AGS/NIA R13 Bench-to-Bedside Conference Series Stress Tests and Biomarkers of Resilience

Integrative omics Predicting Resilience

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No disclosures

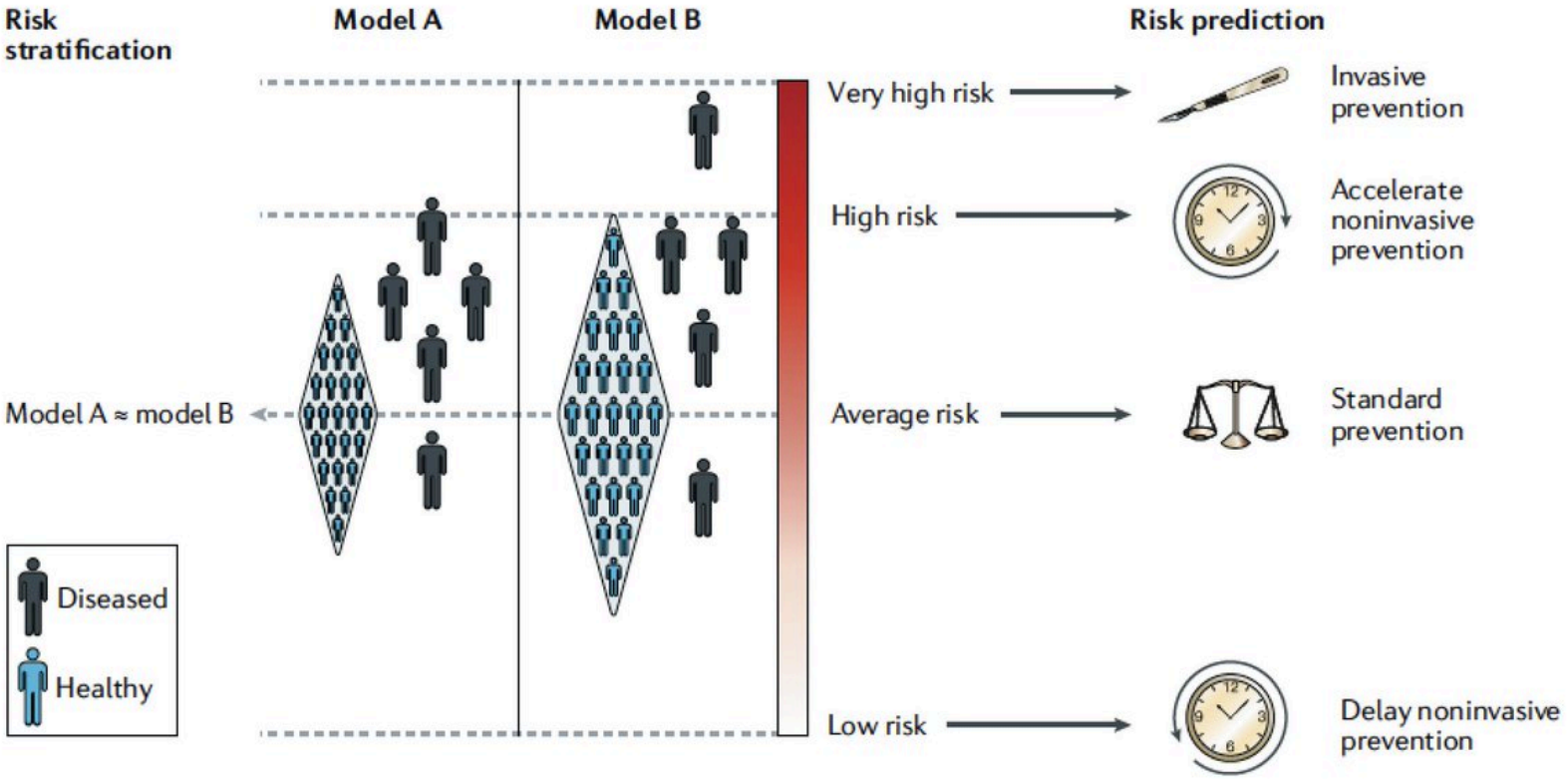
Precision Health aims to integrate an individual's genetic code into their health care.

Integration of genomics can help to

1) identify those at risk, promoting disease prevention strategies;
2) diagnose disease at earlier stages where better control or even mitigation of disease is possible;
3) predict disease severity allowing for early intervention and optimal, effective management; and
4) select the most efficacious treatment.

The promise of the Polygenic Risk Score (PRS)

PRS delivers on the scientific promise of using genetics in predicting disease/health outcomes in a translational framework **that is equitable across populations.**



CHALLENGES

Robust genetic evidence

Sample size

*Heterogeneity**

*Diversity**

Translational value

Dx risk

Dx severity

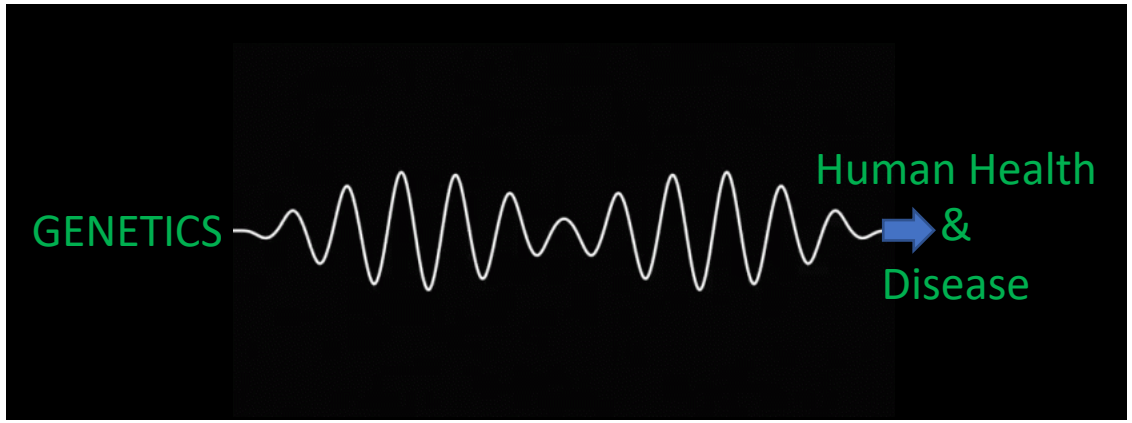
Dx trajectory

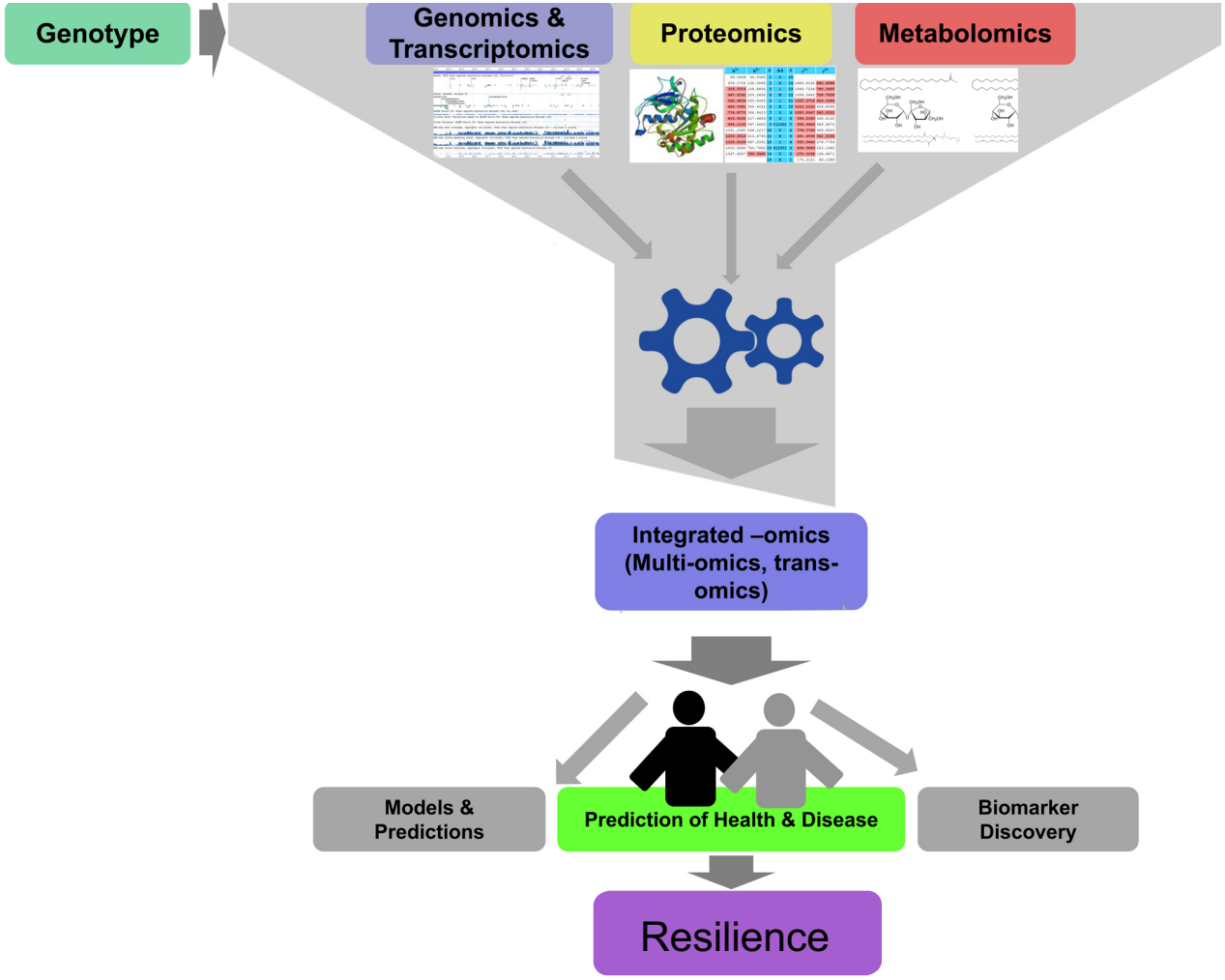
*Dx pathophysiology**

Transferability

Representation

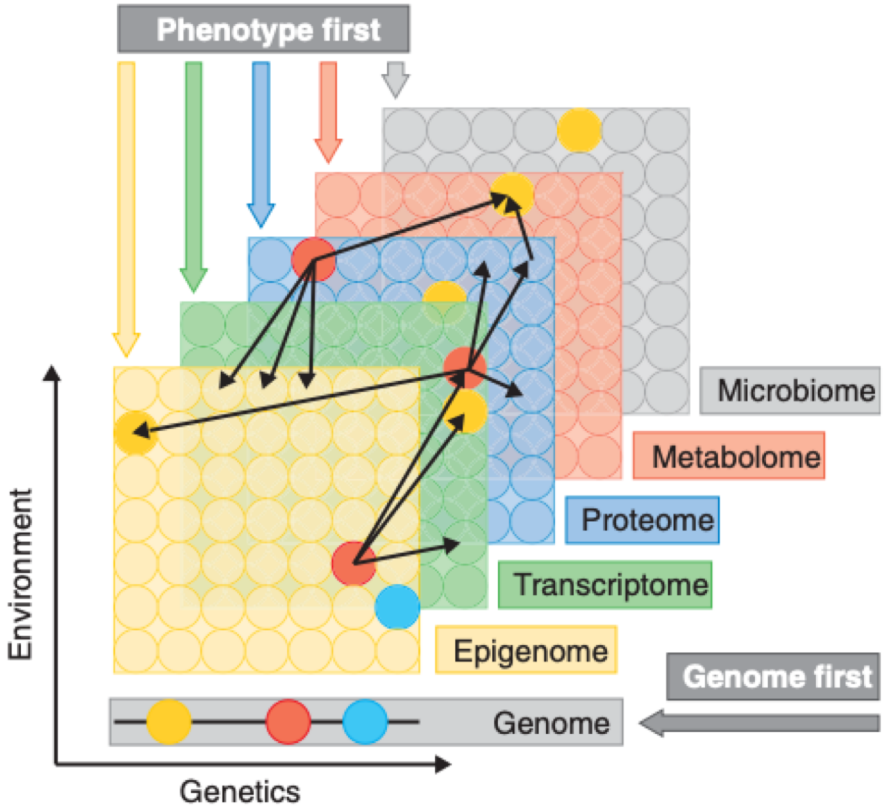
Genomics → Phenotype: far greater than genetics in a silo

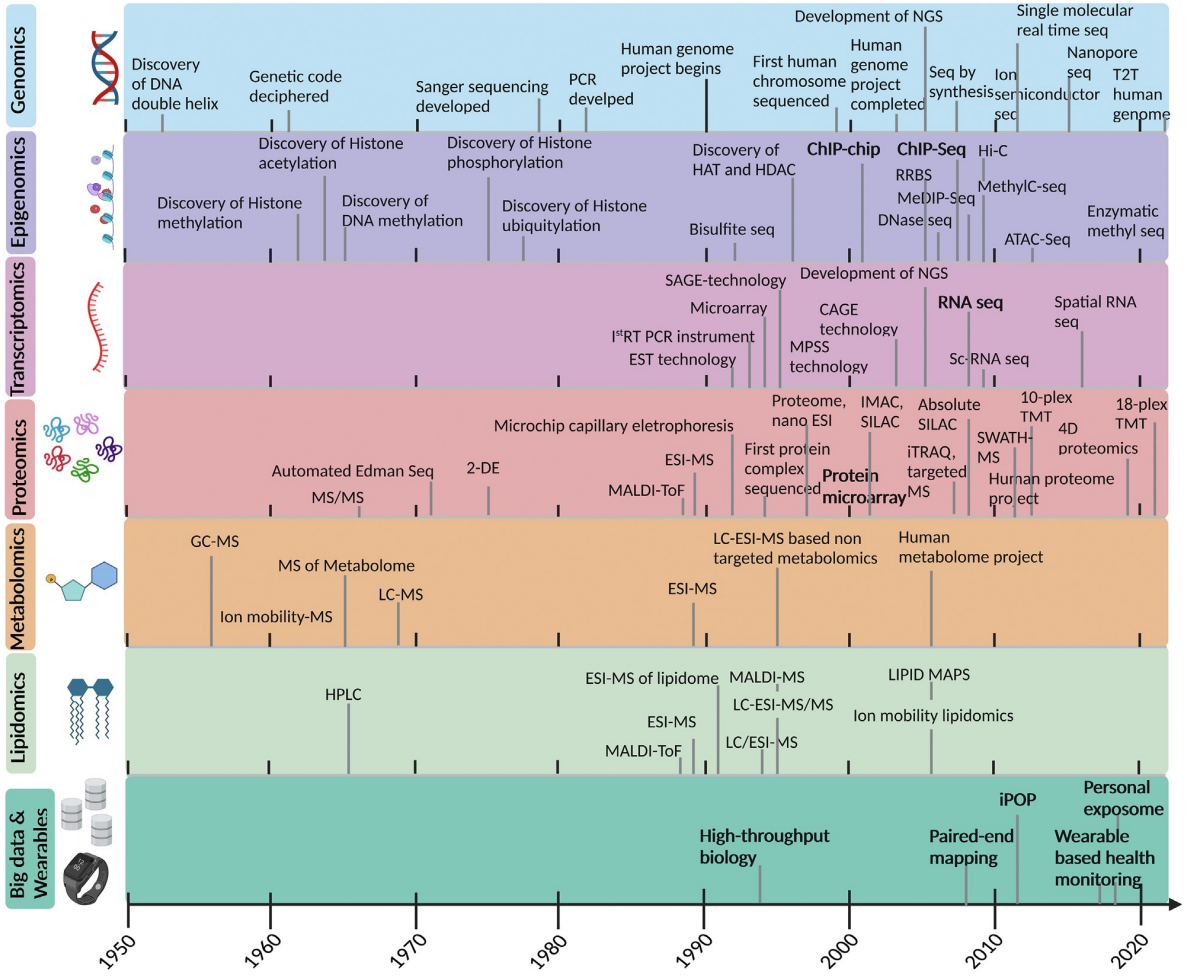




https://jme.bioscientifica.com
https://doi.org/10.1530/JME-18-0055

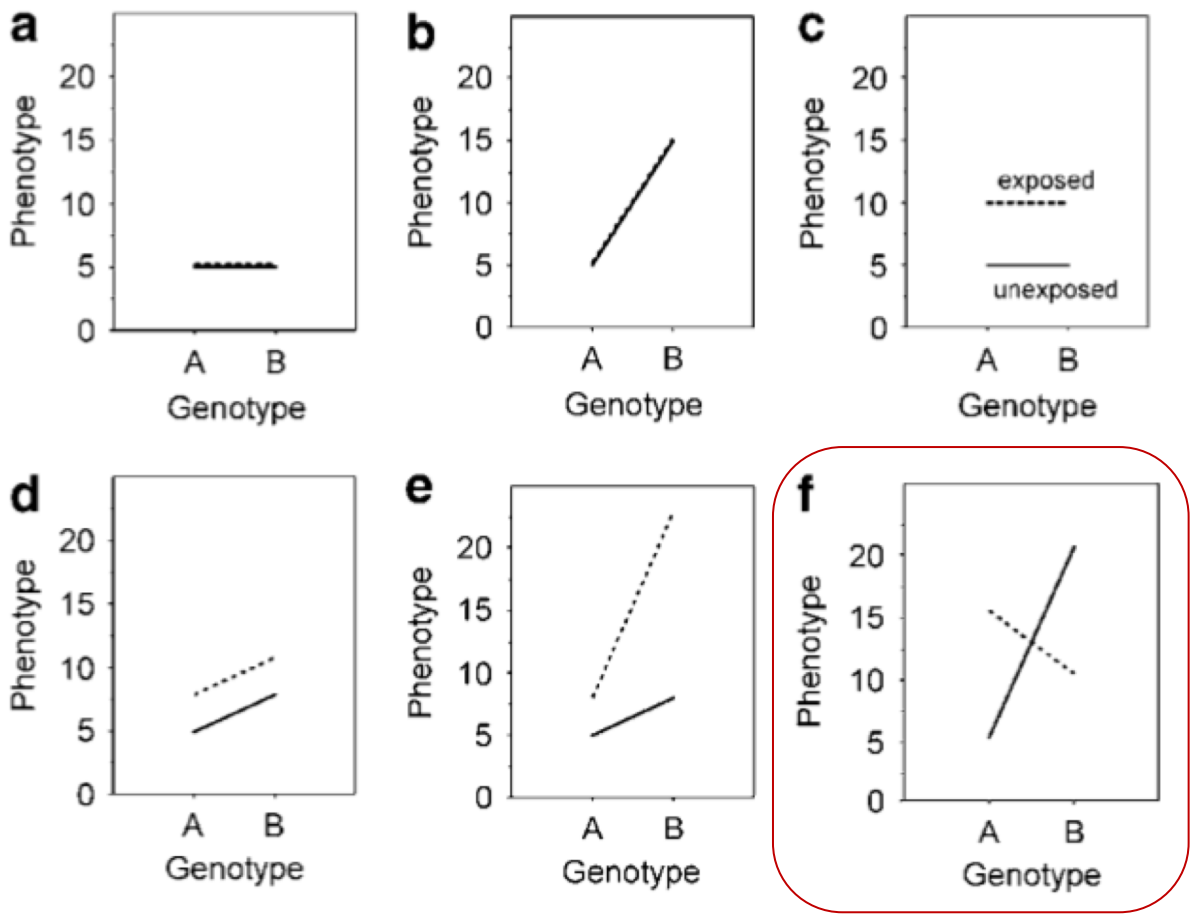
Multi-omics
→ Phenotype

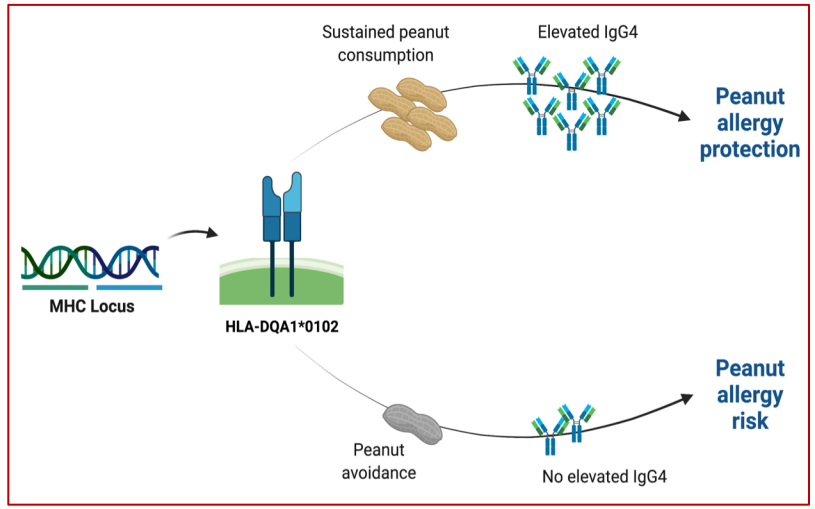




Hasin et al. Genome Biology (2017) 18:83
Babu & Snyder. Mol Cell Proteomics. 2023 Jun;22(6):100561.

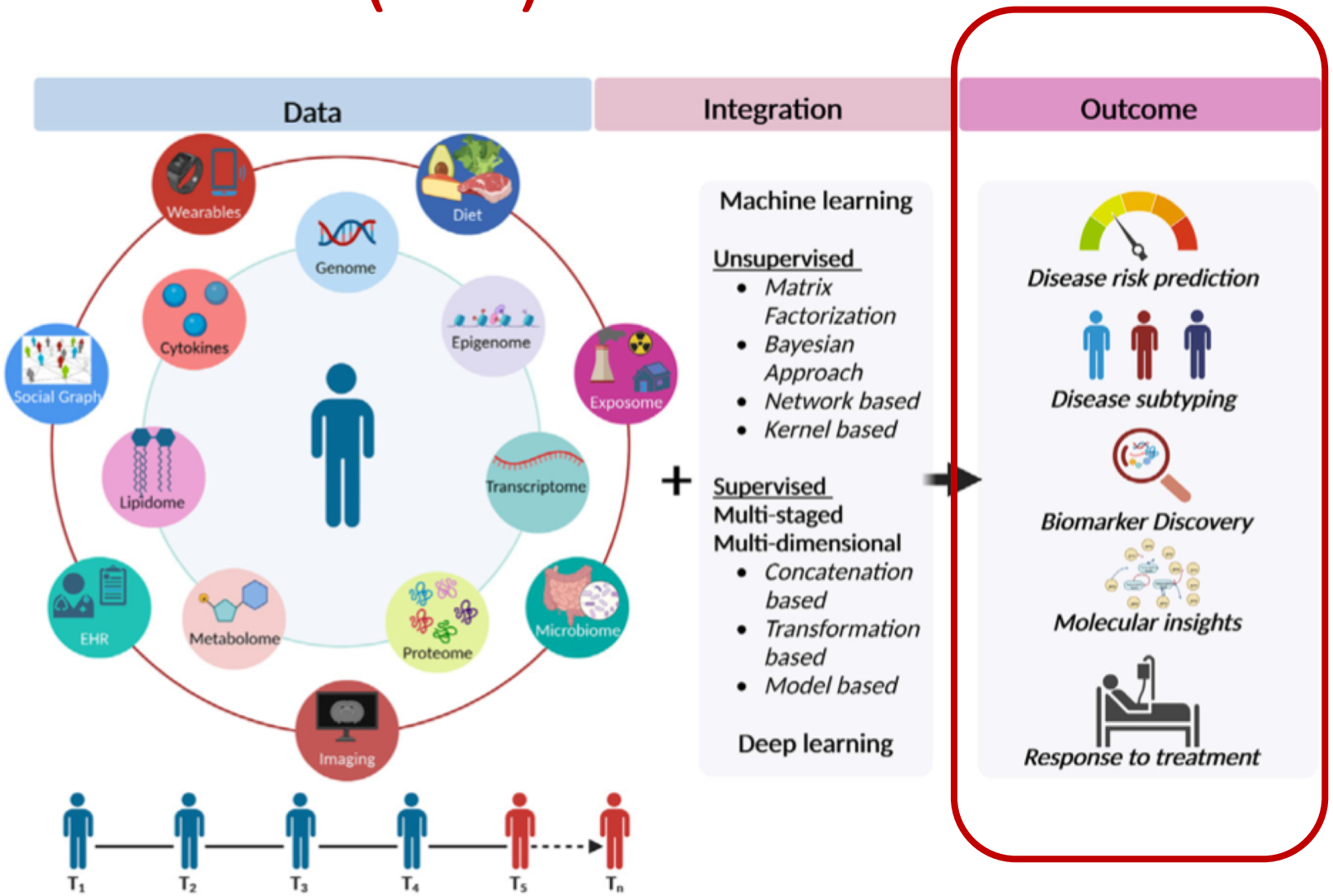
Context matters : gene * environment interactions





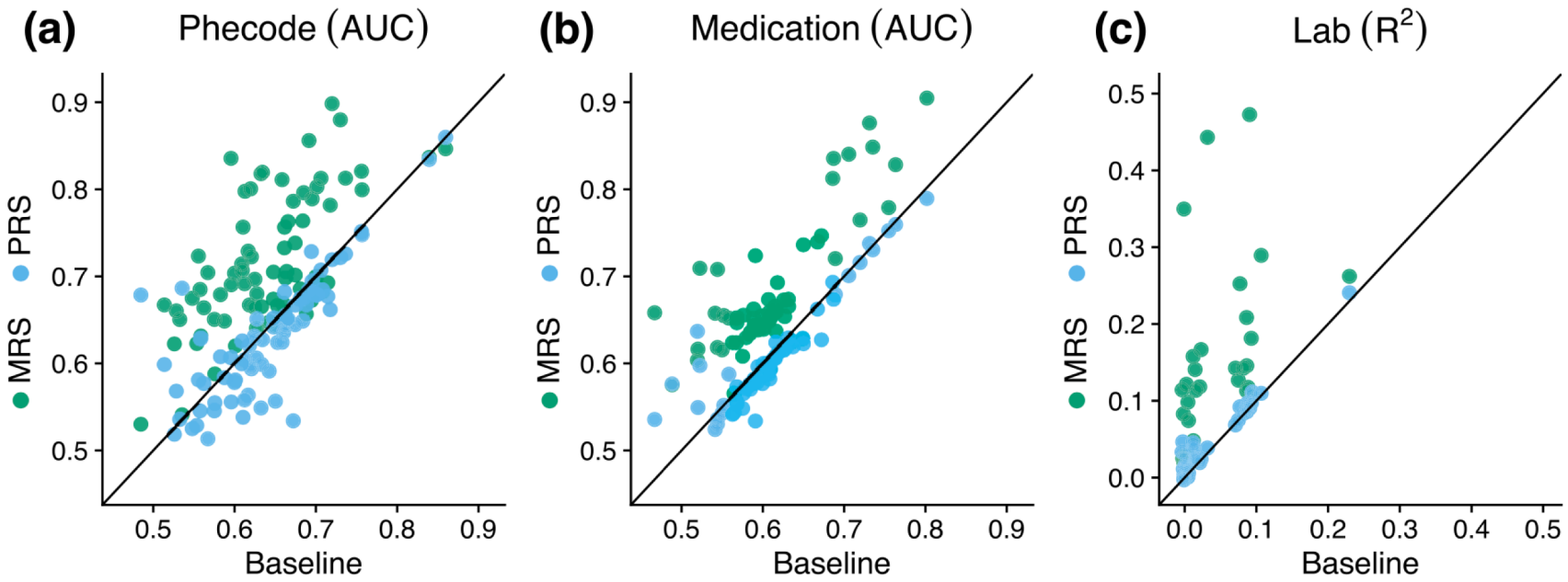
https://www.nature.com/articles/ejhg2008106

Multi-omics → Phenotype: The promise beyond the Polygenic Risk Score (PRS)



Babu & Snyder. Mol Cell Proteomics. 2023 Jun;22(6):100561.

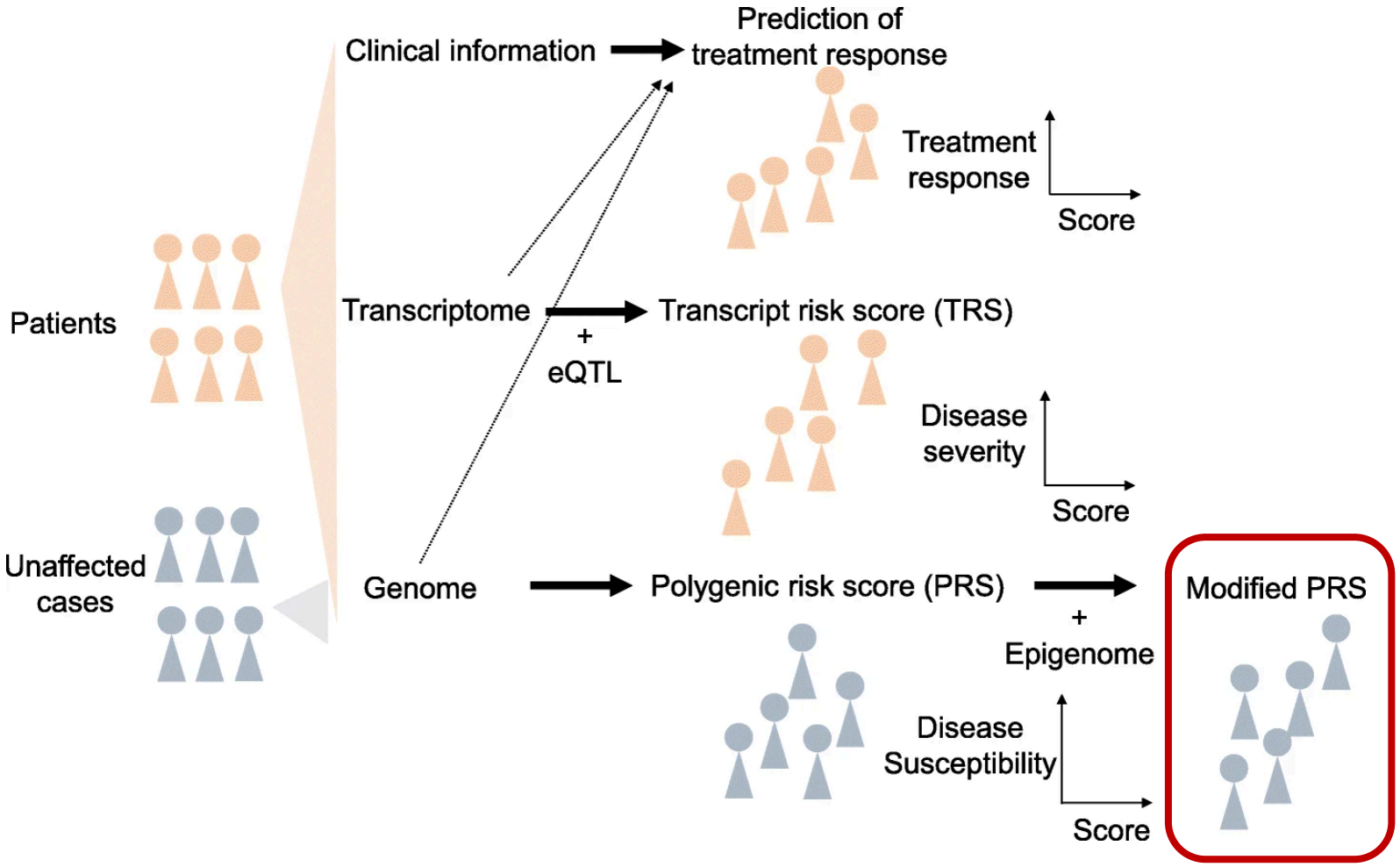
Integrative omics approaches to clinical translation: PRS + MRS



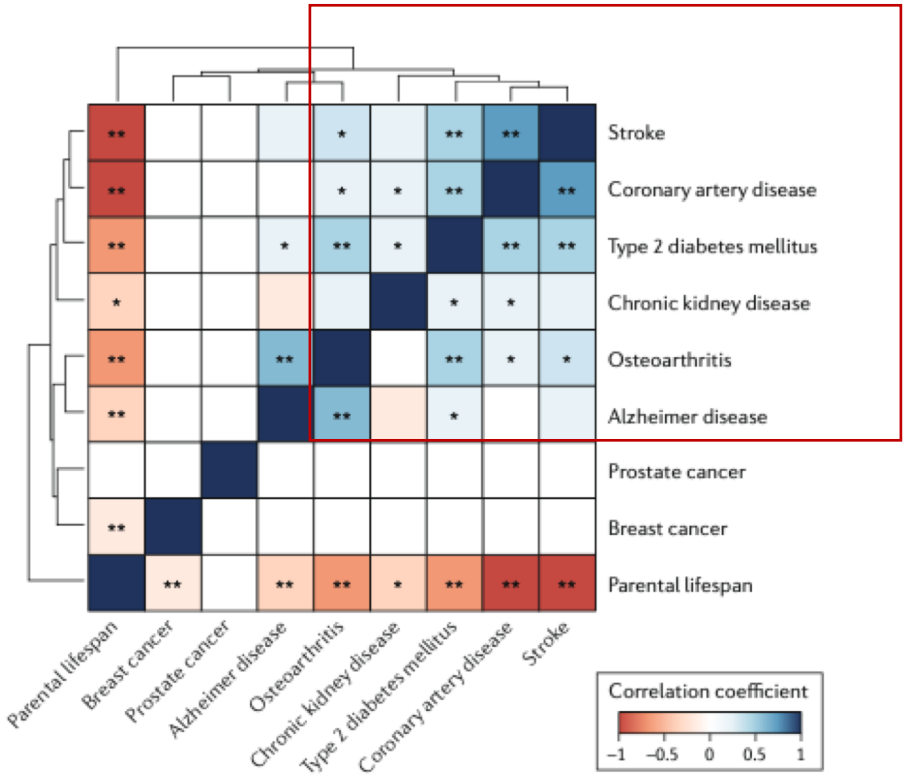
"Methylation risk scores significantly outperform the baseline and PRS models "

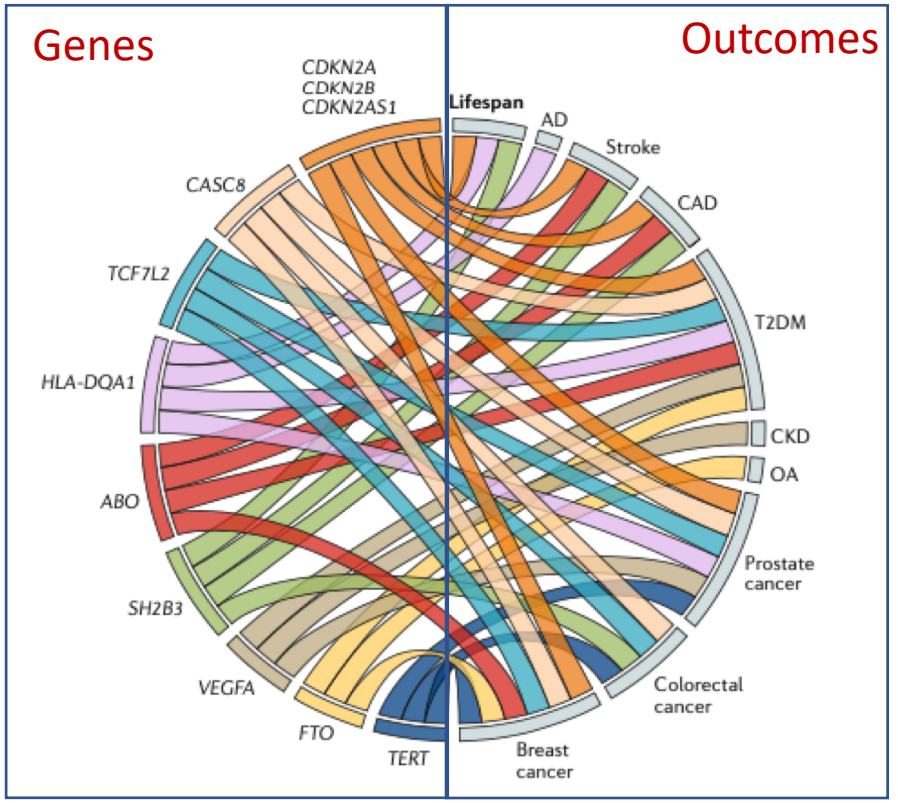
NPJ Genom Med . 25;7(1):50. Methylation risk scores are associated with a collection of phenotypes within electronic health record systems . Thompson et al.

Multi-omics → Phenotype: The promise beyond the Polygenic Risk Score (PRS)



Genetics for Aging: much broader in scope than the genetics of a single biomarker *or* hallmark *or* age-related disease.





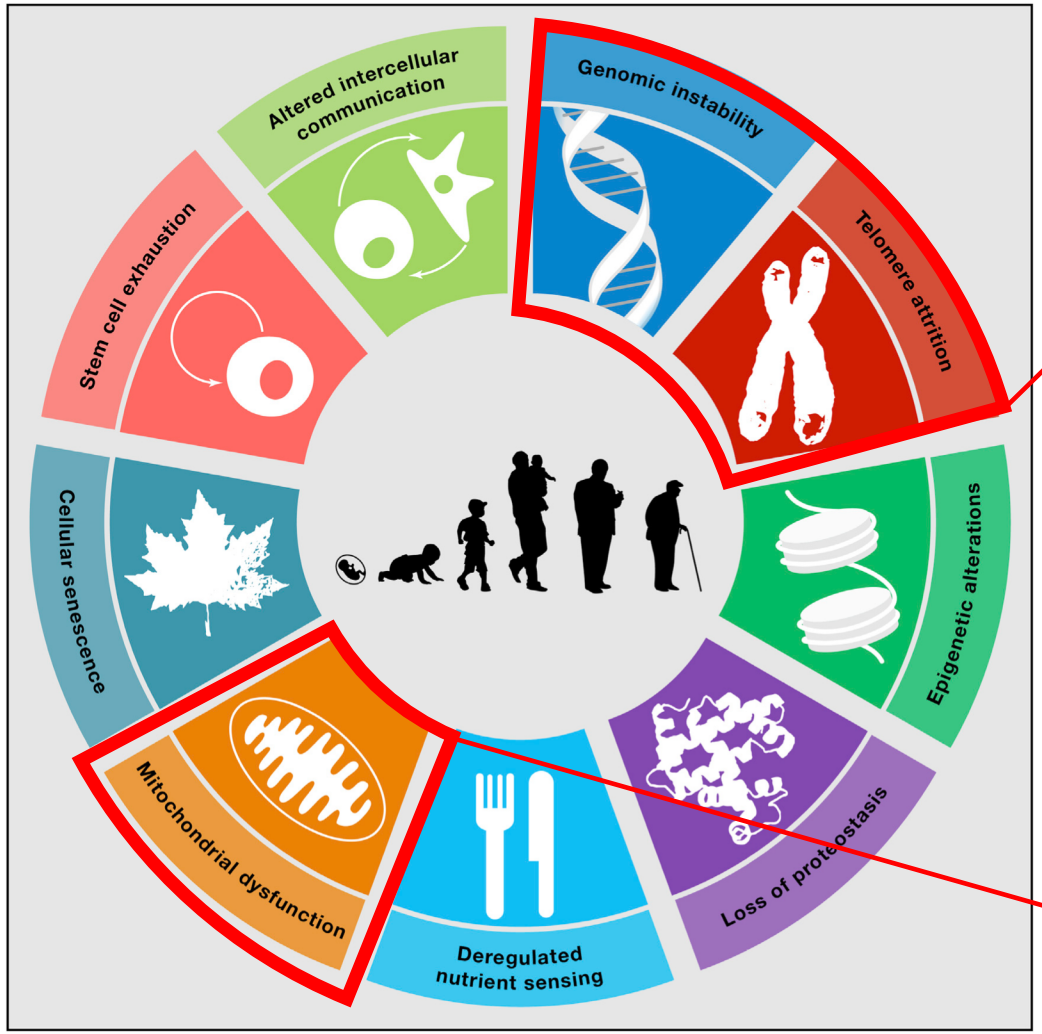
REVIEWS

The genetics of human ageing

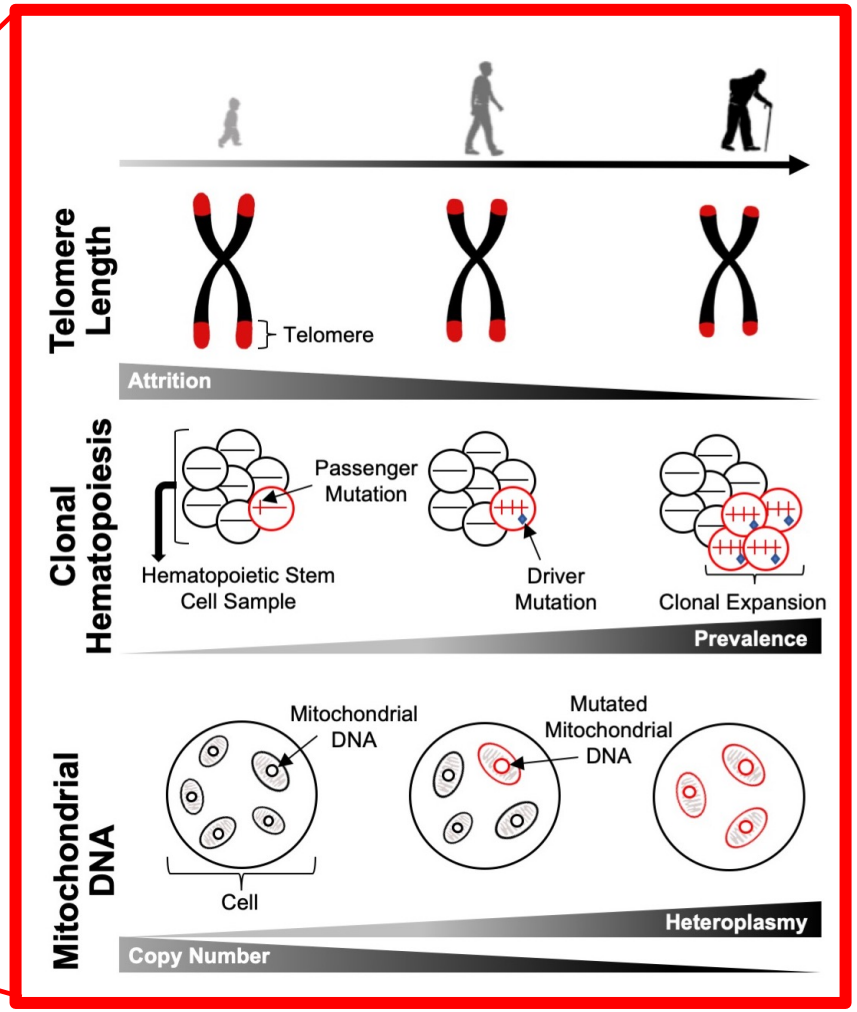
David Melzer[1,2]*, Luke C. Pilling[1,2] and Luigi Ferrucci[3]

Genetics for Aging: much broader in scope than germline variation.

Hallmarks of Aging



The Dynamic Genome

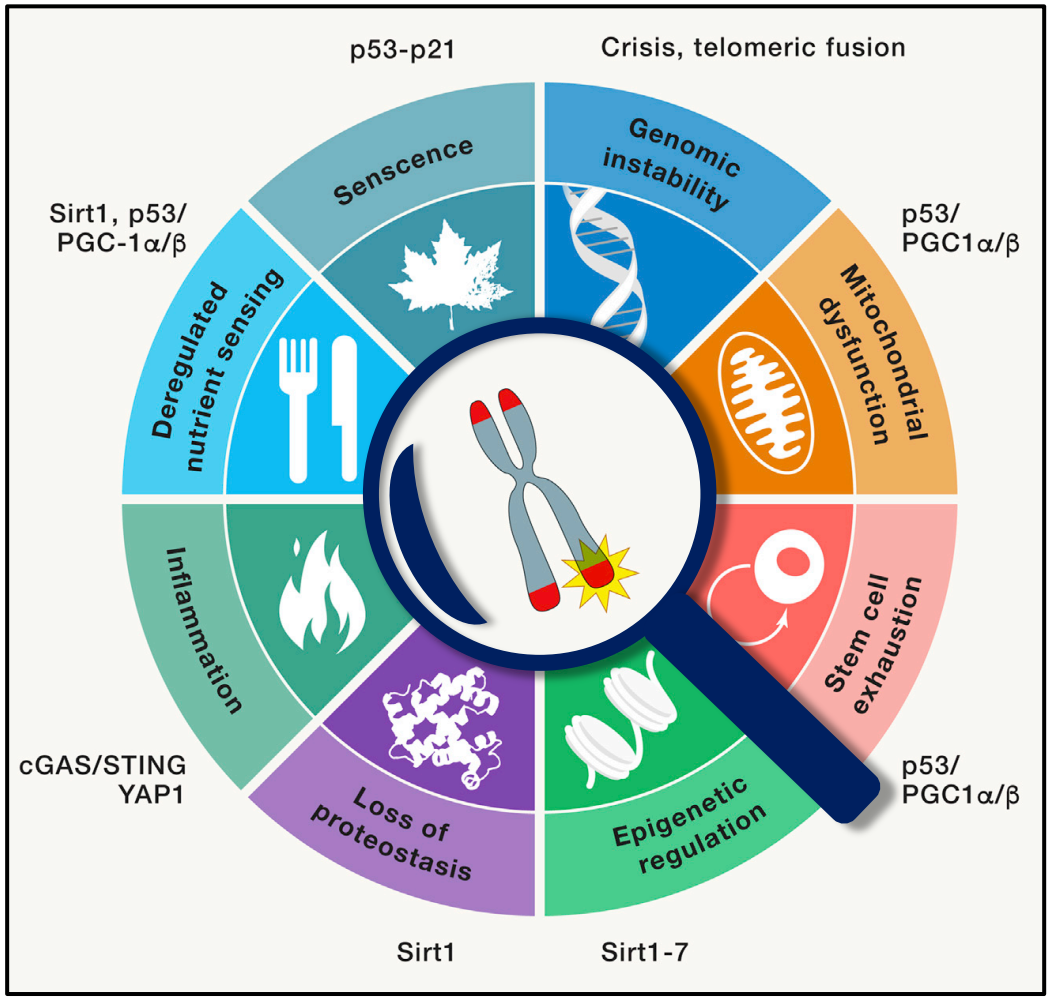


Genetics for Aging: much broader in scope than germline variation and connectivity is high.

Hallmarks of Aging

López-Otín et al. Cell. 2013 Jun 6;153(6):1194-217

A lens on telomere biology



Chakravarti et al. Cell. 2021 Jan 21;184(2):306-322

Genetics for Aging: much broader in scope than germline variation and connectivity is high.

www.nature.com/scientificreports

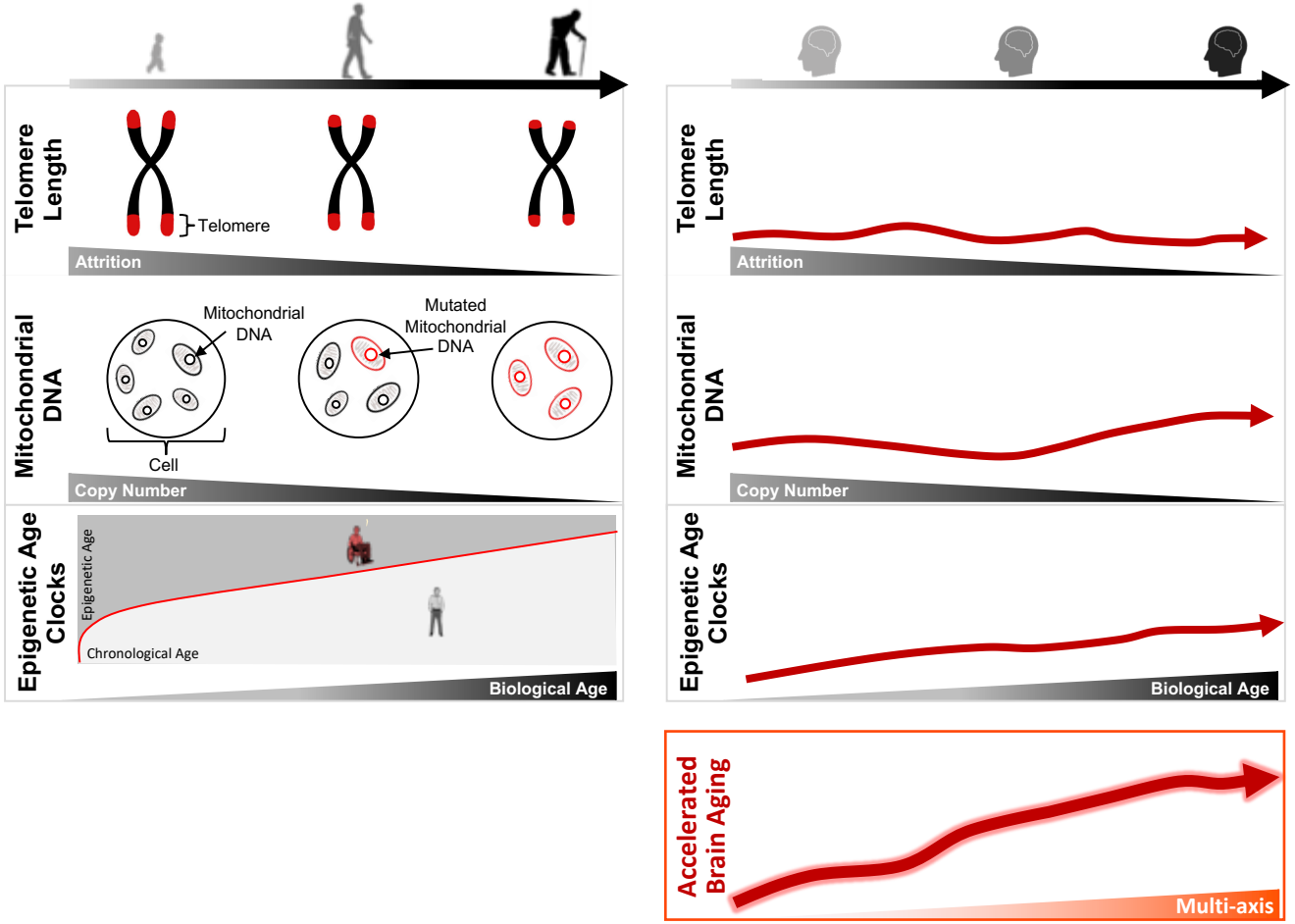
scientific reports

OPEN

Evaluating genomic signatures of aging in brain tissue as it relates to Alzheimer's disease

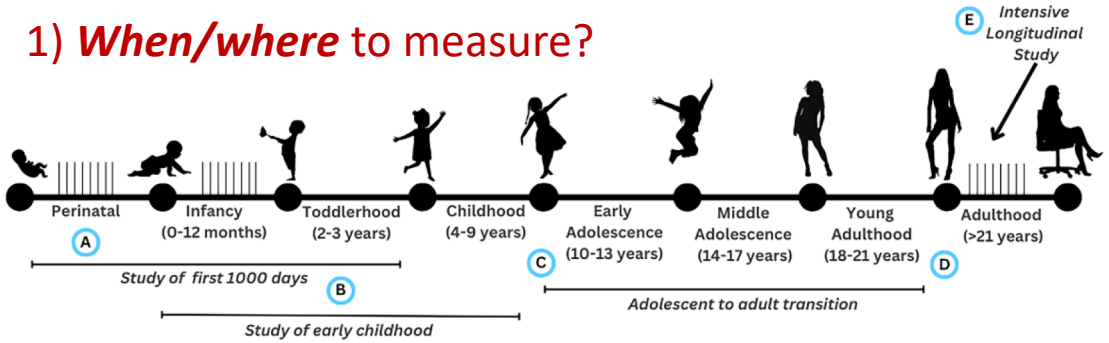
Megan T. Lynch[1], Margaret A. Taub[2], Jose M. Farfel[3], Jingyun Yang[3], Peter Abadir[1], Philip L. De Jager[4], Francine Grodstein[3], David A. Bennett[3] & Rasika A. Mathias[1]

Telomere length (TL) attrition, epigenetic age acceleration, and mitochondrial DNA copy number (mtDNAcn) decline are established hallmarks of aging. Each has been individually associated with Alzheimer's dementia, cognitive function, and pathologic Alzheimer's disease (AD). Epigenetic age and mtDNAcn have been studied in brain tissue directly but prior work on TL in brain is limited to small sample sizes and most studies have examined leukocyte TL. Importantly, TL, epigenetic age clocks, and mtDNAcn have not been studied jointly in brain tissue from an AD cohort. We examined dorsolateral prefrontal cortex (DLPFC) tissue from N = 367 participants of the Religious Orders Study (ROS) or the Rush Memory and Aging Project (MAP). TL and mtDNAcn were estimated from whole genome sequencing (WGS) data and cortical clock age was computed on 347 CpG sites. We examined dementia, MCI, and level of and change in cognition, pathologic AD, and three quantitative AD traits, as well as measures of other neurodegenerative diseases and cerebrovascular diseases (CVD). We previously showed that mtDNAcn from DLPFC brain tissue was associated with clinical and pathologic features of AD. Here, we show that those associations are independent of TL. We found TL to be associated with β-amyloid levels (beta = − 0.15, $p = 0.023$), hippocampal sclerosis (OR = 0.56, $p = 0.0015$) and cerebral atherosclerosis (OR = 1.44, $p = 0.0007$). We found strong associations between mtDNAcn and clinical measures of AD. The strongest associations with pathologic measures of AD were with cortical clock and there were associations of mtDNAcn with global AD pathology and tau tangles. Of the other pathologic traits, mtDNAcn was associated with hippocampal sclerosis, macroscopic infarctions and CAA and cortical clock was associated with Lewy bodies. Multi-modal age acceleration, accelerated aging on both mtDNAcn and cortical clock, had greater effect size than a single measure alone. These findings highlight for the first time that age acceleration determined on multiple genomic measures, mtDNAcn and cortical clock may have a larger effect on AD/AD related disorders (ADRD) pathogenesis than single measures.

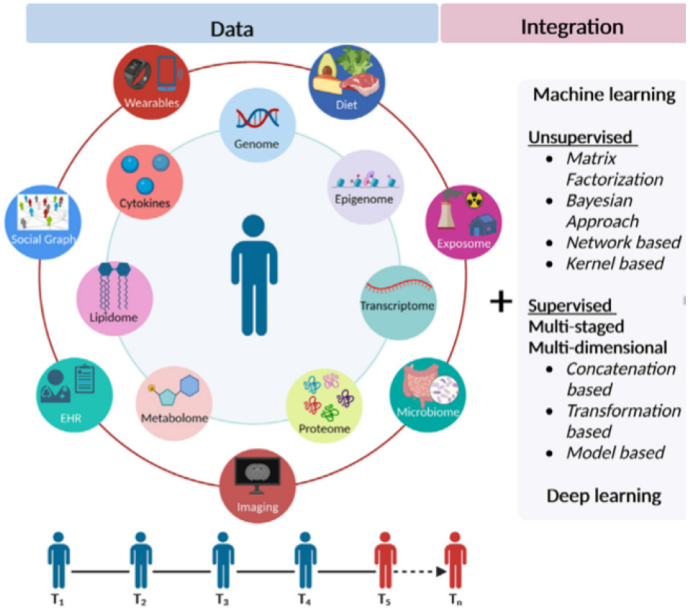


Summary & Challenges

1) *When/where* to measure?



2) *What* to measure?



3) *How* to integrate?

Analytical validity
Accuracy and reliability of a test to measure a specific biomarker

Clinical validity
The accuracy of how well a test detects or predicts clinical diagnosis or outcome

Clinical utility
The likelihood the test is to inform clinical decisions and improve outcome

Analytical sensitivity
How often is the test positive when the biomarker is present?

Analytical specificity
How often is the test negative when the biomarker is not present?

Robustness
Repeatability and reproducibility of the assay within and across laboratories.

Limits of detection
Lowest level of reliable detection of transcripts.

Stability
Collection, handling, transport of sample and impact on robustness.

Gold standards
Reference sets for assessing sensitivity and specificity.

Clinical sensitivity
How often is the test positive in patients with the disease or clinical outcome?

Clinical specificity
How often is the test negative in patients without the disease or clinical outcome?

Prevalence
The proportion of individuals that will have a disease or outcome.

Positive predictive value
Given prevalence, the probability that subjects with a positive test result for a disorder or outcome will have the disease or outcome.

Negative predictive value
For negative tests, the probability that subjects truly will not have the disease or outcome.

Penetrance
The proportion of subjects with the biomarker that have the predicted outcome or diagnosis.

Appropriate intervention
Assessment of test impact on patient care, publishing of clinical trials.

Quality assurance
Quality control measures for tests, reagents and/or facilities.

Monitoring
Long-term monitoring of patients and establishment of guidelines for performance.

Economics
Financial costs and economic benefits associated with test.

Education
Educational materials and informed consent requirements.

ELSI
Assessment of ethical, legal and societal implications that arise in the context of the test.

4) **Evaluating readiness**?

References

1. Multi-Omics Profiling for Health. Babu M, Snyder M. Mol Cell Proteomics. 2023 Jun;22(6):100561.
2. Multi-omics approaches to disease. Hasin Y, Seldin M, Lusis A. Genome Biol. 2017 May 5;18(1):83.
3. Methylation risk scores are associated with a collection of phenotypes within electronic health record systems. Thompson M, Hill BL, Rakocz N, Chiang JN, Geschwind D, Sankararaman S, Hofer I, Cannesson M, Zaitlen N, Halperin E. NPJ Genom Med. 2022 Aug 25
4. A polygenic resilience score moderates the genetic risk for schizophrenia. Hess JL, Tylee DS, et al, Glatt SJ. Mol Psychiatry. 2021 Mar;26(3):800-815.
5. Translating RNA sequencing into clinical diagnostics: opportunities and challenges. Byron SA, et al. Nat Rev Genet. 2016. PMID: 26996076
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