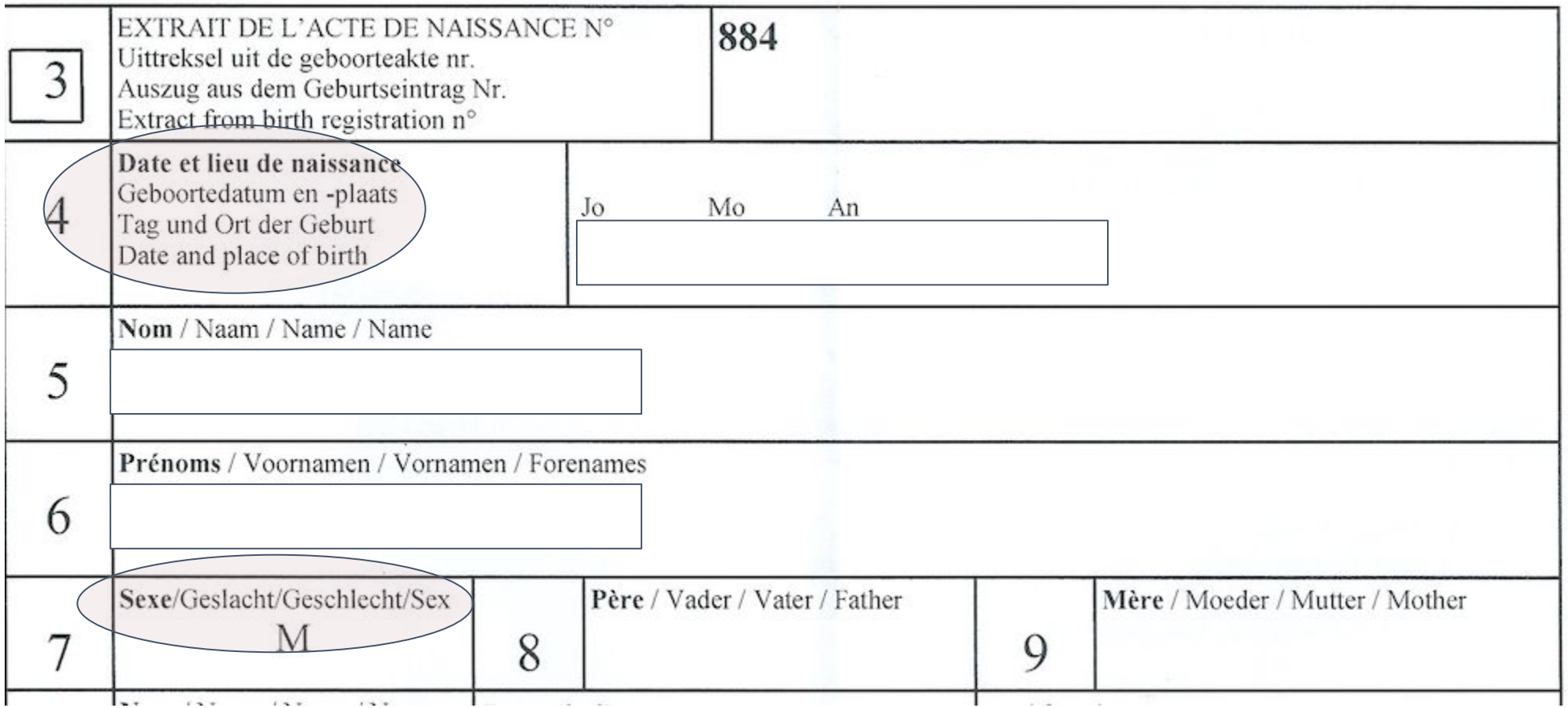
Abstract — This article presents a conceptual discussion of some aspects involved in biomarkers of aging. A biomarker of aging is a biological parameter of an organism that either alone or in some multivariate composite will, in the absence of disease, better predict functional capability at some late age than will chronological age. The reasons for undertaking biomarker research, criteria for putative biomarkers, measurement and assessment of putative biomarkers, and the new initiative by the National Institute on Aging in biomarker research are discussed.

Key Words: physiological age, chronological age, predictors of functional capability, species longevity, age-associated pathologies, biomarkers of aging, interventions in aging, validity of biomarkers

Baker, G. T. & Sprott, R. L. Biomarkers of aging. *Exp. Gerontol.* **23**, 223–239 (1988)

Beat the birth certificate



3	EXTRAIT DE L'ACTE DE NAISSANCE N° Uittreksel uit de geboorteakte nr. Auszug aus dem Geburtseintrag Nr. Extract from birth registration n°		884		
4	**Date et lieu de naissance** Geboortedatum en -plaats Tag und Ort der Geburt Date and place of birth		Jo Mo An		
5	**Nom** / Naam / Name / Name				
6	**Prénoms** / Voornamen / Vornamen / Forenames				
7	**Sexe**/Geslacht/Geschlecht/Sex M	8	**Père** / Vader / Vater / Father	9	**Mère** / Moeder / Mutter / Mother

Biological Age Suggested Properties

- the average biological age of people is their chronological age

  -> reference population
- the group of people with a given biological age exhibit the same AVERAGE
  - health outlook or ?
  - biomarkers or
  - both?
  - as the AVERAGE for the group with that chronological age
- biological age should not be subject to mean reversion

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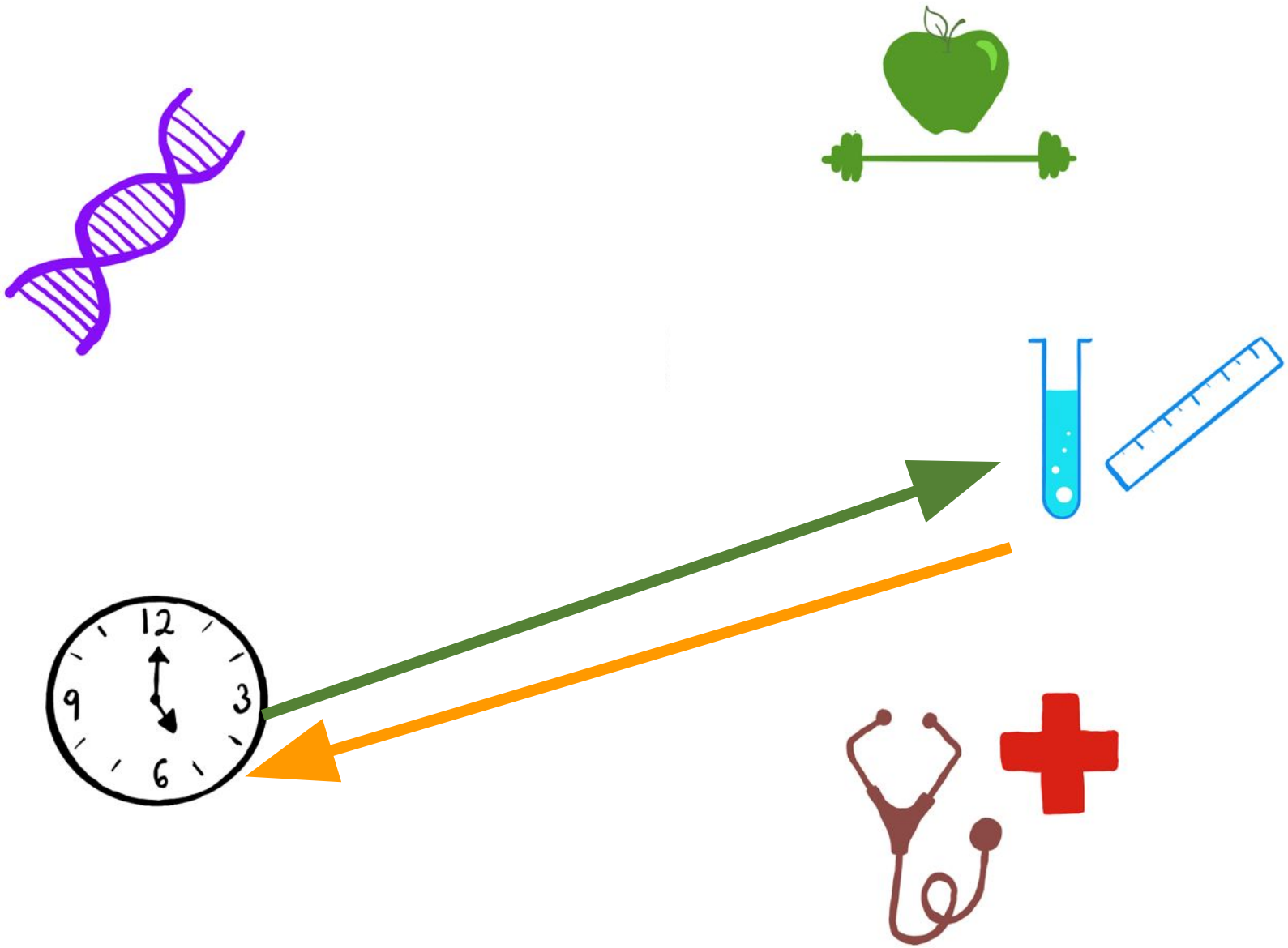
Chronological Age estimation



The NxP prediction problem

Penalised regression

$$y = \mathbf{X}\beta + \varepsilon$$

y: observed outcome (chronological age)

X : nxp matrix of predictors (methylation rates)

$$y = \mathbf{X}\beta + \varepsilon$$

y: observed outcome (chronological age) for **656(n) subjects**

X : nxp matrix of predictors (methylation rates) **at 450k sites**

p>> n

high colinearity amongst the predictors

Ordinary Least Squares

$$y = \mathbf{X}\beta + \varepsilon$$

- likely to lead to overfitting
  - poor prediction in second sample

Principal Components and stepwise Ordinary Least Squares

$$y = PC_n \beta' + \varepsilon$$

+ helps hugely with colinearity
+ / - still uses whole predictor set
- difficult to interpret biologically

Penalised regression

$$M(\theta) = L(\theta|x) + \lambda P(\theta)$$

M: the objective function whose value is to be minimised
L: loss function, proportional to the residual sum of squares
P: penalty function
λ: controls the trade-off between the two parts.
P: penalises non-zero effect estimates - discouraging overfitting

Ridge regression: L_2 penalty

$$M(\theta) = L(\theta|x) + \lambda P(\theta)$$

$$P(\beta) = \sum_{j=1}^{p} \beta_j^2$$

Because derivative of P(0) is zero, many small beta are favoured
Issues with colinearity of predictor (eg two perfectly colinear)

LASSO - L_1 penalty

$$M(\theta) = L(\theta|x) + \lambda P(\theta)$$

$$P(\beta) = \sum_{j=1}^{p} |\beta_j|$$

Does not especially favour of small estimates:
Variable selection as well as shrinkage

=> Sparse models

Elastic Net - mix of L_1 penalty, L_2 penalty

$$M(\theta) = L(\theta|x) + \lambda P(\theta)$$

$$P(\beta) = \alpha P_1 + (1 - \alpha) P_2$$

α : fixed or optimised via cross validation

Will focus on LASSO and elastic net

Training and testing

- models risk overfitting
  - Q:how would we know?
  - A:look at quality of prediction in fresh sample
- Training set - random (75-90%) subset of data
- Test set - complement
- compare r in training and test set
  - similar implies no overfitting

Omics Measures in ORCADES 1

Omic	N	Mean Age	SD Age	Min Age	Max Age	% Female
DEXA	1158	55.85	14.19	18.02	88	59.93
DNAme Horvath CpGs	957	52.93	15.66	17.12	100.18	55.38
MS Fatty Acids Lipidomics	952	53.41	15.49	16.84	91.47	55.78
MS Metabolomics	861	52.81	15.05	17.12	90.79	57.38
Clinomics	1815	53.35	15.03	16.5	91.47	59.56
DNAme Hannum CpGs	1033	53.43	15.68	17.12	100.18	55.86
UPLC IgG Glycomics	1937	53.13	15.29	16.5	100.18	60.51
MS Complex Lipidomics	940	53.54	15.27	17.12	91.47	55.74
NMR Metabolomics	1643	52.96	14.91	16.5	91.47	59.95
PEA Proteomics	805	52.88	15.59	17.12	91.47	54.91
Mega Omics	796	53.1	15.31	17.12	91.47	56.78

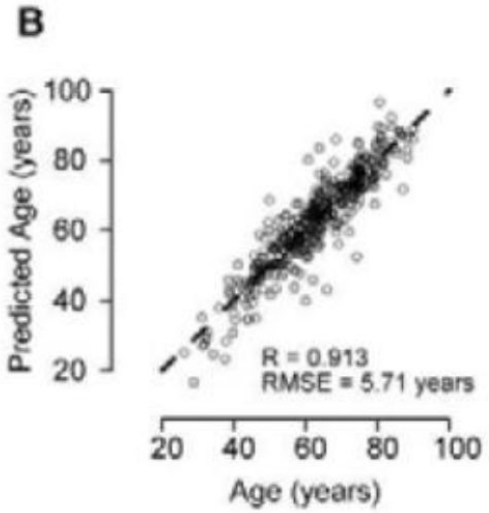
Results

www.aging-us.com AGING 2022, Vol. 14, No. 2

Research Paper

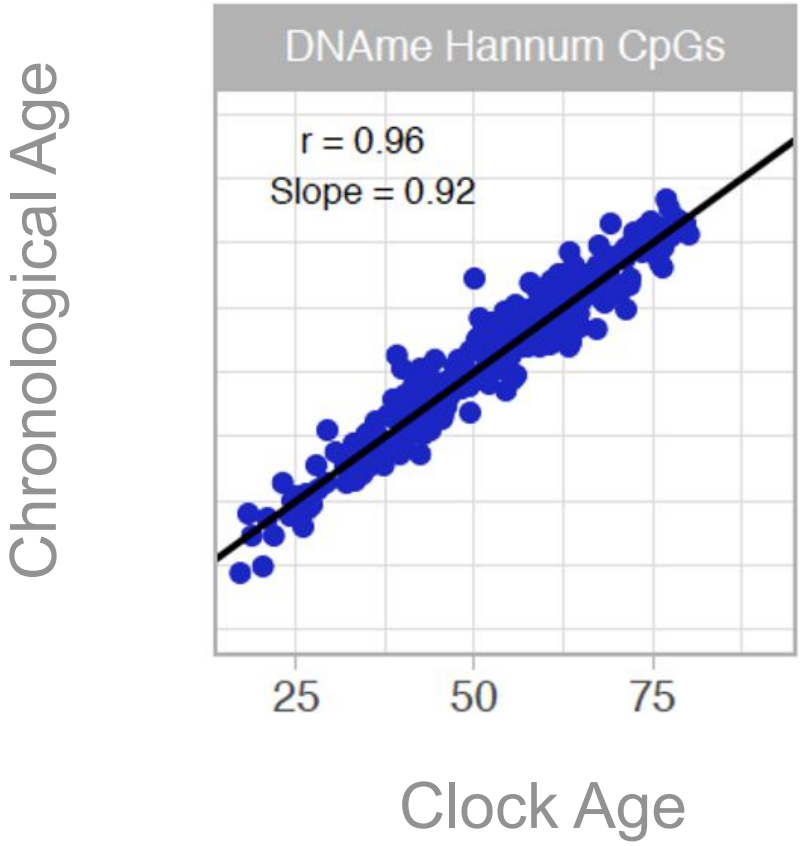
A catalogue of omics biological ageing clocks reveals substantial commonality and associations with disease risk

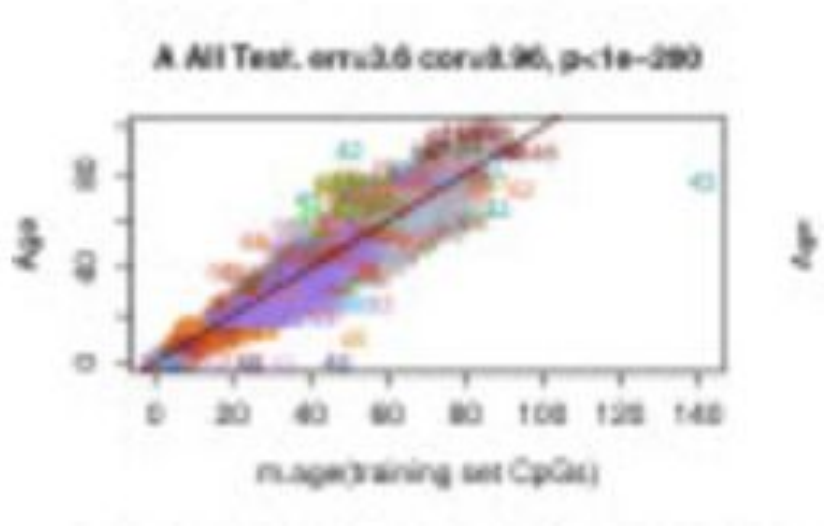
Erin Macdonald-Dunlop[1], Nele Taba[2,3], Lucija Klarić[4], Azra Frkatović[5], Rosie Walker[6], Caroline Hayward[4], Tõnu Esko[2,7], Chris Haley[4], Krista Fischer[2,8], James F. Wilson[1,4,*], Peter K. Joshi[1,*]

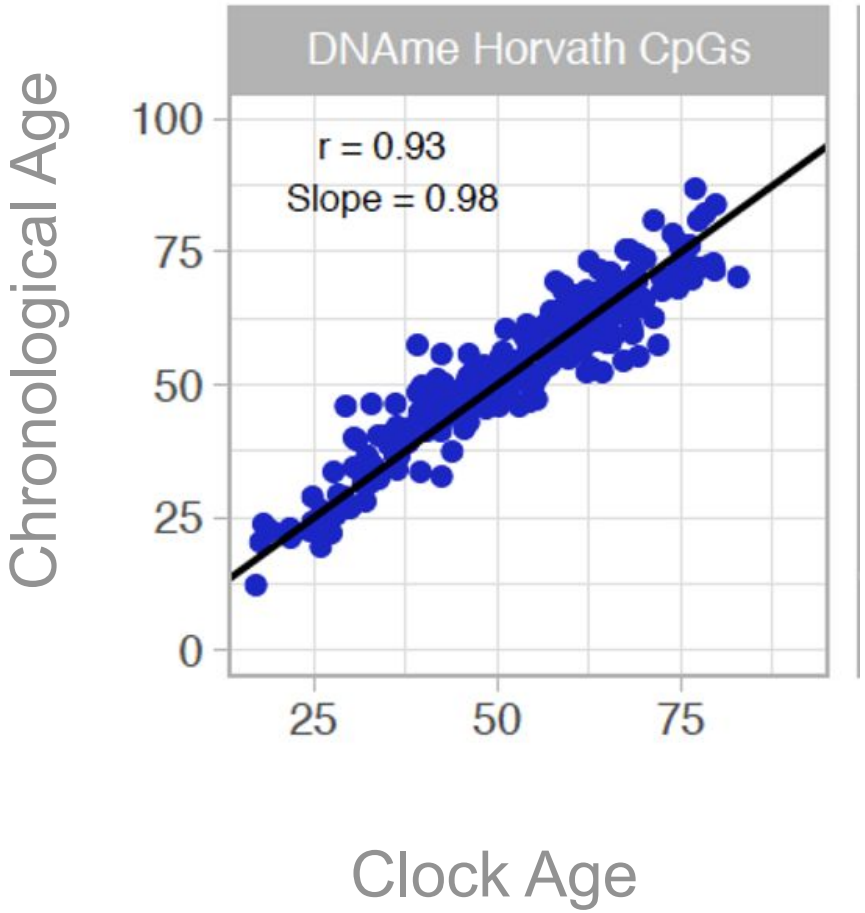


Genome-wide Methylation Profiles Reveal Quantitative Views of Human Aging Rates

Gregory Hannum[#1], **Justin Guinney**[#2], **Ling Zhao**[3,4,5], **Li Zhang**[3,4,5,6], **Guy Hughes**[4,5], **SriniVas Sadda**[7], **Brandy Klotzle**[8], **Marina Bibikova**[8], **Jian-Bing Fan**[8], **Yuan Gao**[9], **Rob Deconde**[1,10], **Menzies Chen**[1], **Indika Rajapakse**[11], **Stephen Friend**[2], **Trey Ideker**[†,1,4,10], and **Kang Zhang**[†,3,4,5]





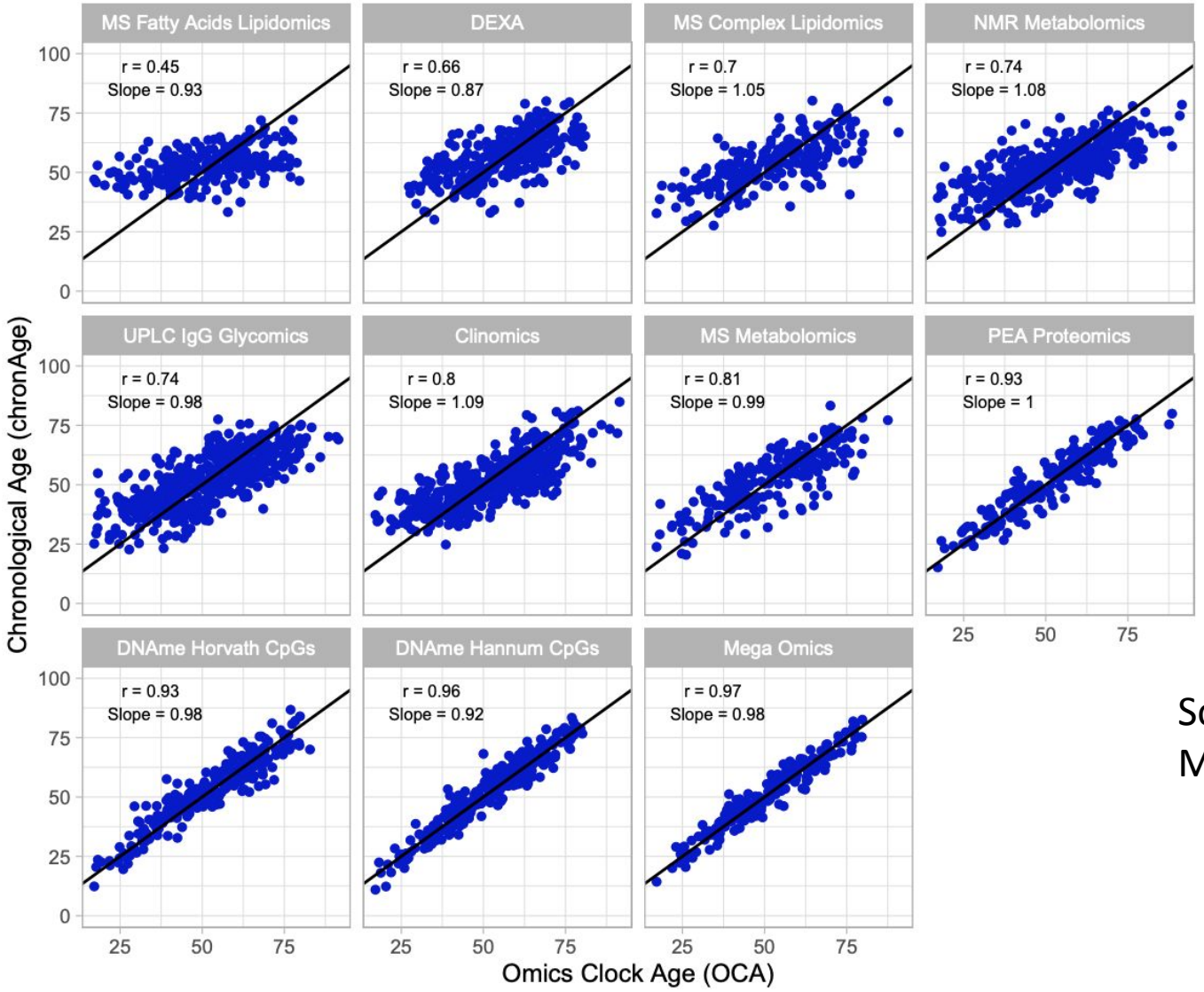


DNA methylation age of human tissues and cell types

Steve Horvath

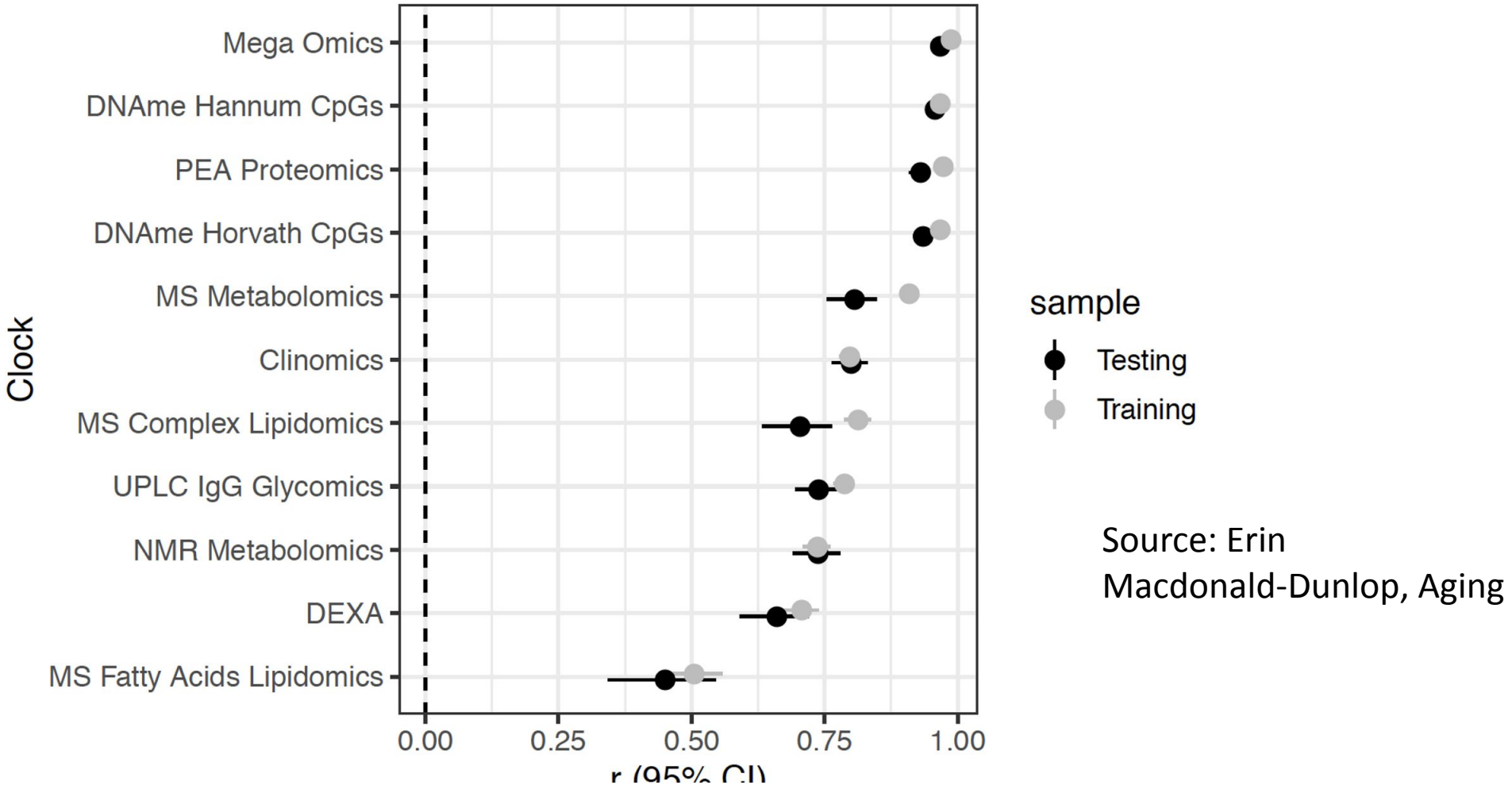
PMID: 24138928 PMCID: PMC4015143 DOI: 10.1186/gb-2013-14-10-r115

Free PMC article



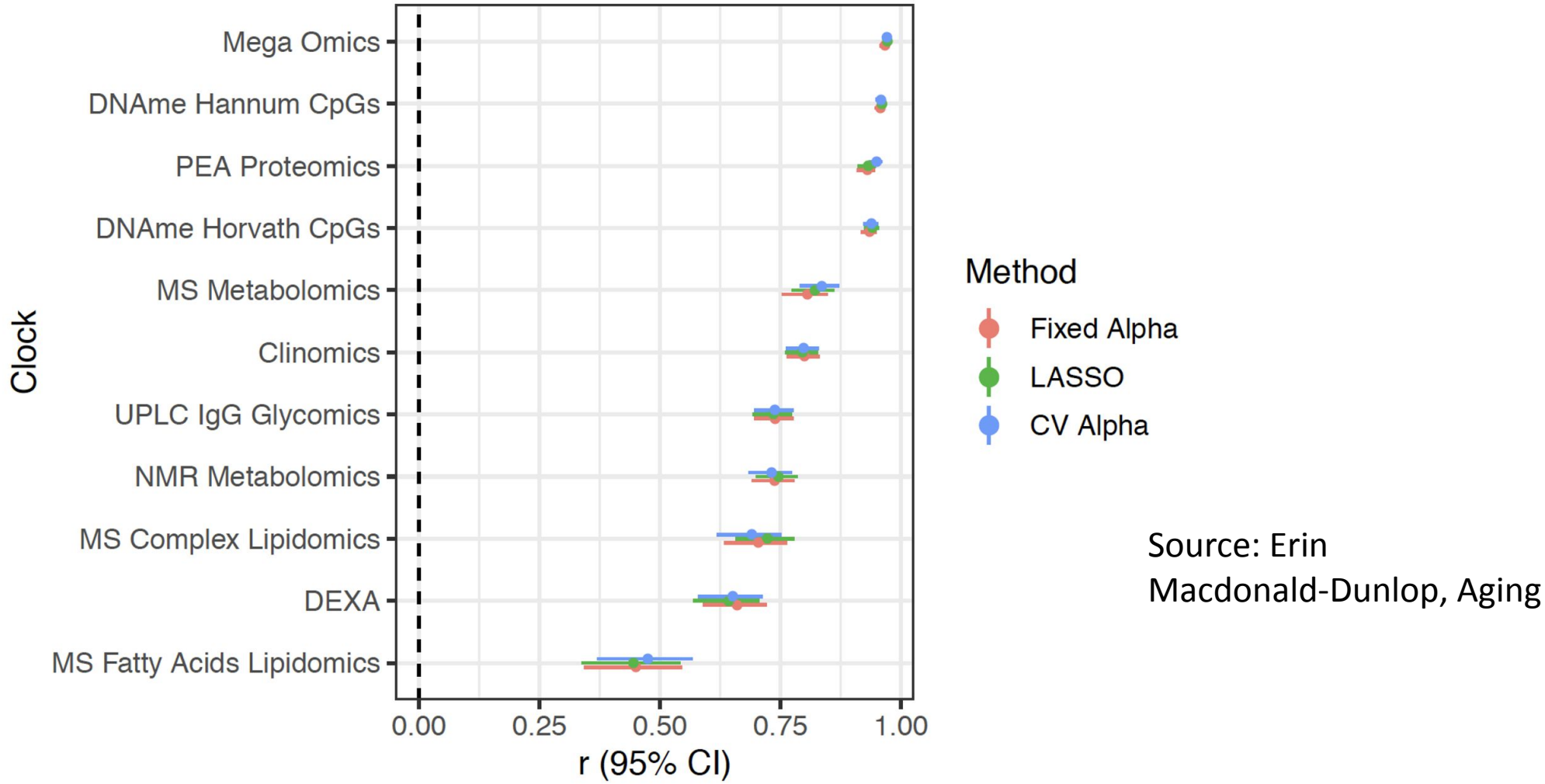
Source: Erin Macdonald-Dunlop, Aging

No evidence of substantial overfitting



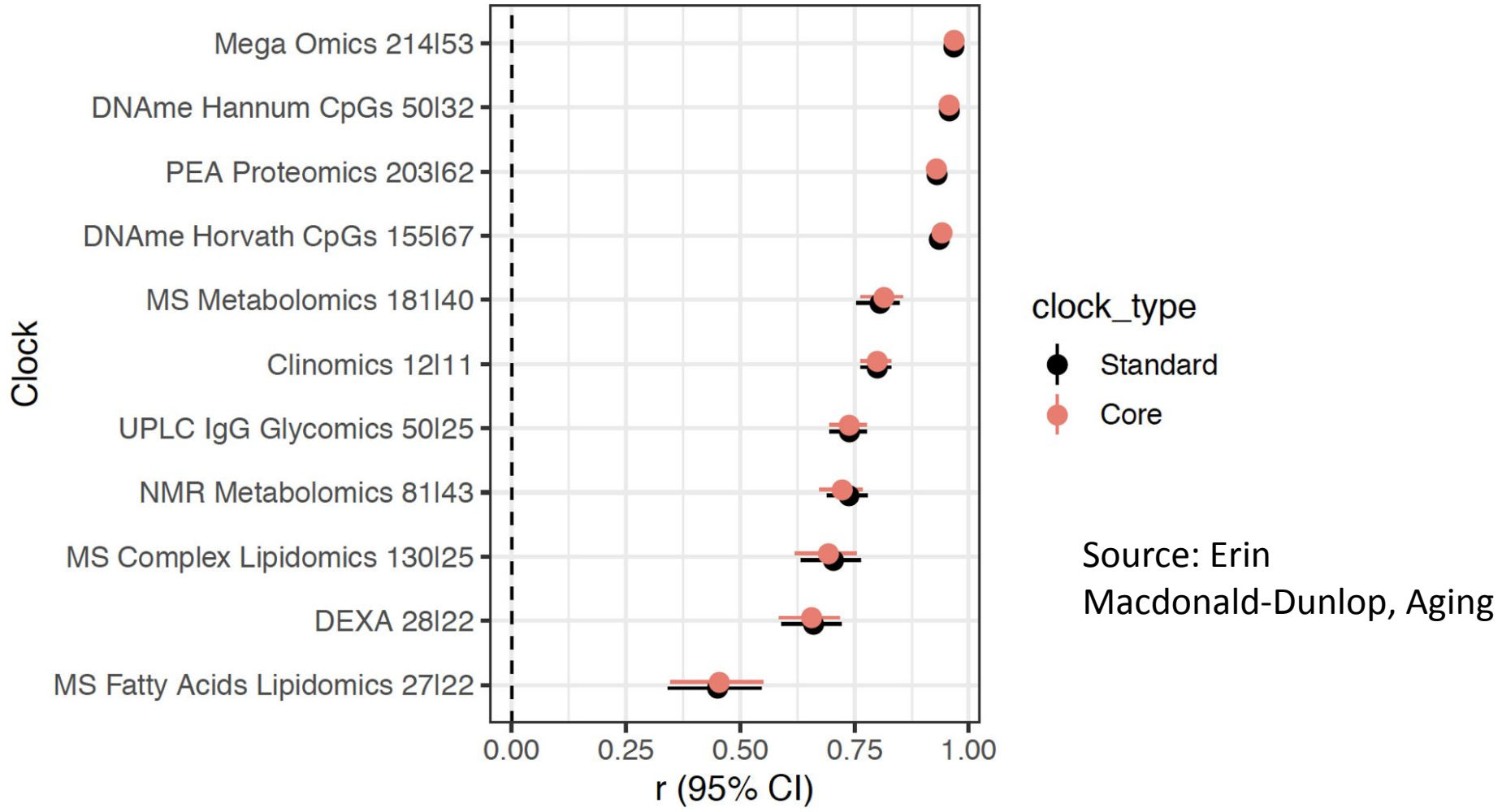
Source: Erin Macdonald-Dunlop, Aging

Correlation of ChronAge and OCA consistent, across penalised regression method



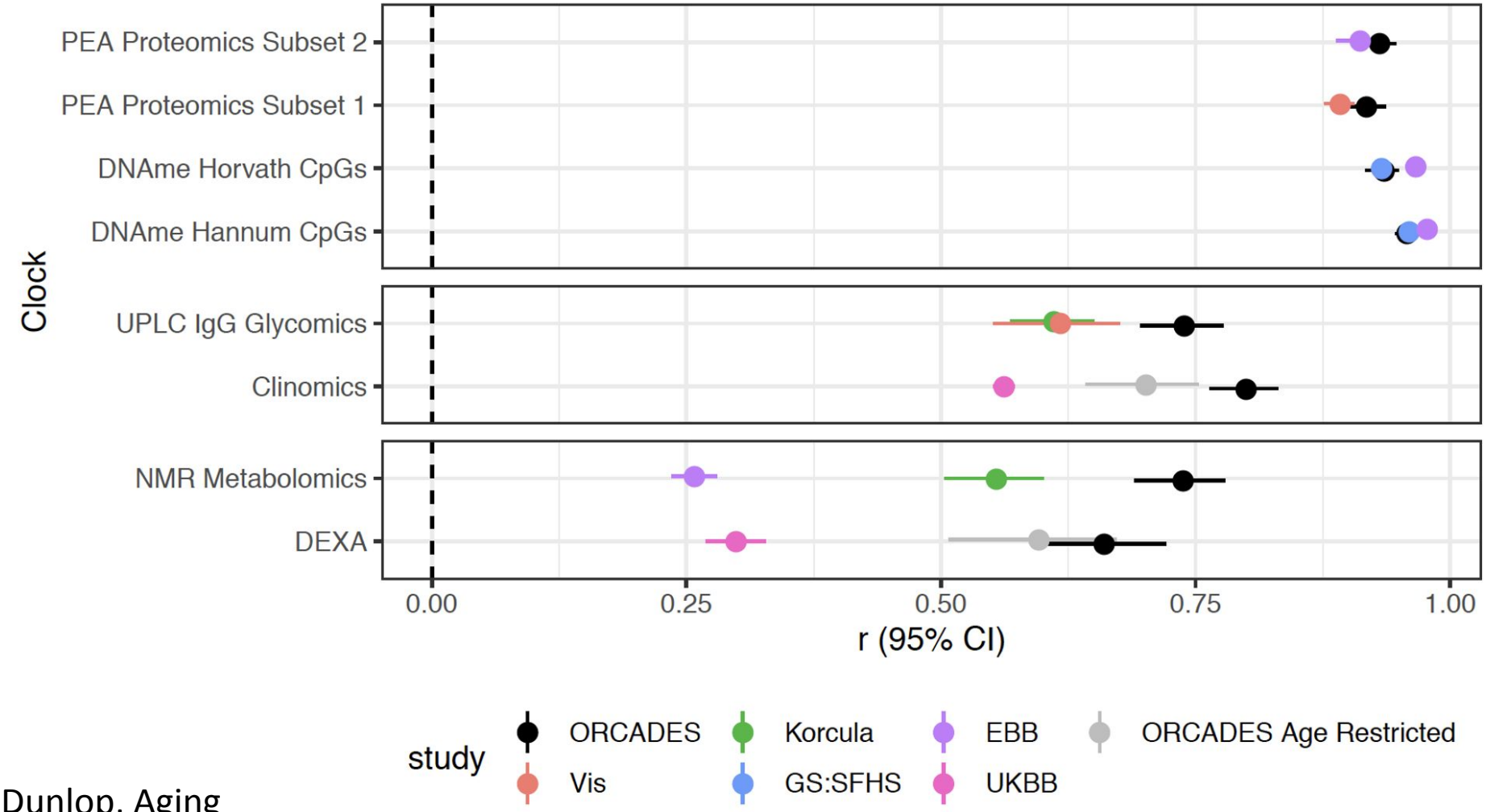
Source: Erin Macdonald-Dunlop, Aging

Not penalised enough?



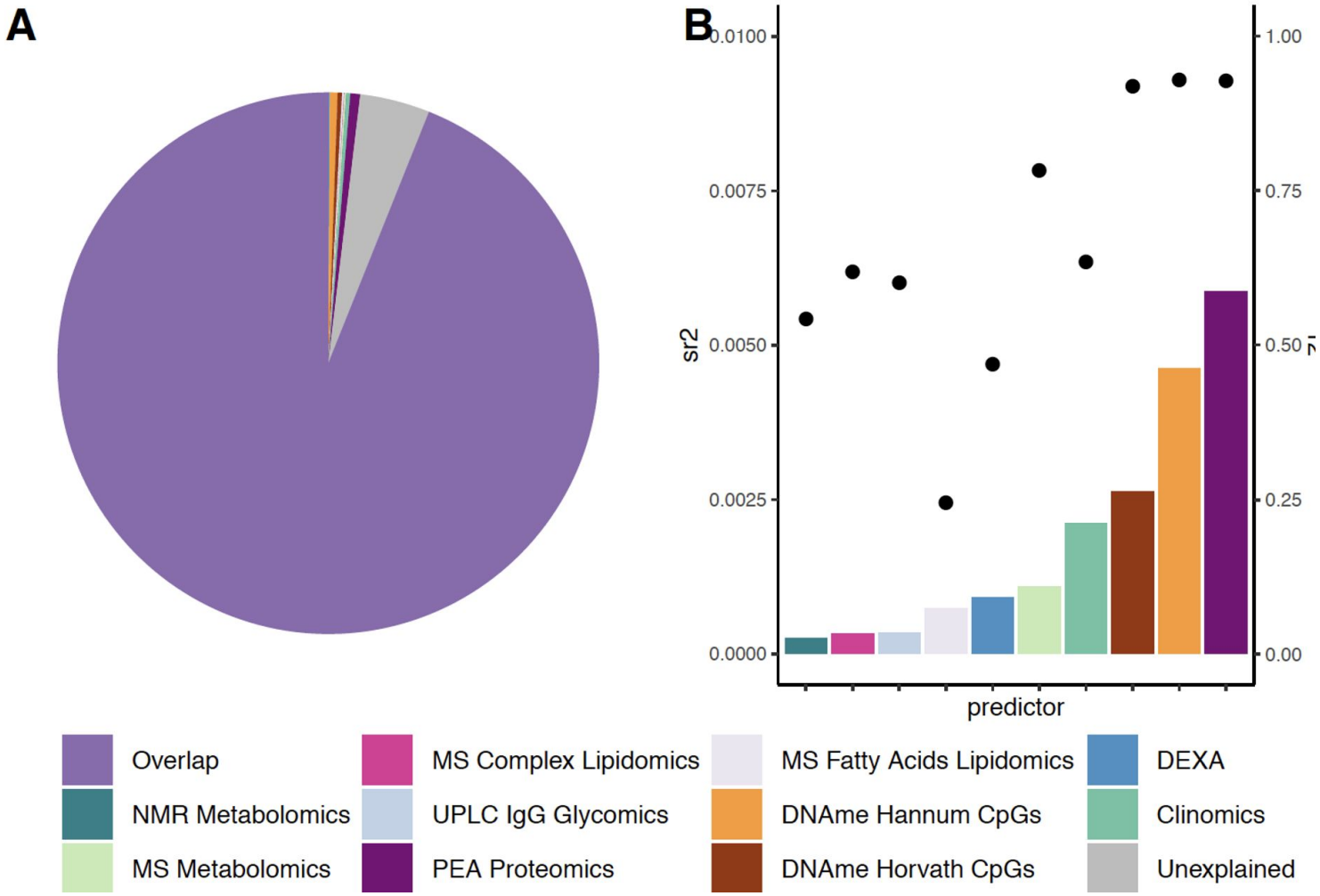
Source: Erin Macdonald-Dunlop, Aging

Some predictions generalise, some don’t



Source: Erin Macdonald-Dunlop, Aging

Most variation captured by multiple clocks -Proteomics most unique



Source: Erin Macdonald-Dunlop, Aging

Conclusions

- Penalised regression can create good estimates of chronological age
  - using a wide variety of different -omics assays
  - the assays tend to capture relatively similar features
- Optimising the penalty for correlation using cross validation may include more biomarkers than really needed
- Thoughts
  - use a more intelligent penalty function: $L_{0.5}$, cost ?
  - is Omics clock age acceleration a biological age, or an artefact

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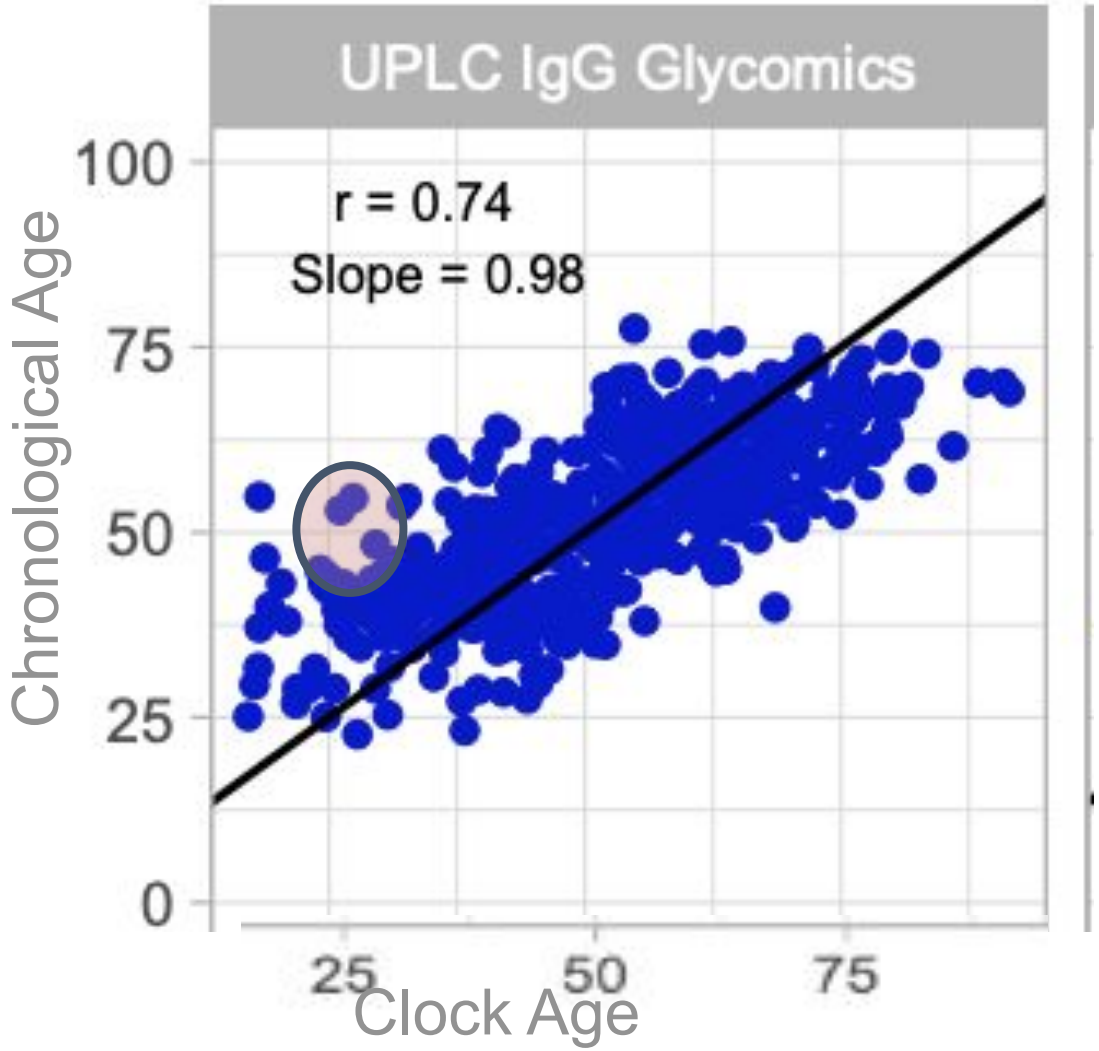
Biological Age

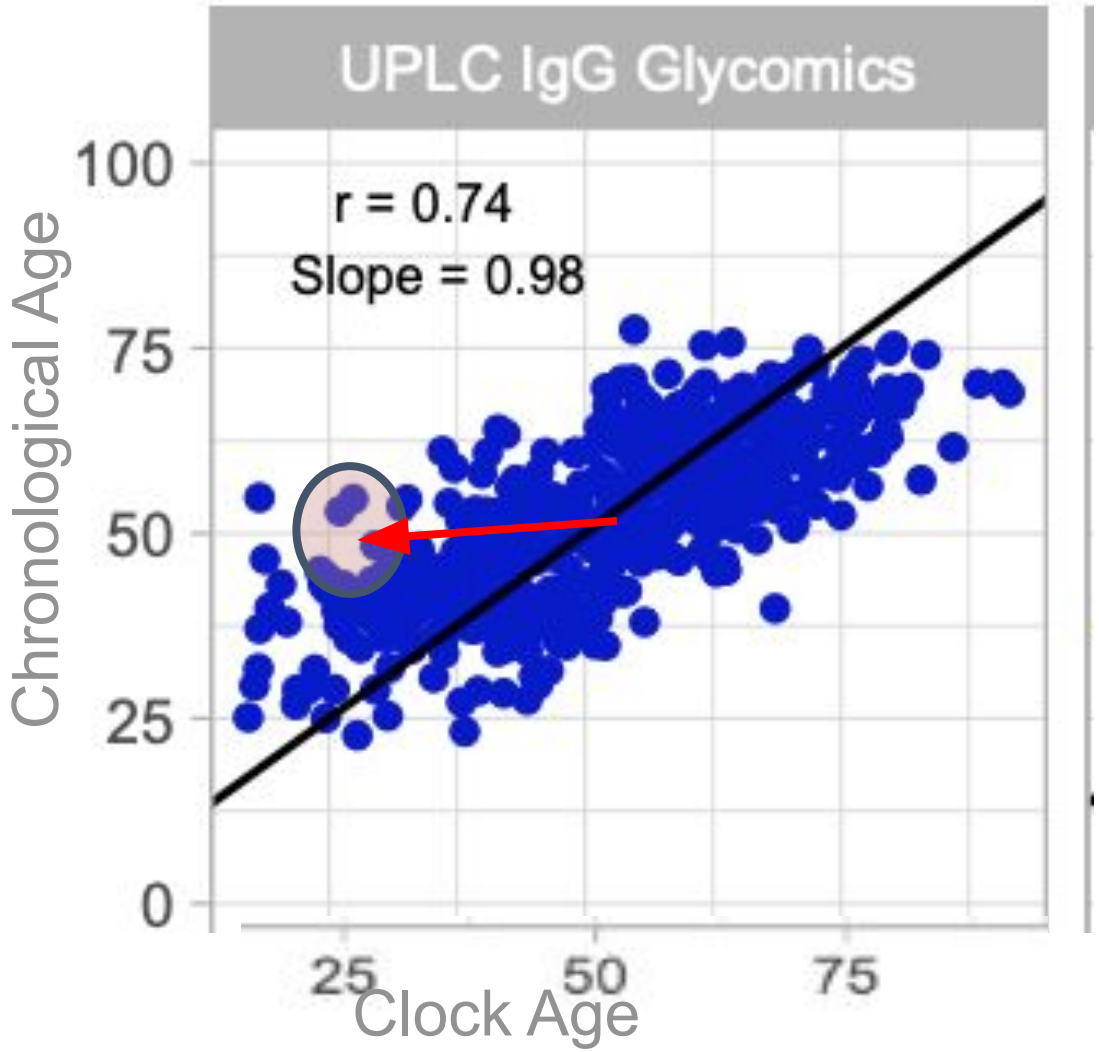
Omics clock acceleration

Biological age

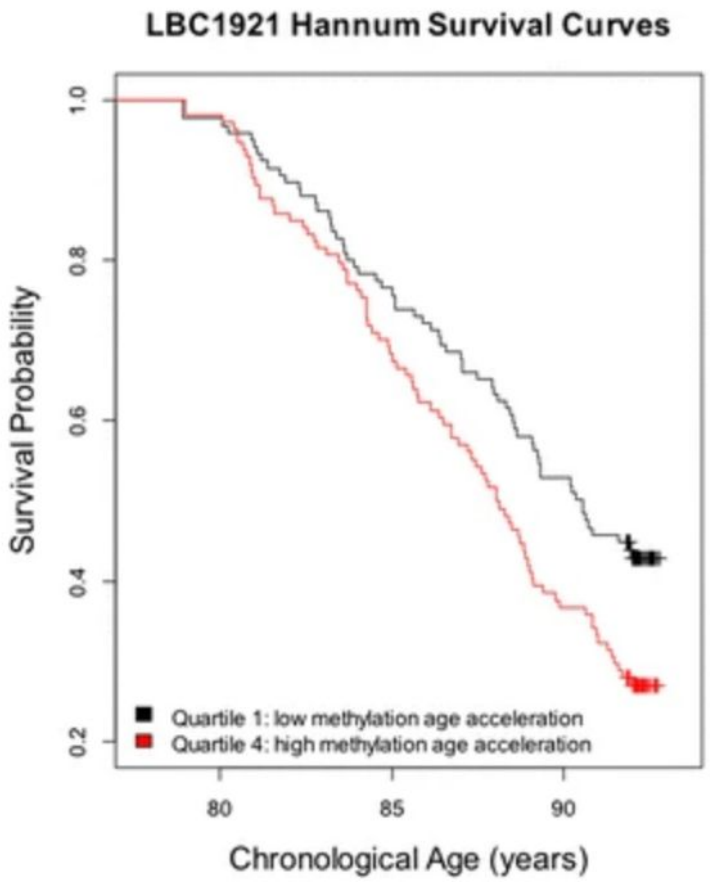


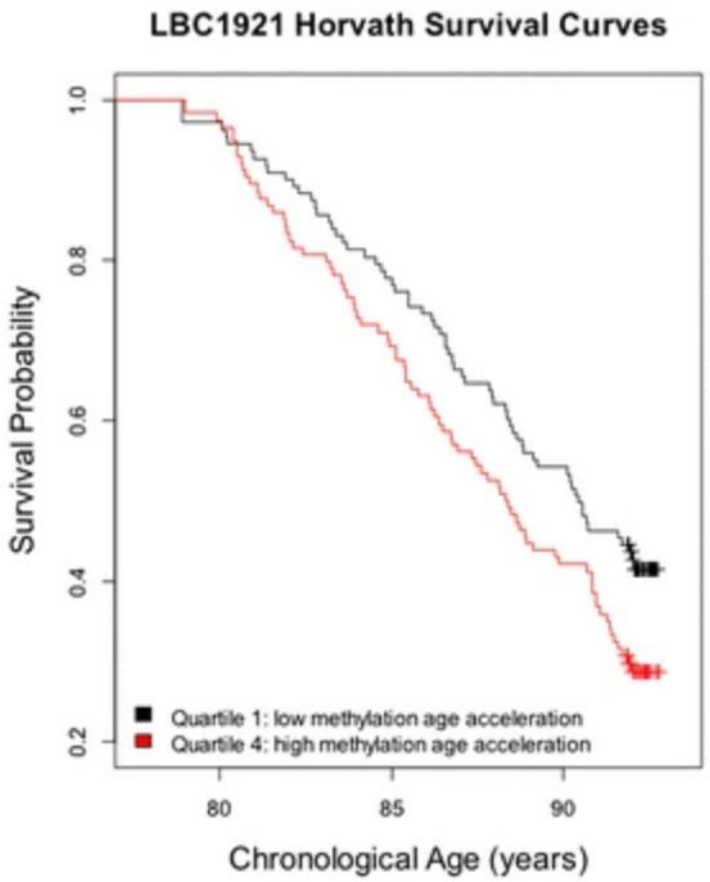
Source: Erin Macdonald-Dunlop, Aging

Biological age



Age acceleration does predict mortality



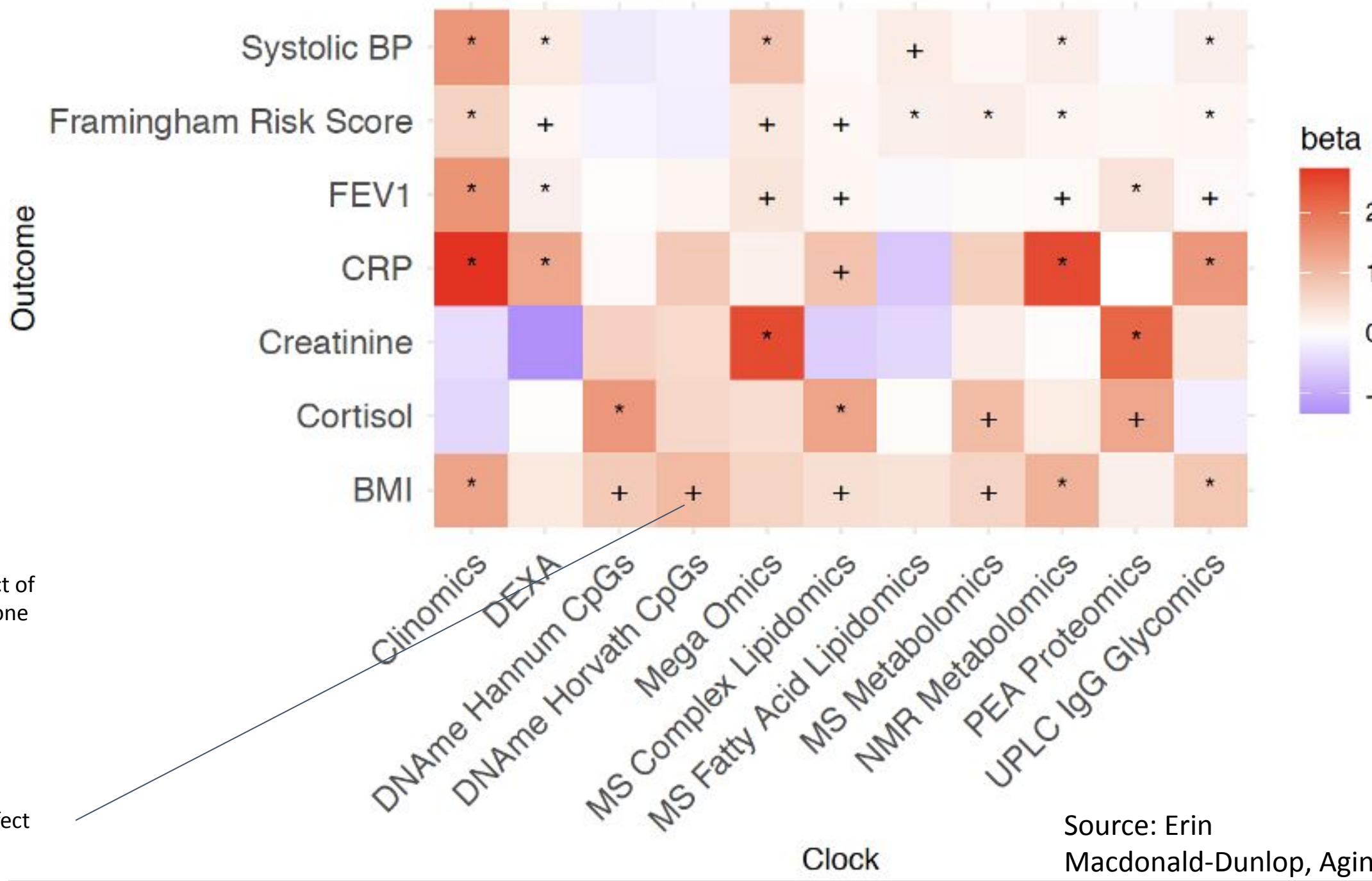


DNA methylation age of blood predicts all-cause mortality in later life

Riccardo E Marioni, Sonia Shah, [...] Ian J Deary

Genome Biology **16**, Article number: 25 (2015) | Cite this article

35k Accesses | **466** Citations | **334** Altmetric | Metrics



Beta : ratio of effect of one year of AA to one year of CA

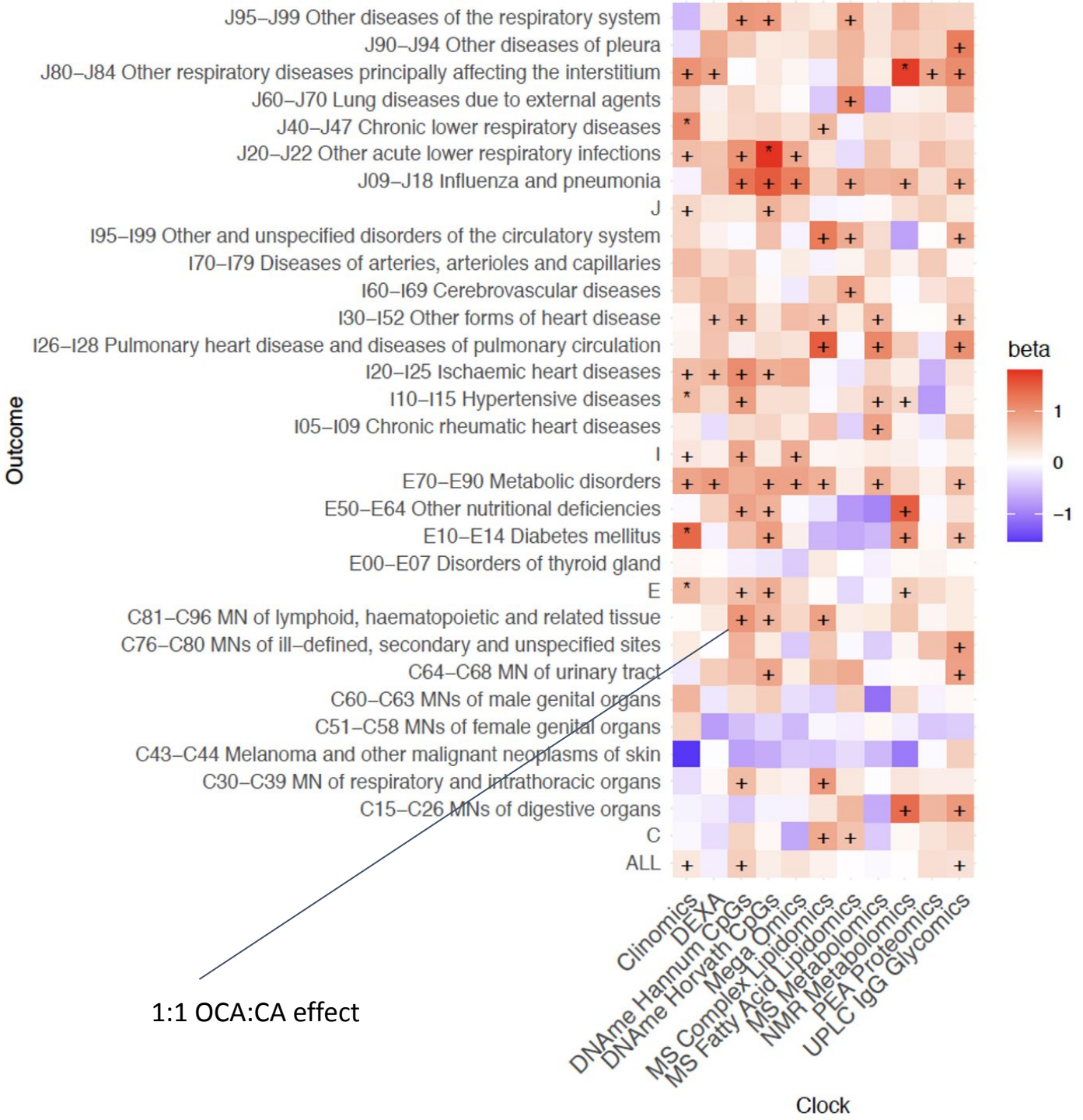
1:1 OCA:CA effect

Source: Erin Macdonald-Dunlop, Agin

Positive age acceleration associations observed with increased disease risk..

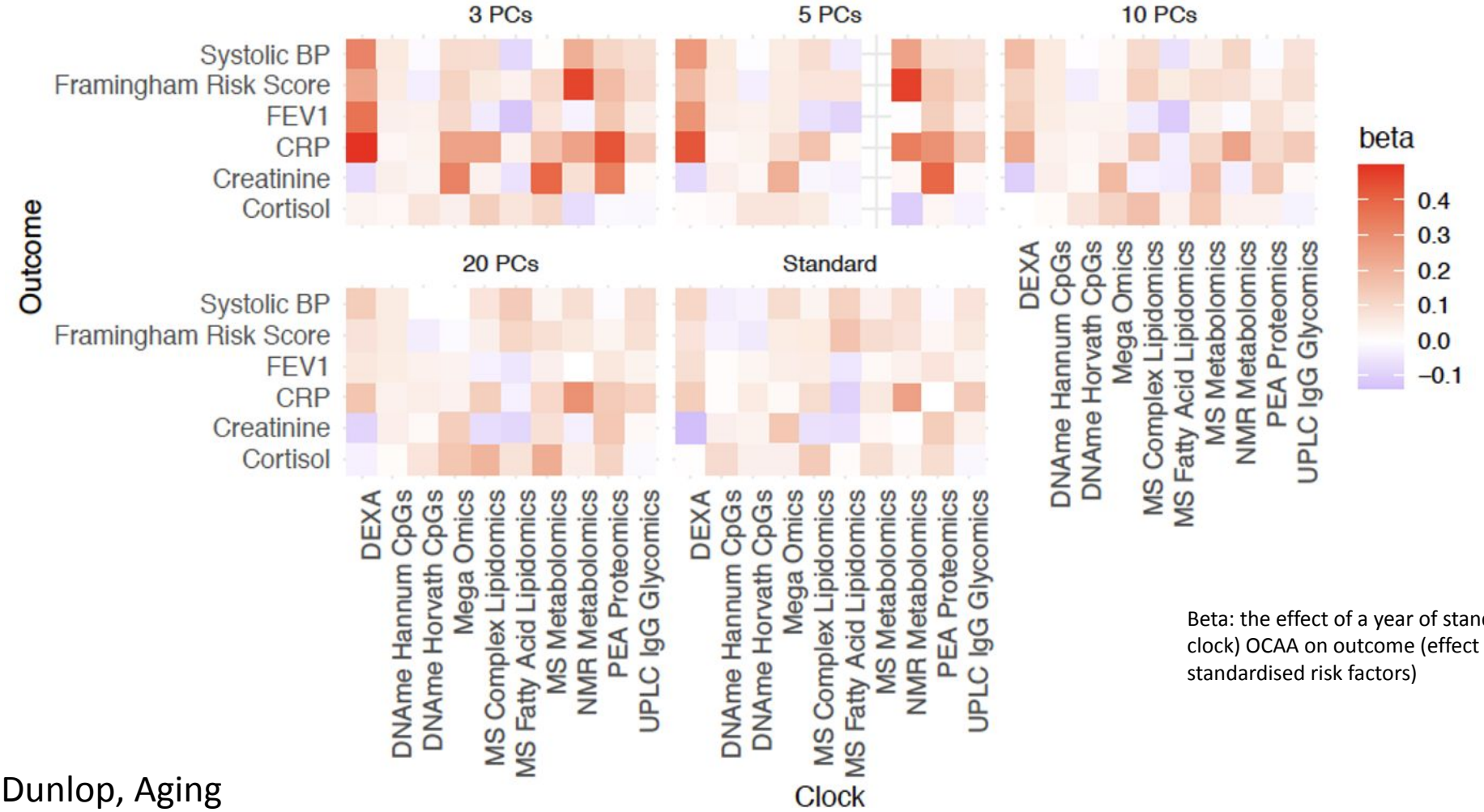
Beta : ratio of effect of one year of AA to one year of CA

Source: Erin Macdonald-Dunlop, Aging



1:1 OCA:CA effect

Clock residuals built using a few PCs more predictive



Beta: the effect of a year of standardised (within clock) OCAA on outcome (effect sizes for standardised risk factors)

Source: Erin Macdonald-Dunlop, Aging

Conclusion

- Chronological age derived biological age models are somewhat predictive of health

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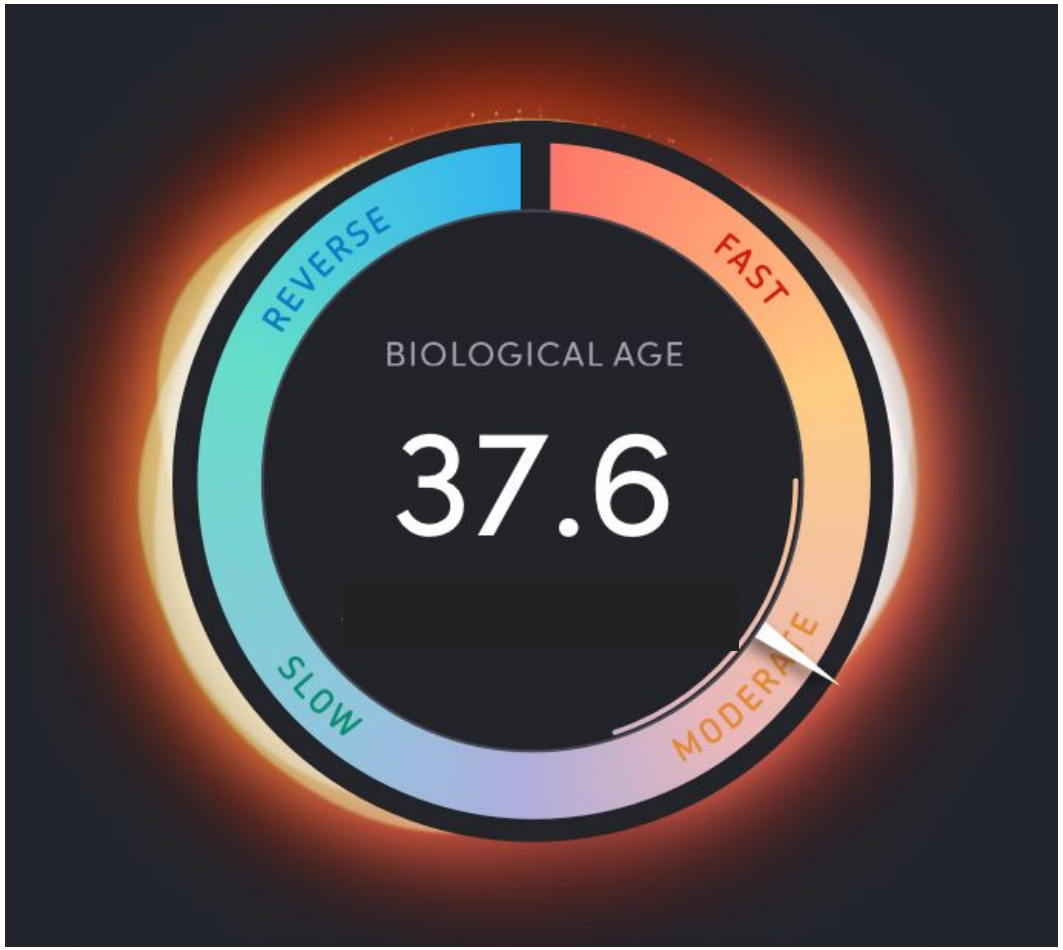
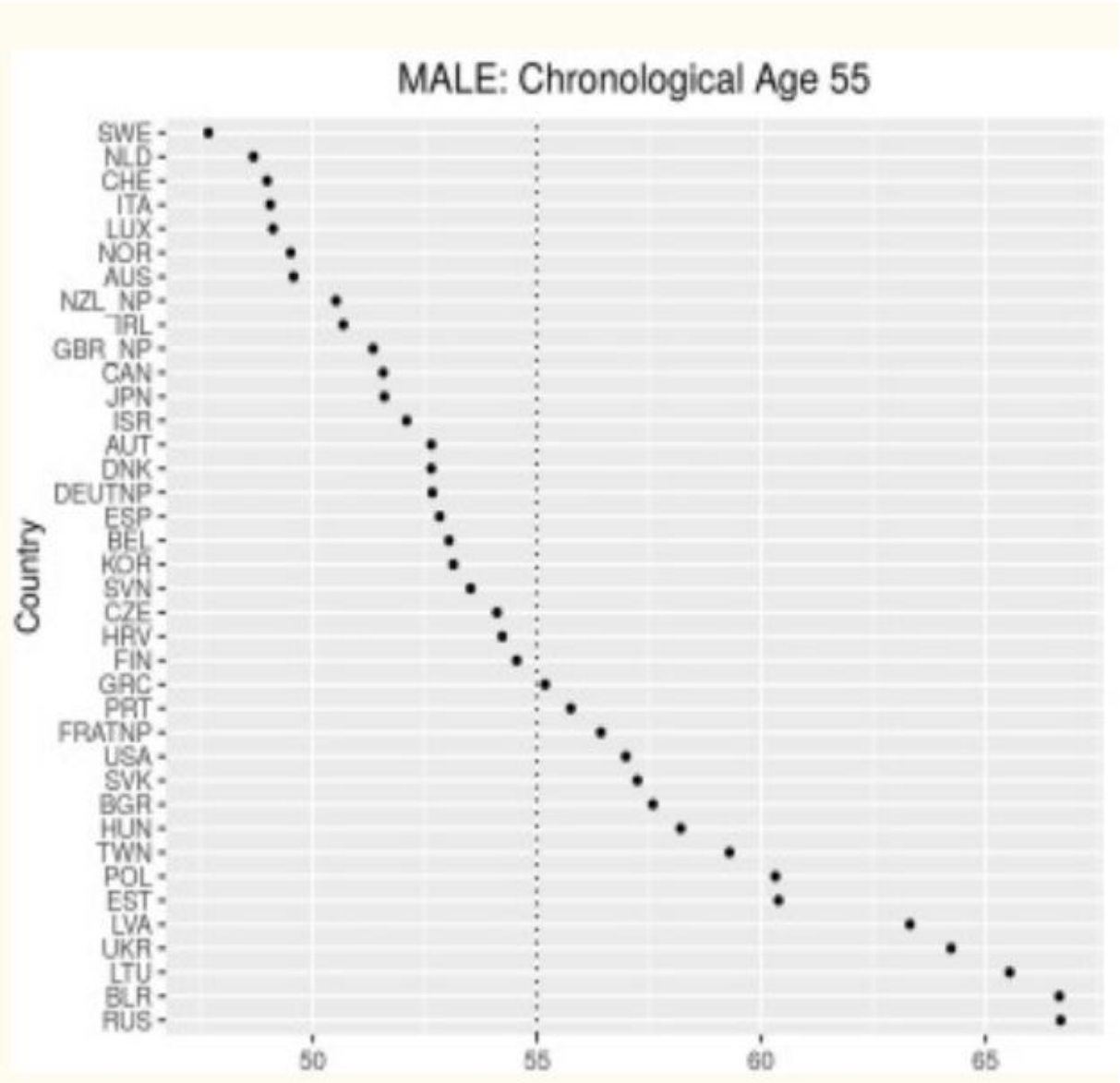
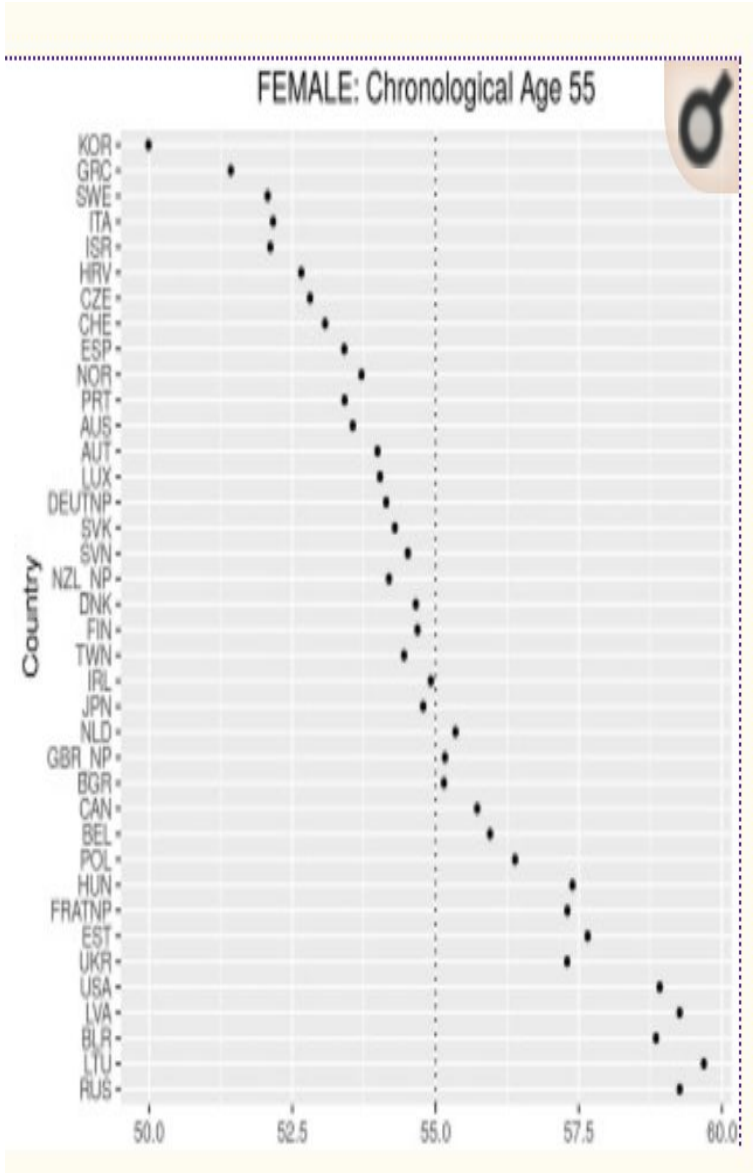


HUMANITY

An alternative approach





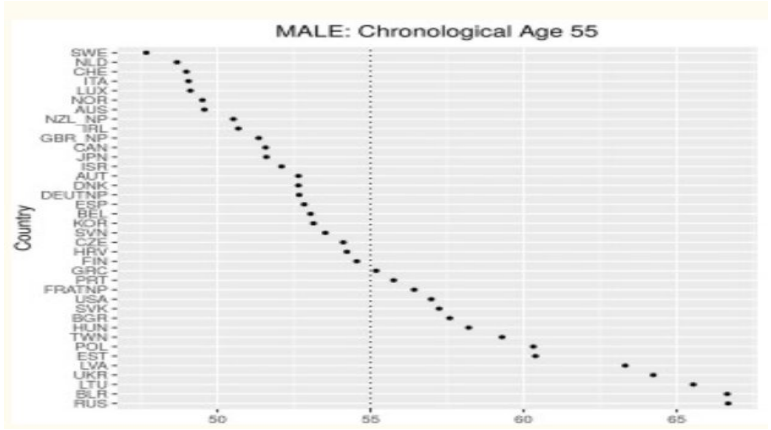
An alternative approach

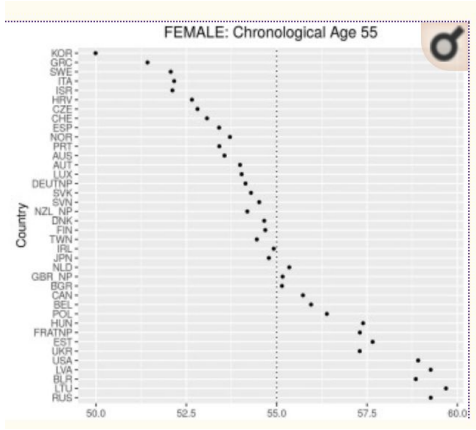
- Interesting but is it useful?
  - birth certificate
- reference population
- regress -omics age for each country against (period ??) expectation of life

Calibrating Gompertz in reverse: What is your longevity-risk-adjusted global age?☆

Moshe A. Milevsky*

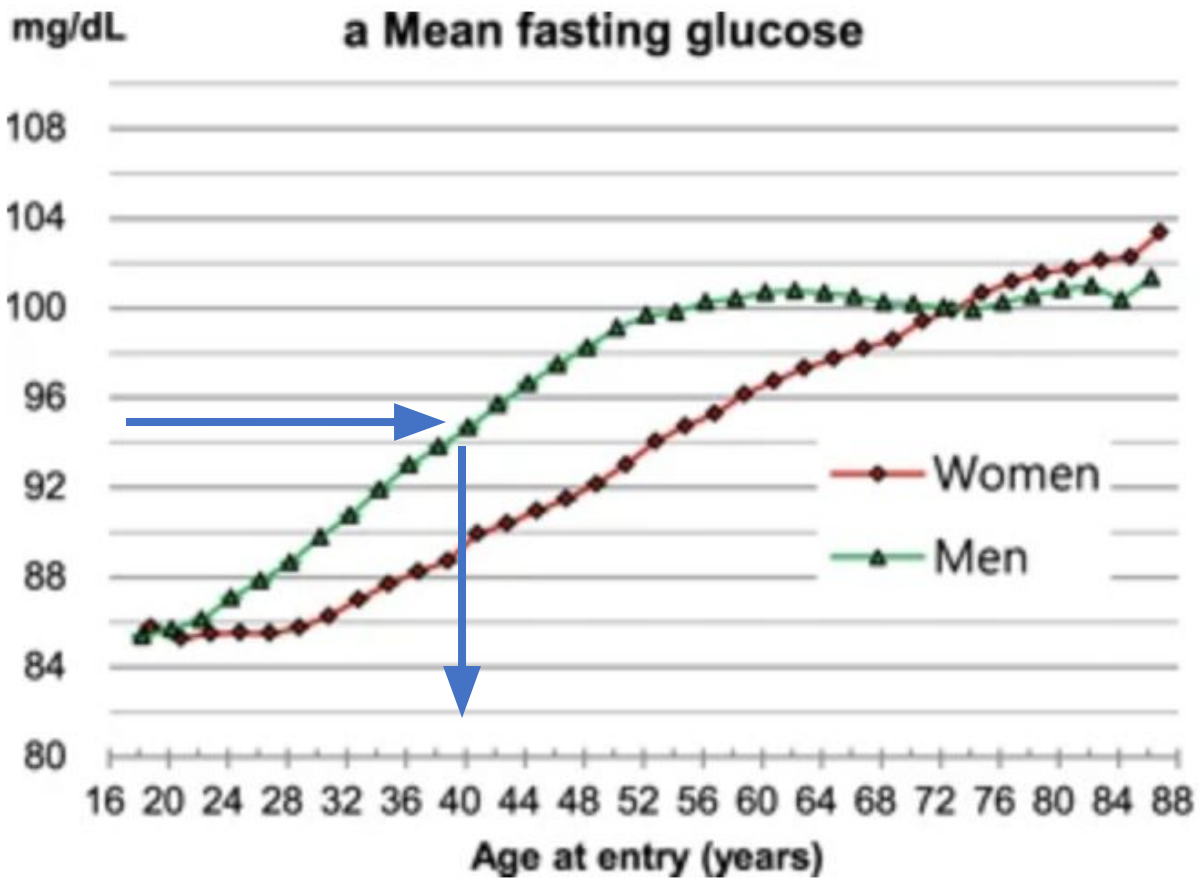
Schulich School of Business, York University, Canada
Graduate Faculty of Mathematics and Statistics, York University, Canada





A simpler aging clock

Figure 1



Association between fasting glucose and all-cause mortality according to sex and age: a prospective cohort study

Sang-Wook Yi, Sangkyu Park, Yong-ho Lee, Hyang-Jeong Park, Beverley Balkau & Jee-Jeon Yi

Scientific Reports **7**, Article number: 8194 (2017) | Cite this article

Outlook

- Chronological age predictors have potential forensic value
  - in the absence of a verified birth certificate
- Biological age is gaining ground due to its intuitive and helpful interpretation
- Work needs to be done focussing on it providing value beyond the birth certificate
- The field needs to standardise its metrics and agree objectives
  - a p-value or AUC are not enough
- Experiments need to be devised to distinguish an intrinsic hidden biological age from its correlates

Acknowledgements

A catalogue of omics biological ageing clocks reveals substantial commonality and associations with disease risk

Erin Macdonald-Dunlop, Nele Taba, Lucija Klaric, Azra Frkatovic, Rosie Walker, Caroline Hayward, Tonu Esko, Chris Haley, Krista Fischer, James F Wilson, Peter K Joshi

doi: https://doi.org/10.1101/2021.02.01.429117

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Appendix

We need better metrics

Study	n training	training outcome	r training outcome	second outcome	performance	
marioni(horvath)	656	chron age	r=0.91	death	HR 1.11 [1.05,1.16]	
levine (PhenoAge)	456	blood marker age	?	death	HR 1.045 [1.04,1.05]	
Lui (GrimAge)					HR 1.1 [1.09,1.12]	

“It is not meaningful to compare HR estimates (here HR=1.02 and HR=1.10, respectively) because these HR estimates critically depend on the scale/distribution of the respective mortality predictors. To provide a meaningful and scale-independent comparison, we focused on the meta-analysis P-values.”