Emerging Molecular Biomarkers of Aging

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Disclosures

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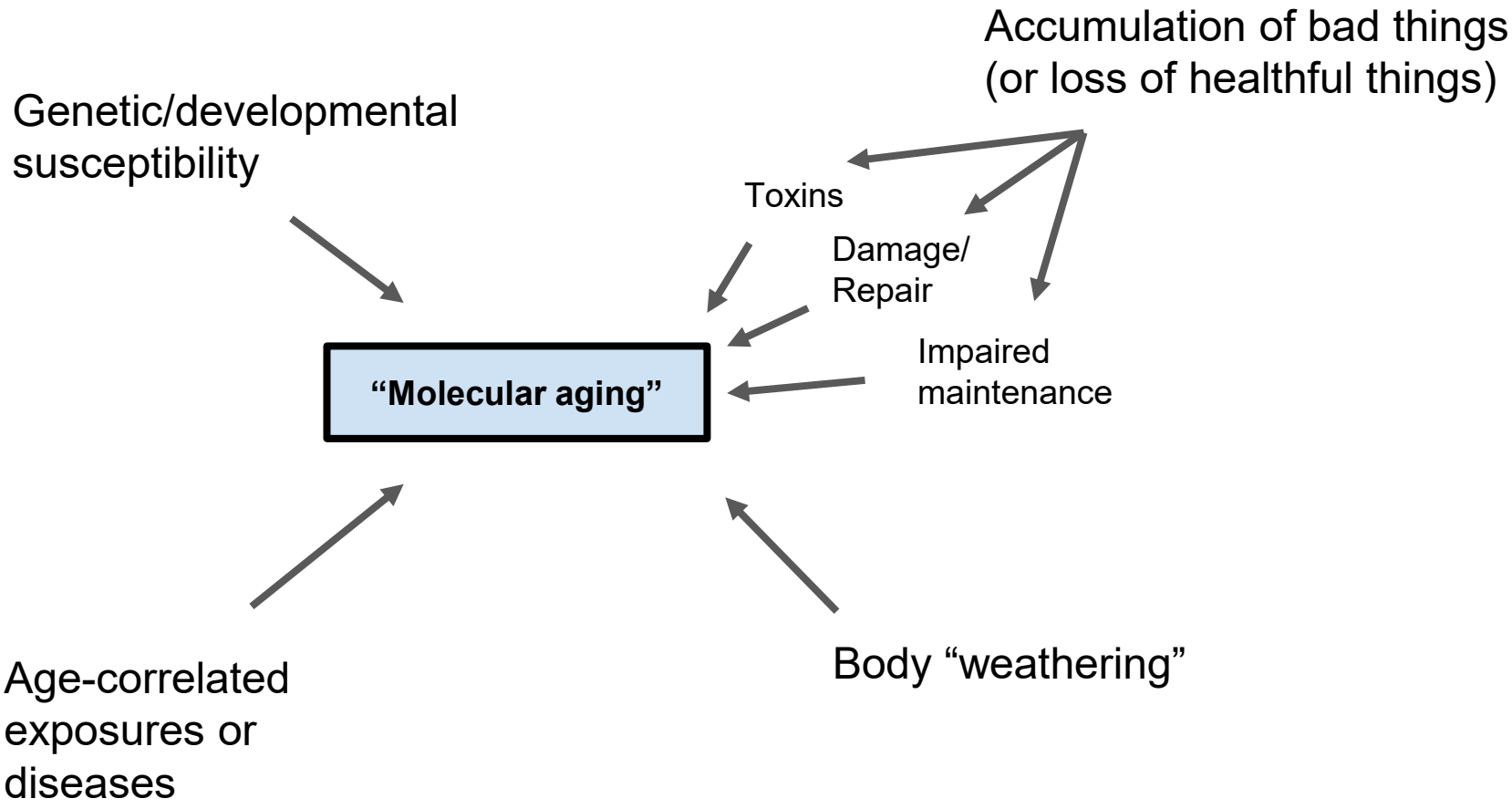
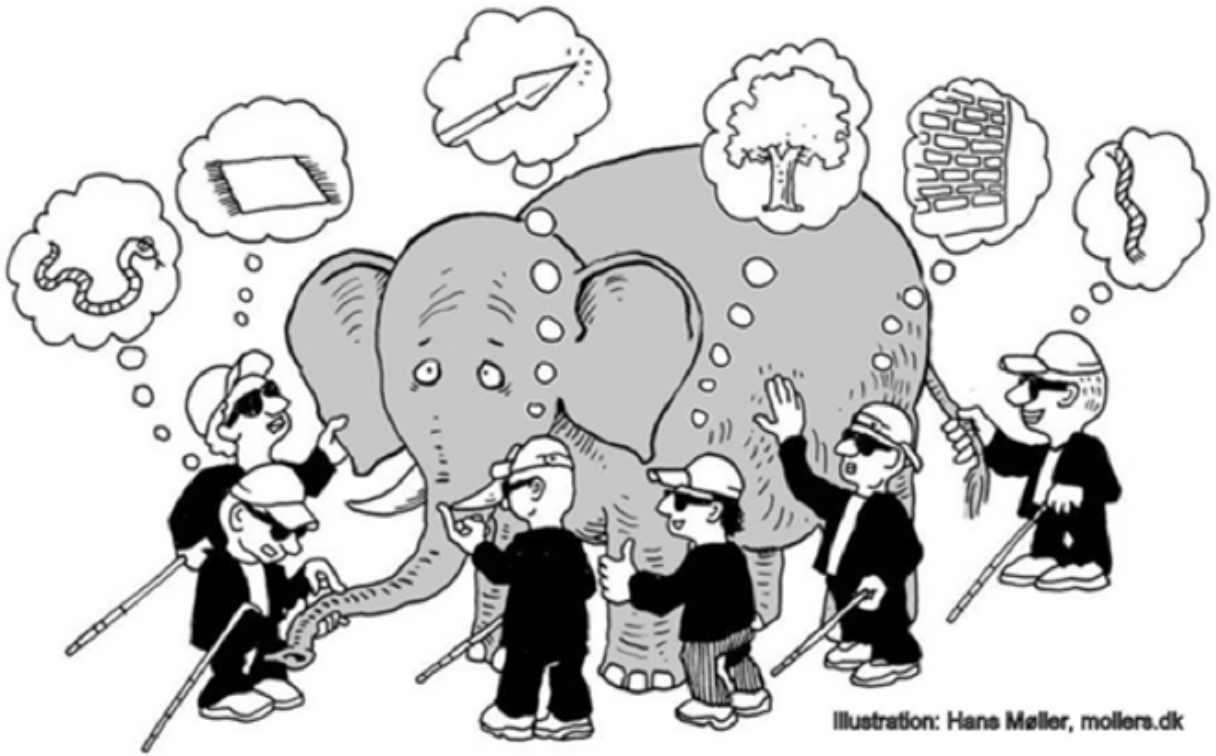
Have you ever…

1. Adjusted for “age” in your statistical models?
2. Conducted gene-pathway enrichment analysis and thought, “That makes sense,” but it really doesn’t?
3. Questioned why so many of the diseases share the same exposures or biological pathways?

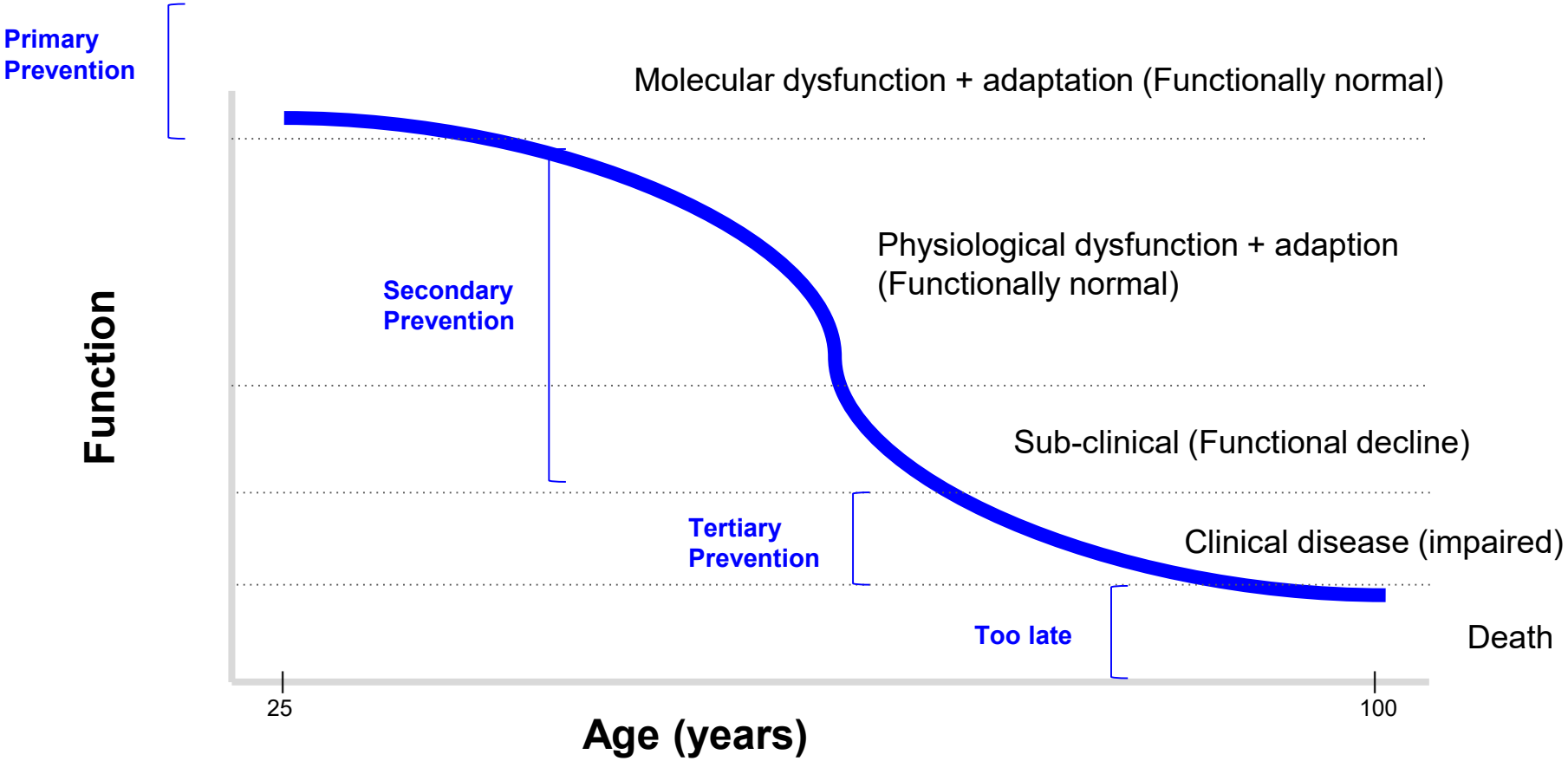
What is “Aging?”



(D) All of the above

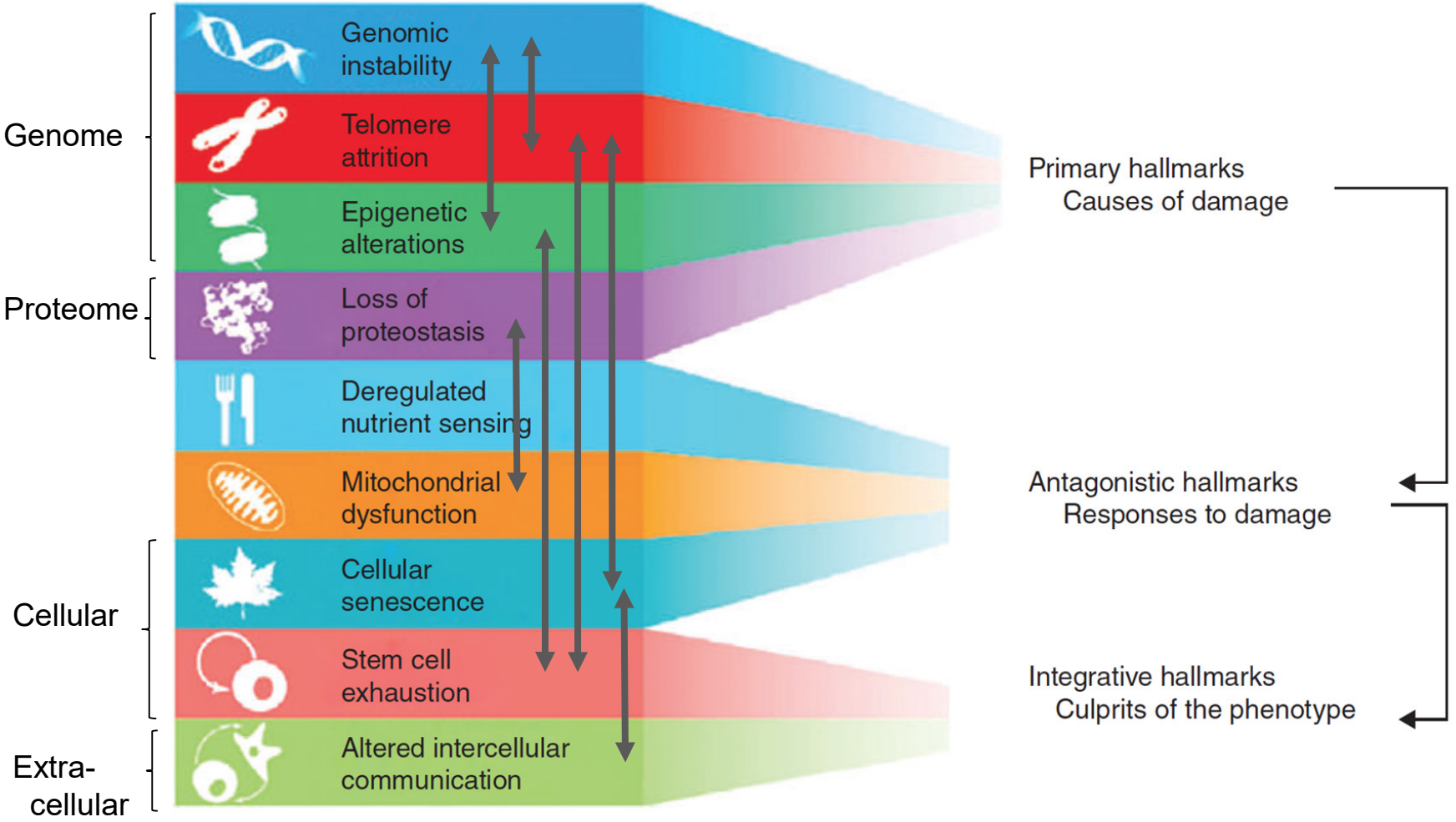


Molecular biomarkers = “canary in the mine”

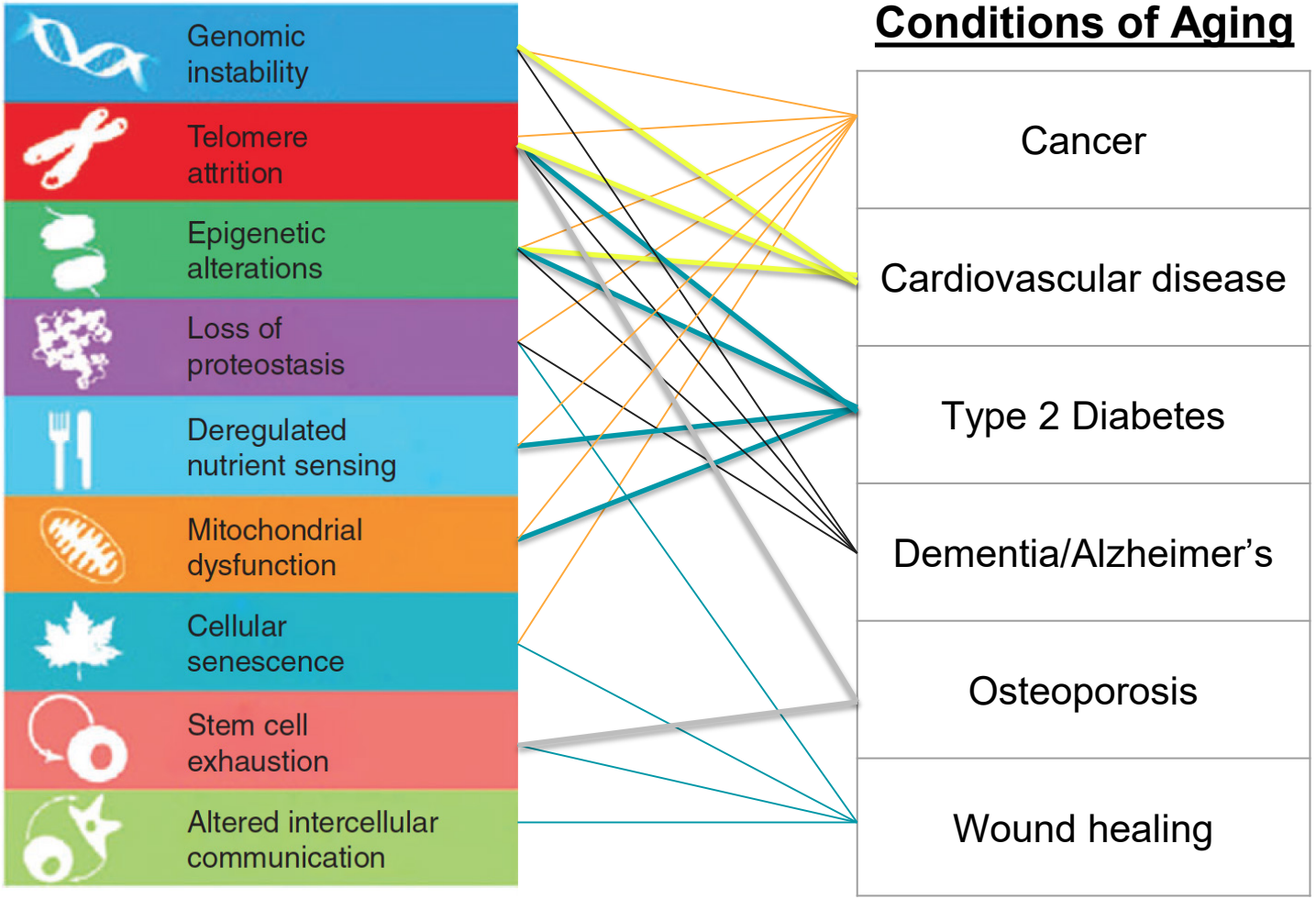


The Hallmarks of Aging

Lopez-Otin et al. *Cell*, 2013)



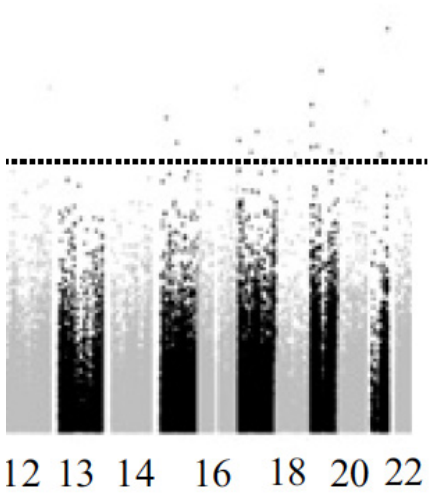
Aunan JR, et al. *Br J Surg*, 2016


Genomic instability
Telomere attrition
Epigenetic alterations
Loss of proteostasis
Deregulated nutrient sensing
Mitochondrial dysfunction
Cellular senescence
Stem cell exhaustion
Altered intercellular communication
Conditions of Aging
Cancer
Cardiovascular disease
Type 2 Diabetes
Dementia/Alzheimer's
Osteoporosis
Wound healing

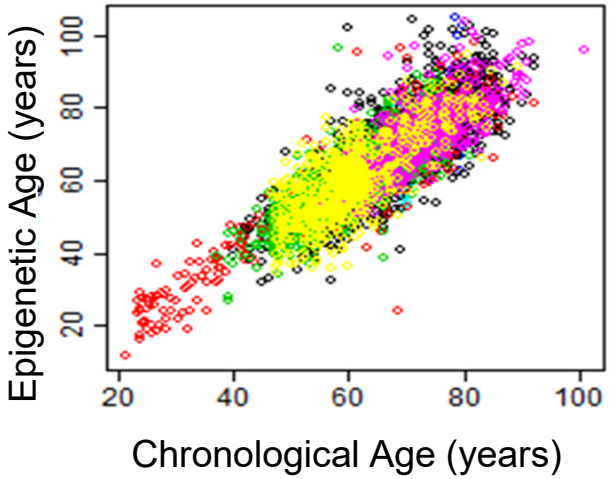
 Genomic instability	
 Telomere attrition	Leukocyte telomere length
 Epigenetic alterations	DNA methylation, miRNA
 Loss of proteostasis	
 Deregulated nutrient sensing	insulin insensitivity, GH, IGF1
 Mitochondrial dysfunction	Bioenergetics (Oroboros), Reactive Oxygen Species, mtDNA deletions
 Cellular senescence	$p16^{INK4a}$, SASP (proinflamm cytokines, matrix metalloproteinases, interleukins, growth factors)
 Stem cell exhaustion	
 Altered intercellular communication	Cytokines, neuroendocrine systems (eg, renin-angiotensin system, insulin-IGF response)

Example: Epigenetics

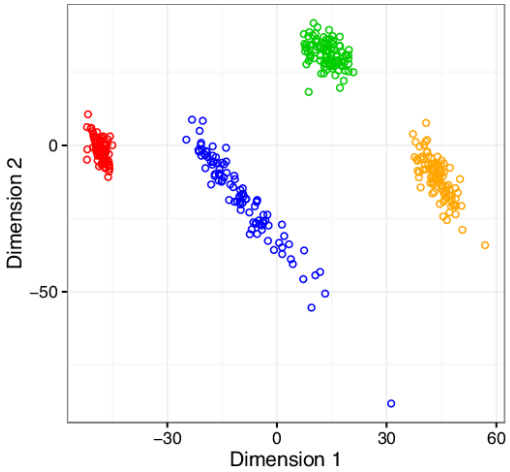
Range of epigenetic time scales



Air pollution
(minutes/hours)



Age
(years)



Cell identity
(lifetime)

Permanence of epigenetic marks

Low

High

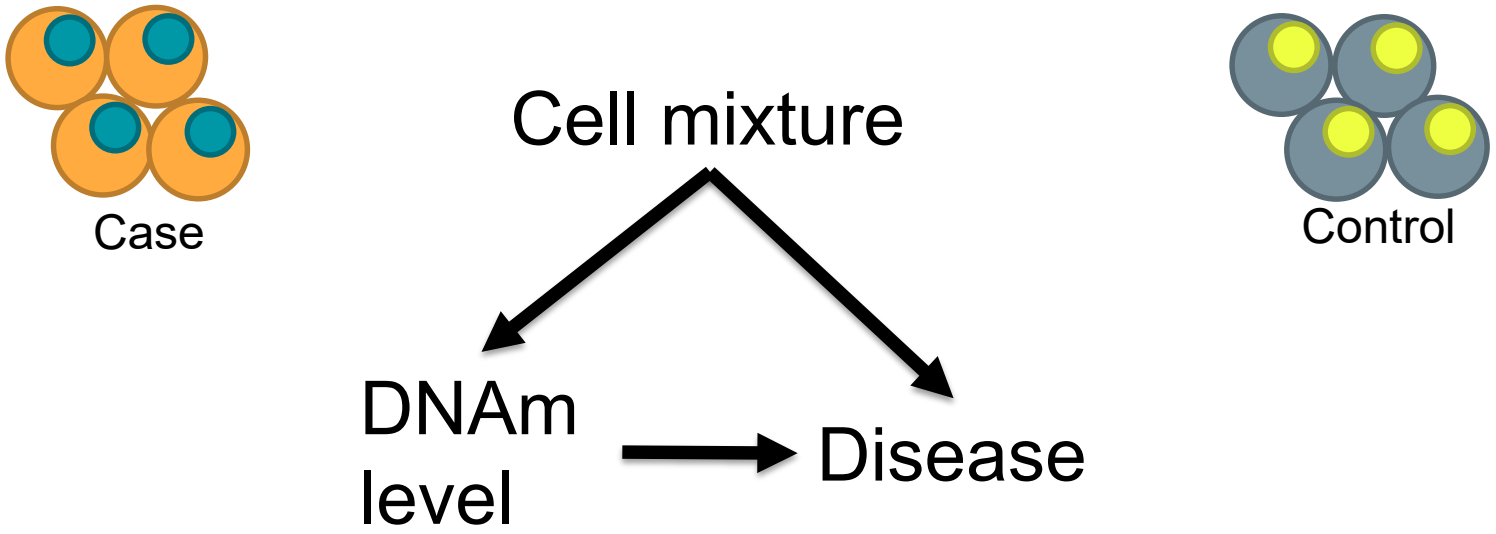
1. Are we examining the relevant tissue?

- Tissue-agnostic
    - e.g., Epigenetic clock
- Tissue-specific
    - e.g., Cell identity mark

Does it matter?

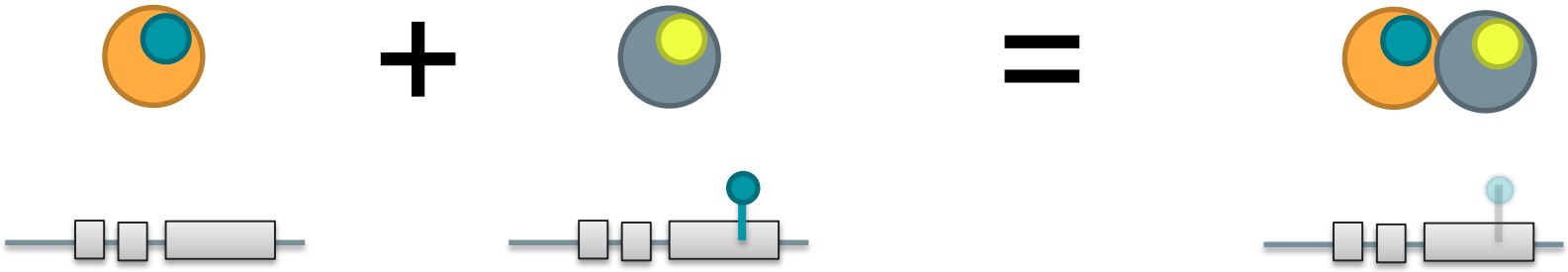
- For prediction: No, as long as it works.
- For mechanism: Yes, but this should be part of any effort to understand mechanism (molecular, cellular, tissue, organismal, societal contexts).

2. Confounding by cellular heterogeneity



- Solution: Purified cells, single-cell analysis, or cell counting

3. Single vs Bulk cells

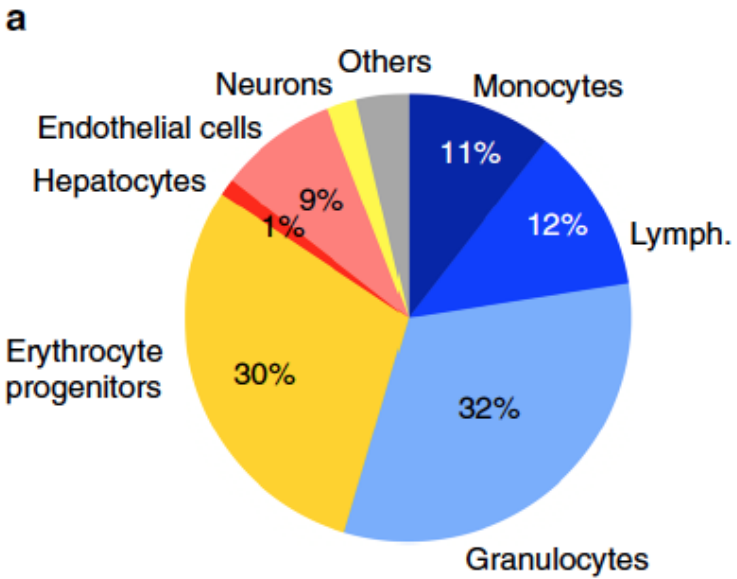


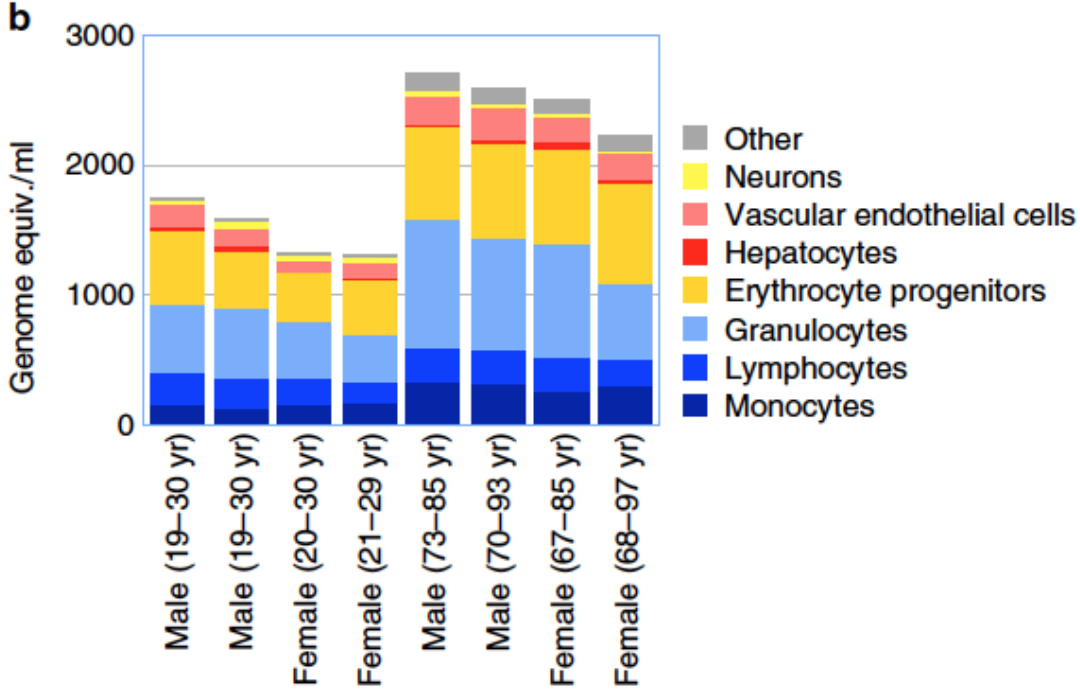
Unmethylated (0%) Methylated (100%) Methylated (50%)

(Average across thousands of cells)

- Solution: Cell sorting and cryopreservation

4. Cell-free DNA (‘liquid biopsy’) as window into other tissues





Moss et al. *Nat Comm* (2018)

Current trends in sample collection

1. Addressing cellular heterogeneity
    a. Cell counting
        i. Flow cytometry (HRS)
        ii. Cryopreservation (UK Biobank, All Of Us, CARDIA)
    b. Purify cells
        i. FACS (GESTALT)
        ii. Monocytes (MESA)
        iii. CD4+ T-cells (GOLDN)

2. Tissues Cell compartments
    a. Non-blood tissues
        i. GTEx Project
        ii. Animal studies + small human validation studies
    b. cfDNA
    c. Exosomes

Conclusions

1) Opportunity for early detection

- Prediction: Molecular biomarkers may serve as early signs of biological dysfunction, preceding physiological and clinical detection.
- Mechanism: Provide deeper understanding of biology

2) Match stored samples to emerging technology

- Need longitudinal studies to confirm clinical utility of biomarkers.
- New sample collection (tissues and sample prep) needs to start now.