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Epigenetics and the science behind biological age clocks - InflammAge as a case study

Lisa J. Schmunk, PhD
Research & Development Manager

Visit us at stand B38

Today’s agenda:

~20 min presentation
~10 min Q&A

1. Introduction to the world of Science & Epigenetics
2. Deep dive into Epigenetics and Ageing
3. What epigenetic clocks can tell us about our health
4. InflammAge as a case study
5. The role of epigenetics clocks in the diagnostic journey
6. Summary
7. Q&A

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Biology in a nutshell - Nature vs Nurture

Our bodies are made up of **cells**, each with the same **DNA** inside that we inherit from our parents.

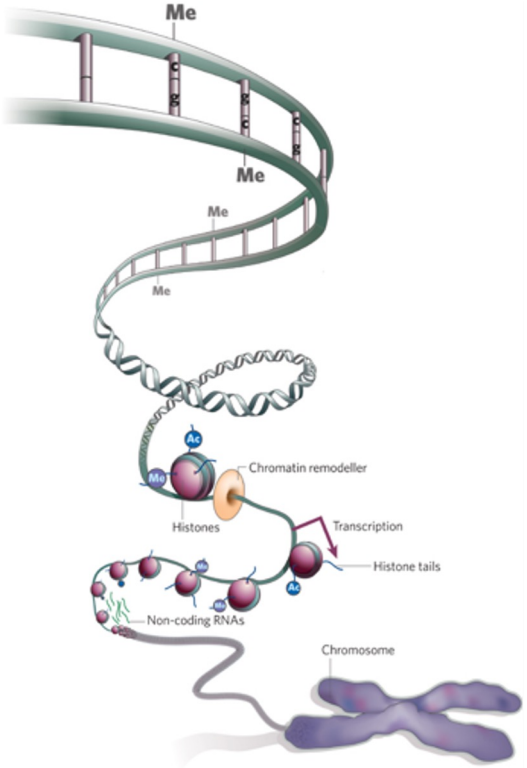
Our **genetic makeup** is fixed at birth

- DNA code ATCG, 3 billion letters per copy, 23 x 2 chromosomes

Central dogma of Biology:

- **DNA** -> **RNA** -> **Protein**
- **Gene** = stretch of DNA that can be “expressed” to create a functional product (e.g. an enzyme)

Epigenetics refers to the layer of non-genetic influences on gene expression and can change over time.



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Images: Force & European Union, 2008

What is epigenetics?

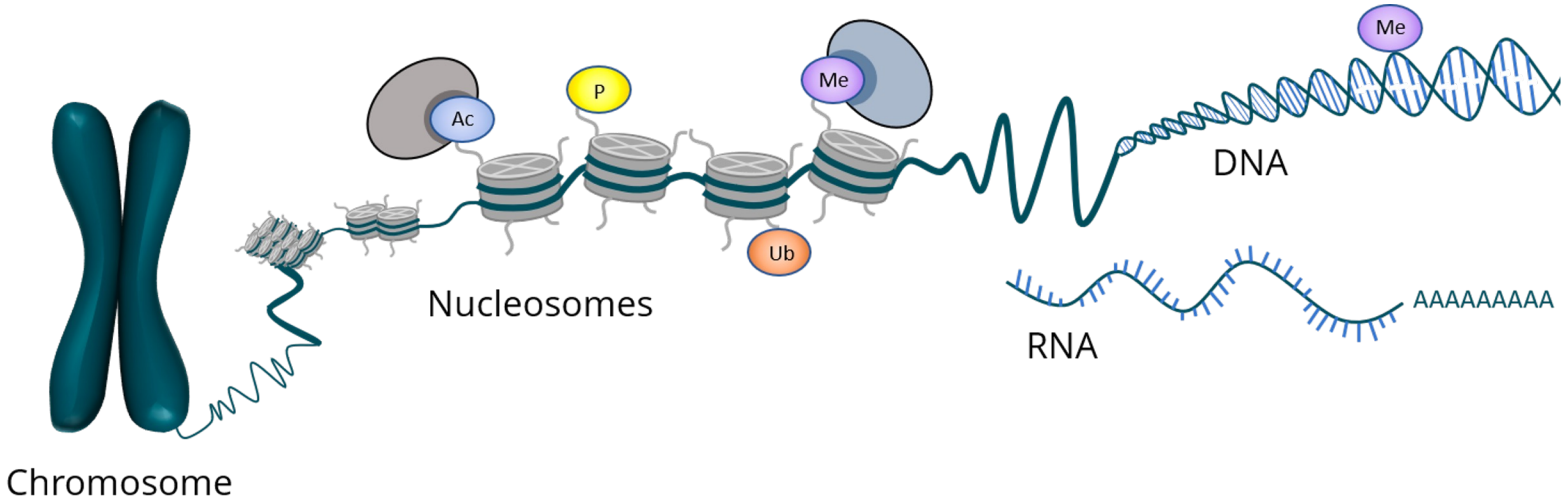

Image: BPS Bioscience 2023

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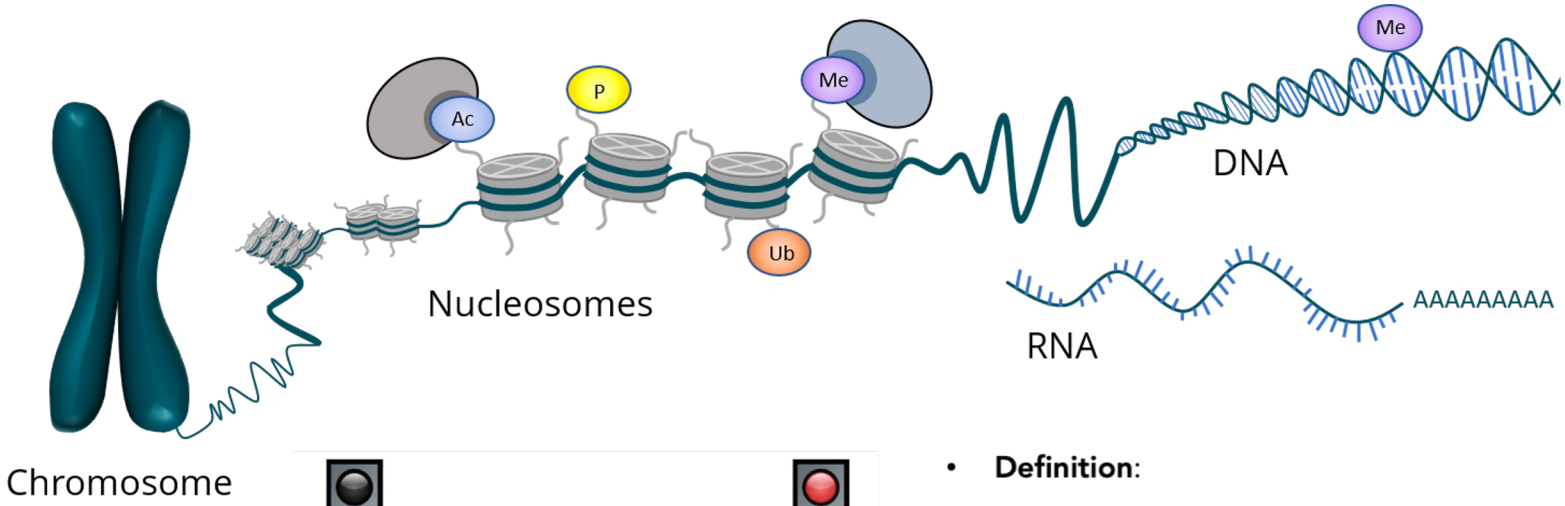

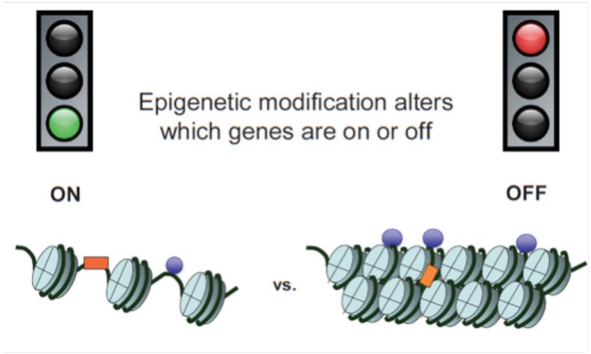

- **Definition**:

Molecular variation that is beyond changes in the DNA sequence, that is inherited after cell division and that regulates gene expression.

DNA methylation.

Histone modifications.

Others (non-coding RNAs?).

Image: BPS Bioscience 2023

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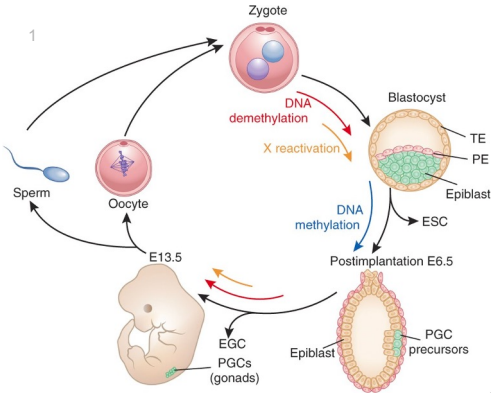
Epigenetics and physiology

Early development



Images: 1. Zhang et al. 2020, Nature Mol Cel Biol; 2. Australian Academy of Science 2023; 3. Cantone & Fisher 2013, Nature Struc Mol Biol;

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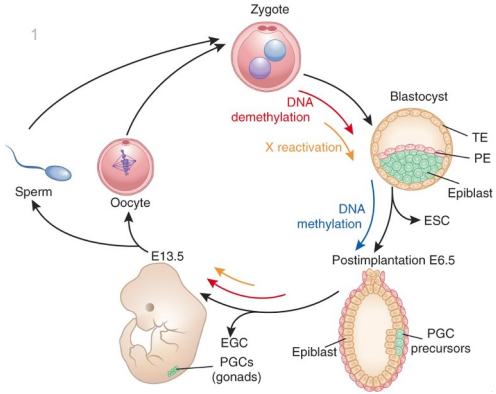
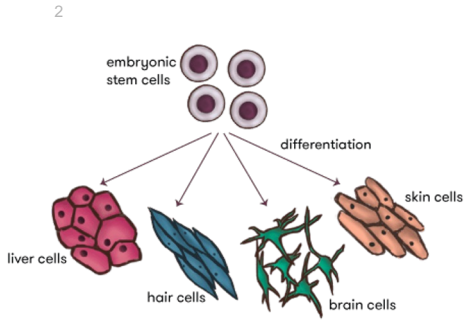
Epigenetics and physiology

Early development



Cell differentiation



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Epigenetics and physiology

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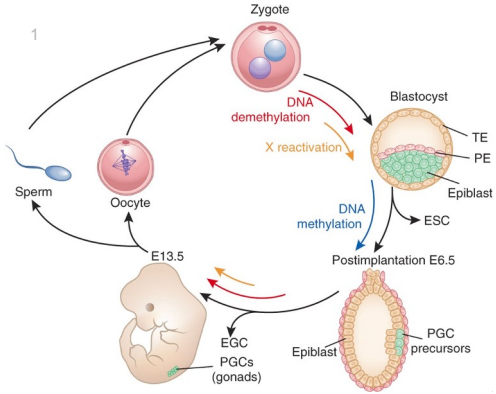

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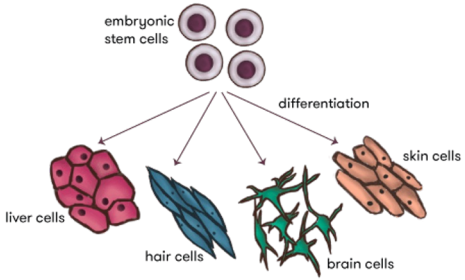
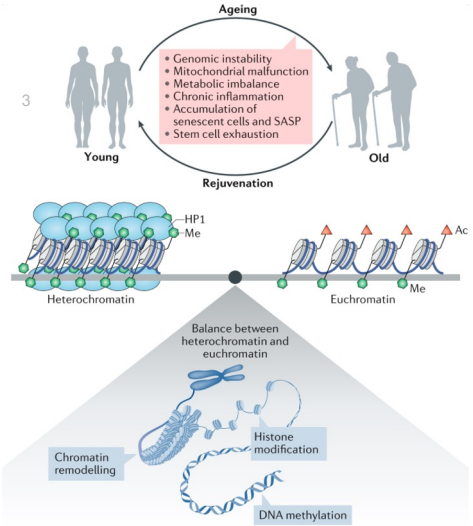


Ageing



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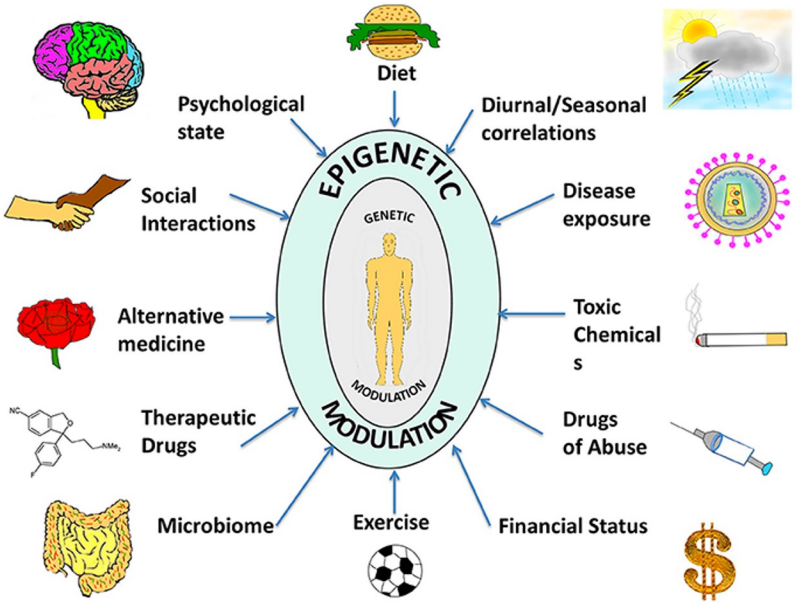
Epigenetics integrates genetics x environment



Kankerhan et al. Front. Cell Dev. Biol., 2014

Identical twins

Mark and Scott Kelly

Source: https://www.nasa.gov/feature/nasa-twins-study-confirms-preliminary-findings

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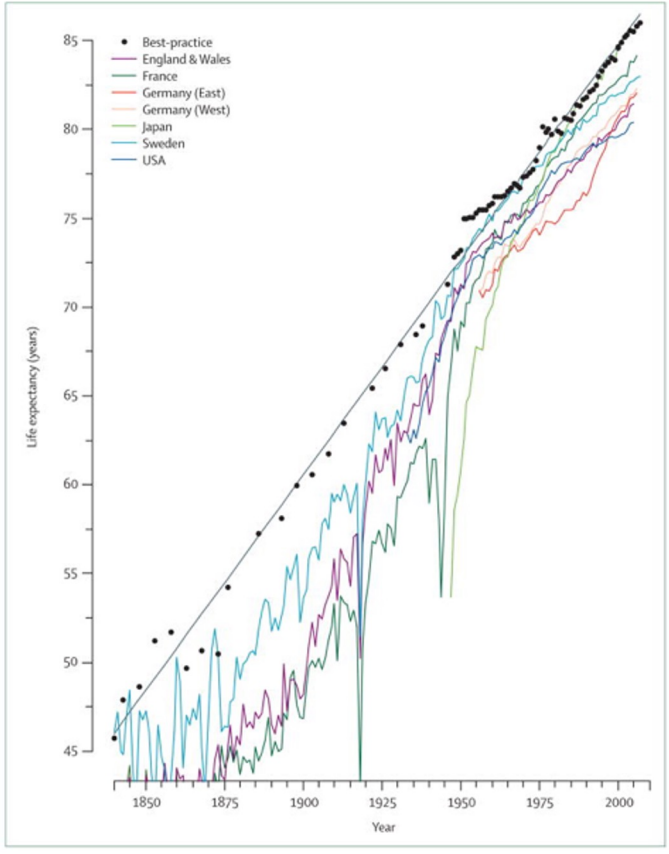
Modern Ageing - Lifespan vs healthspan



The Lancet, vol. 374, no. 9696, pp. 1196-1208, Oct. 2009

- **We are living longer**:

  Almost 2X lifespan since 200 years ago.

- **Yet sicker: rise of NCDs:**

  Cardiovascular, cancer, diabetes, neurodegenerative, …
  Largely preventable through lifestyle interventions.

  Focus → extend healthspan.

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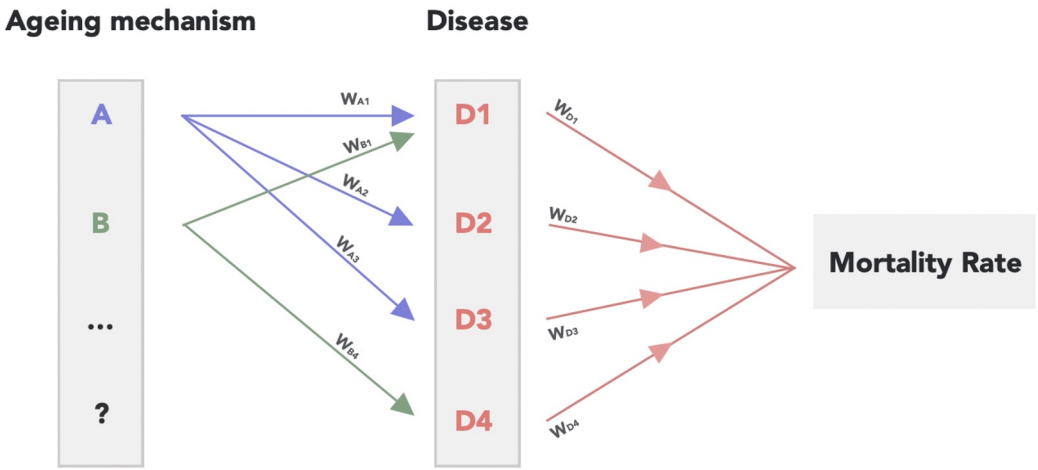
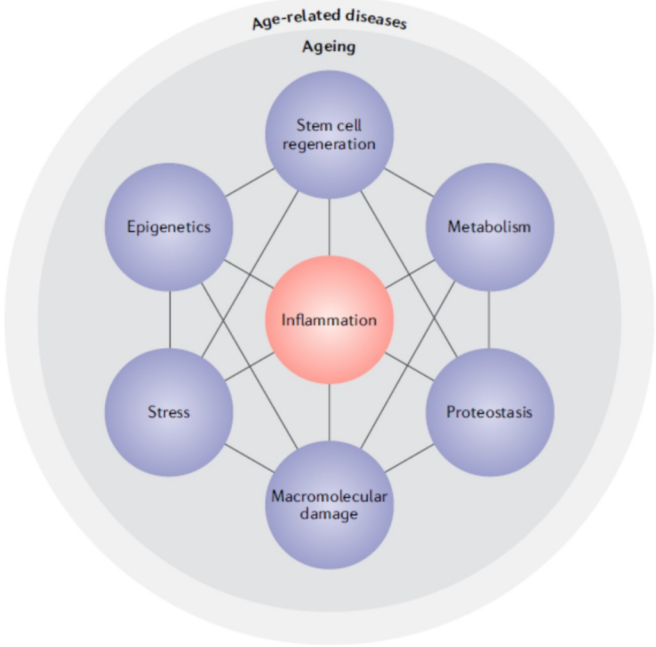
Ageing is composed of many molecular mechanisms (hallmarks)





- How can we measure biological ageing?

Source: Martín Herranz, D. E. (2019). *On the epigenetic ageing clock in humans*. https://doi.org/10.17863/CAM.44841

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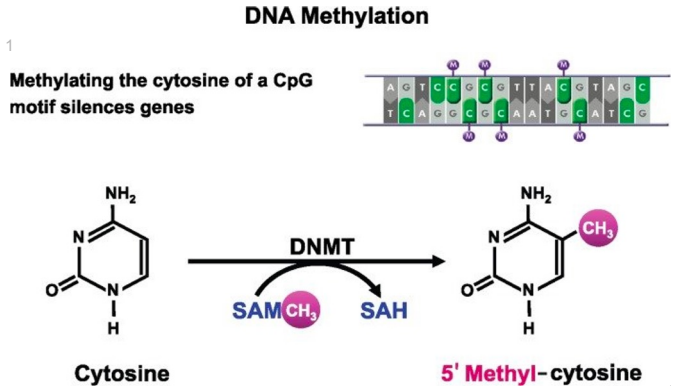
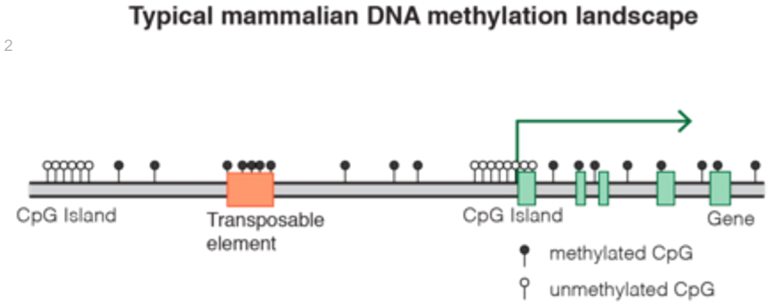
DNA methylation - the archetypal epigenetic modification





- The first molecular epigenetic mechanism discovered (early as 1948)
- **DNA methyltransferase (DNMT)** enzymes - attach methyl group to carbon 5 of cytosine on CpG motifs
- Most common cytosine modifications in mammals are 5-methylcytosine (5-mc) and 5-hydroxymethylcytosine (5-hmc)

- There are *circa* 30 million CpG sites across the human genome
- Methylation of CpG sites can promote or repress gene expression

Images: 1. Wikipedia 2023; 2. Samir 2013 Alcohol res: curr rev;

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DNA methylation as a source of biomarkers

Images: 1. Diagenode 2023; 2. Biostars 2023; 3. Li et al. 2023, PNAS; 4. Slieker et al. 2018, Epi & Chrom;

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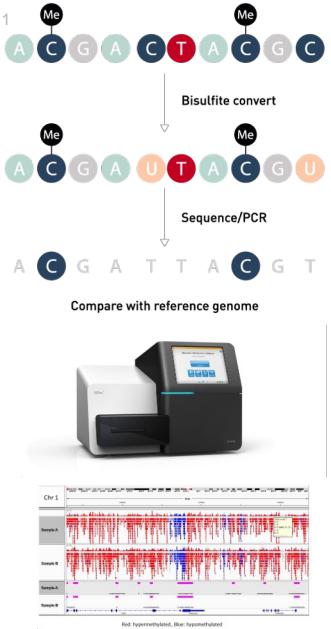
DNA methylation as a source of biomarkers

Measuring methylation patterns



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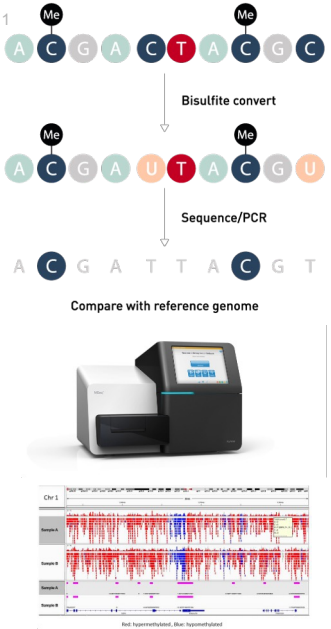
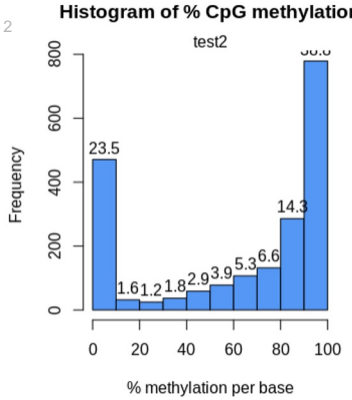


Quantifying methylation levels



Machine learning

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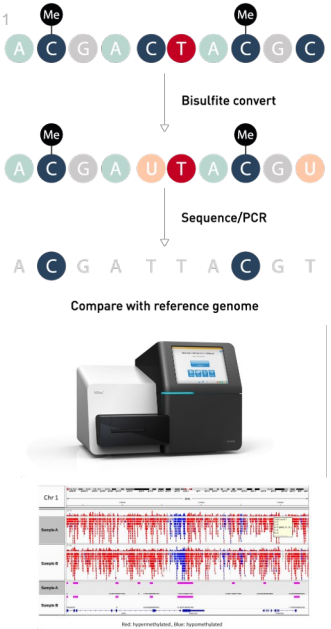

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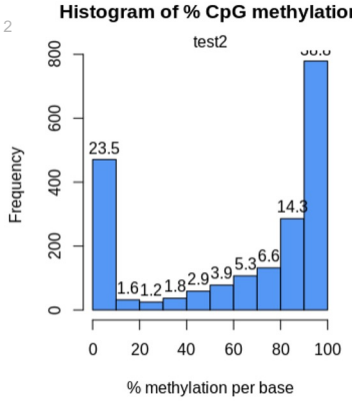
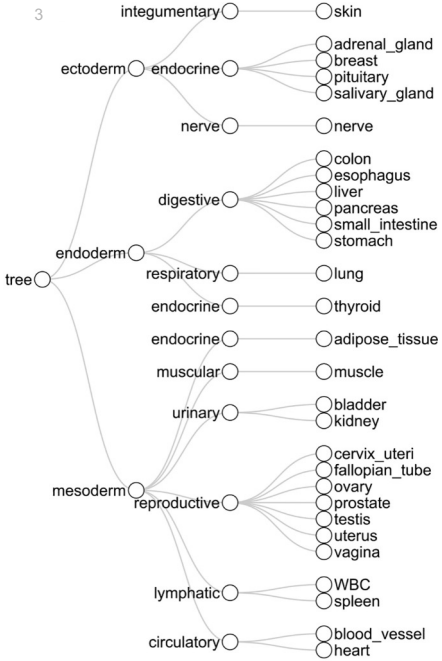


Machine learning

Cell type deconvolution



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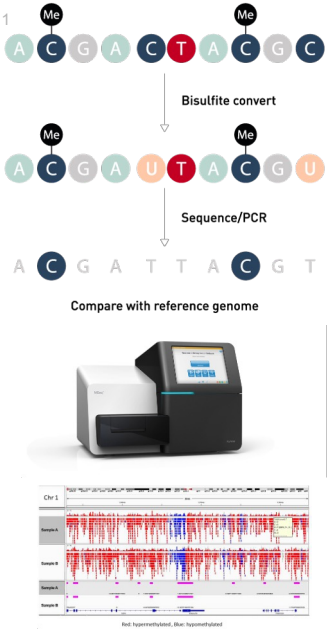

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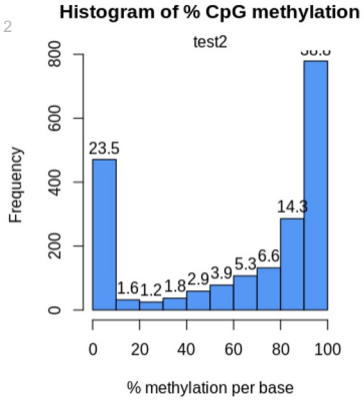

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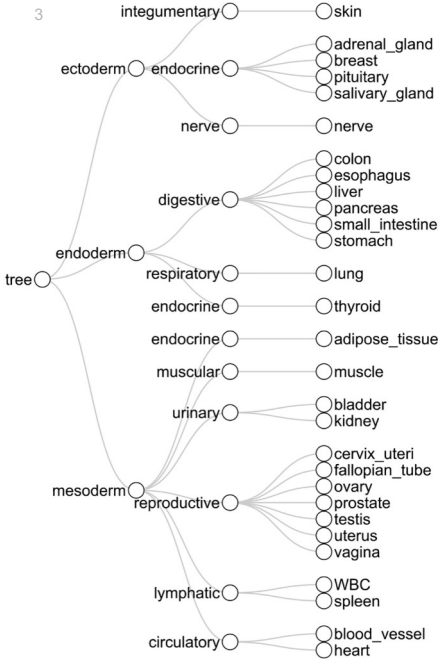
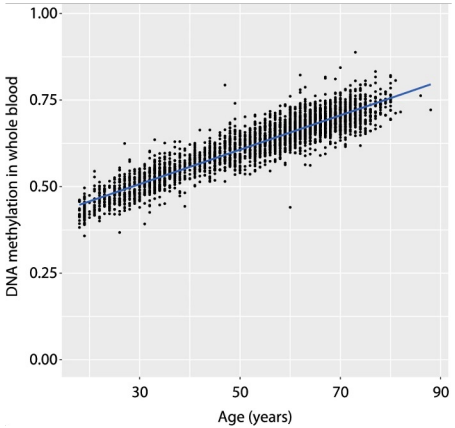


Tracking methylation changes

4



ELOVL2 promoter methylation changes with age in blood

Images: 1. Diagenode 2023; 2. Biostars 2023; 3. Li et al. 2023, PNAS; 4. Slieker et al. 2018, Epi & Chrom;

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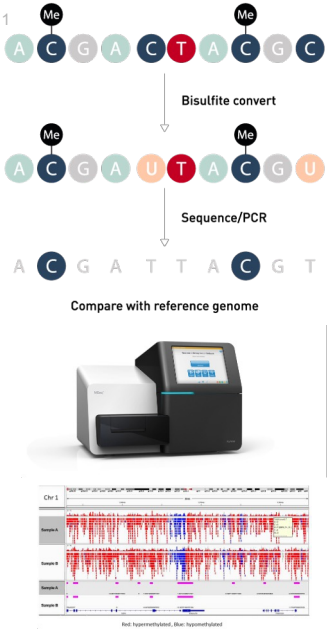
DNA methylation as a source of biomarkers

Measuring methylation patterns

1



Quantifying methylation levels

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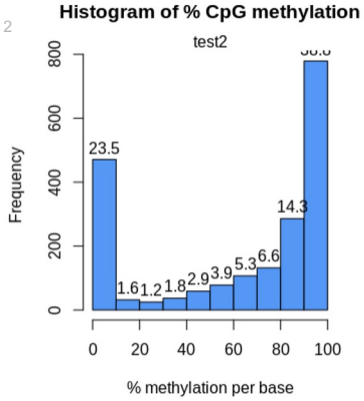

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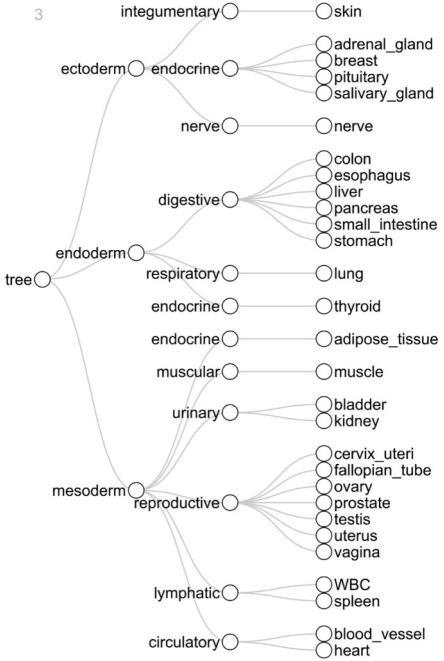

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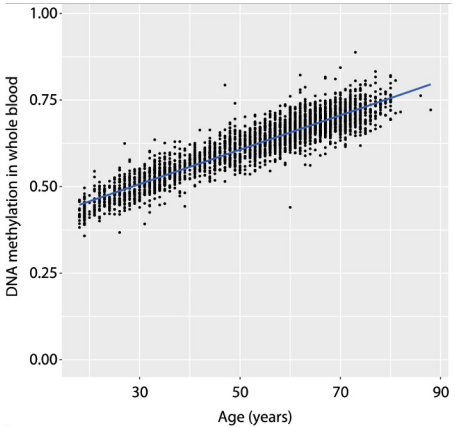

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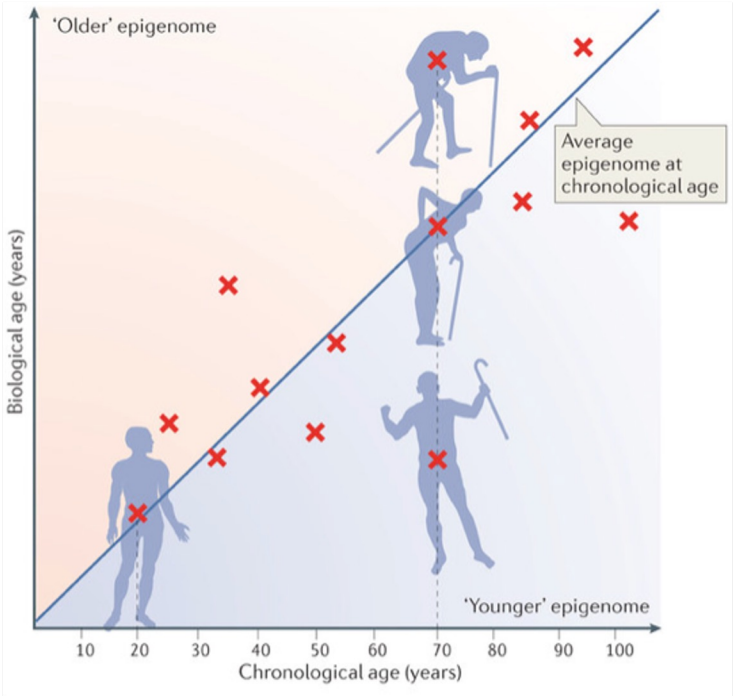
Measuring the ageing process with epigenetics



Nature Rev. Mol. Cell Biology, vol. 16, no. 10, pp. 593–610, 2015.

- **Epigenetic clocks**:

The most accurate biomarkers of the ageing process.

They measure your biological age.

Development of anti-ageing therapies.

Chronomics epigenetic clock → saliva

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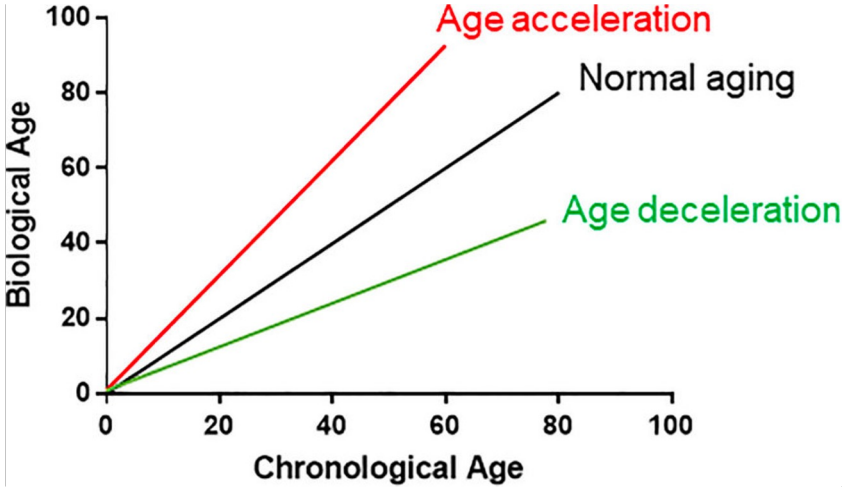
Epigenetic clocks and their clinical relevance

- **Epigenetic age acceleration** (EAA) is associated with meaningful variables in humans.

Biological aging methylation ‘clocks’



Clinical

- All-cause mortality
- Obesity
- Cancer
- Cardiovascular disease
- Alzheimer’s
- Werner’s syndrome
- Huntington’s disease
- Down syndrome
- Sotos syndrome
- HIV infection
- …

Nat. Review Genetics, vol. 19, pp. 371-384, 2018.

Images: 1. Yu *er al.* 2019, *Cancer Research*; 2. Fasanelli *et al.* 2015, *Nat Comms*

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Epigenetic clocks and their clinical relevance

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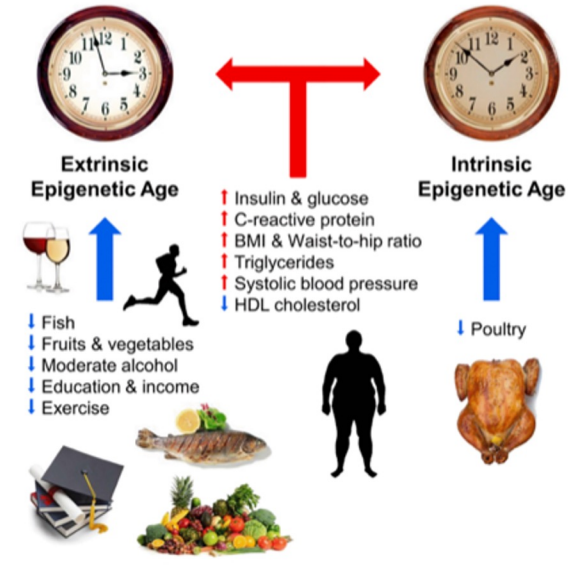
Pre-clinical / lifestyle factors



Aging, vol. 9, pp. 419-446, 2017.

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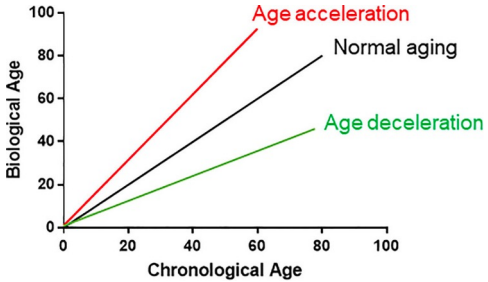
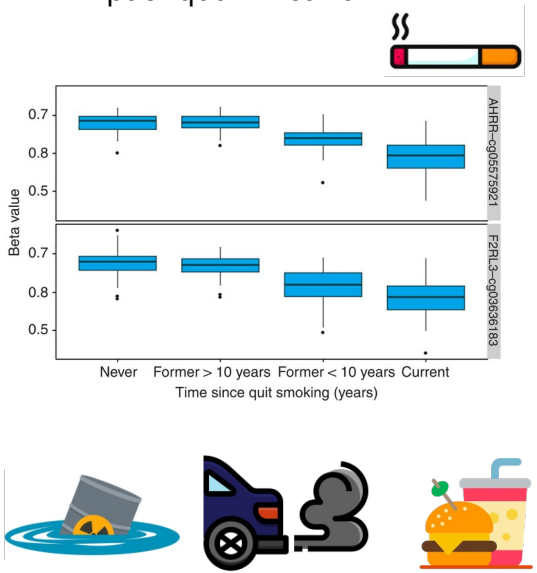
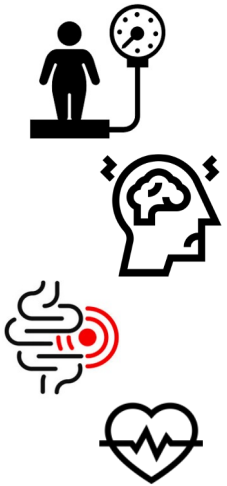


Environmental risk factor impact quantification



Measuring physiological risk factors



Images: 1. Yu *er al.* 2019, *Cancer Research*; 2. Fasanelli *et al.* 2015, *Nat Comms*

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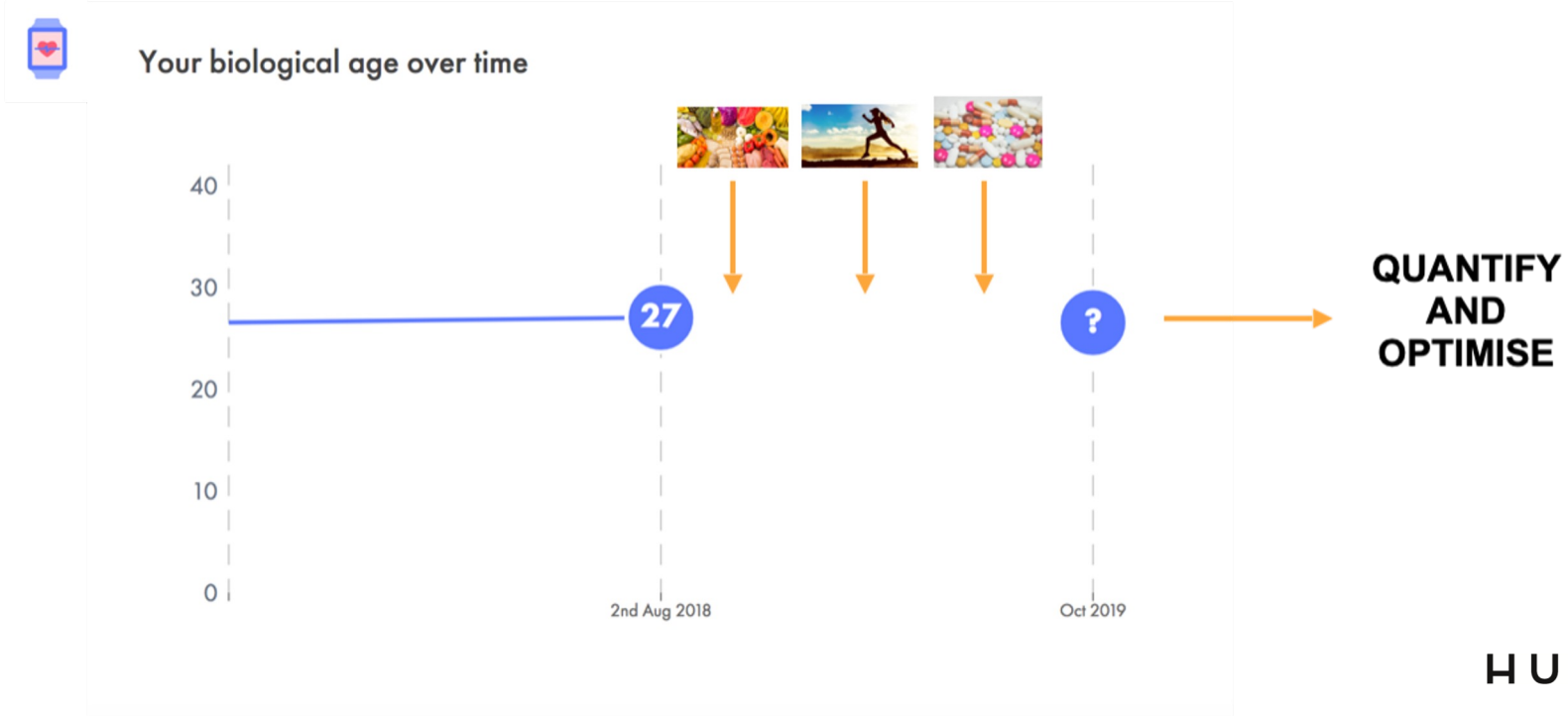
Epigenetic clocks to track intervention success



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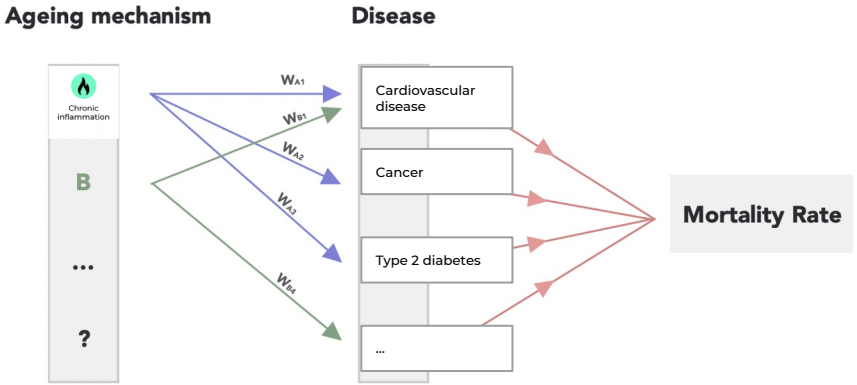
Preventive healthcare and epigenetics - InflammAge

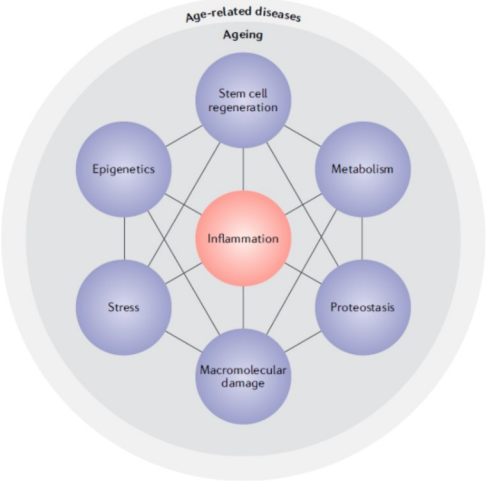
- At **Hurdle** we trained a novel DNA methylation aging clock using biologically informed by features related to systemic chronic inflammation. This work was supported by Bayer Consumer Health

- First biomarker of its kind rooted in biology of chronic inflammation and epigenetic aging
- Non-invasive and accessible saliva test
- Easily deployable as screening self test
- Captures long term inflammation trends (think HbA1c vs glucose)
- Actionable measurement of a major driver of biological-age related chronic disease risk

BAYER HURDLE

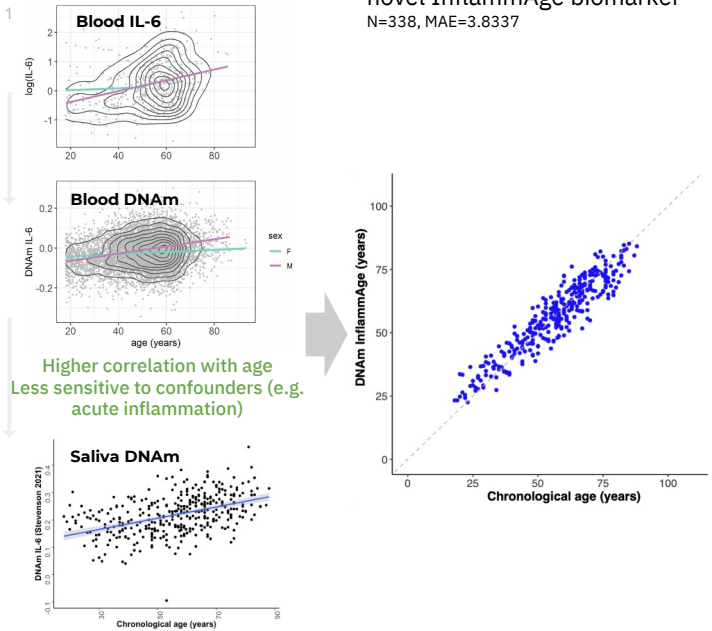
Preventive healthcare and epigenetics - InflammAge





Preventive healthcare and epigenetics - InflammAge

Built saliva DNAm proxies
for blood SCI markers



Higher correlation with age
Less sensitive to confounders (e.g. acute inflammation)

Higher accessibility and scalability

Trained age predictor ML model
using 42 SCI saliva DNAm proxies:
novel InflammAge biomarker
N=338, MAE=3.8337

Images: 1. Stevenson *et al.* 2021, *J. Gerontol A Biol*;

Preventive healthcare and epigenetics - InflammAge

Built saliva DNAm proxies
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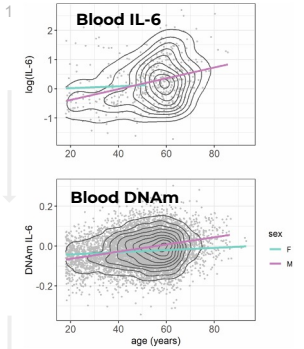
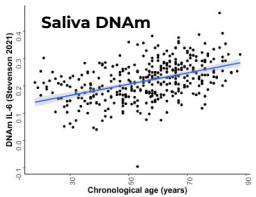
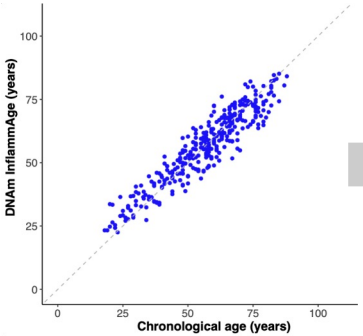


Higher correlation with age
Less sensitive to confounders (e.g. acute inflammation)

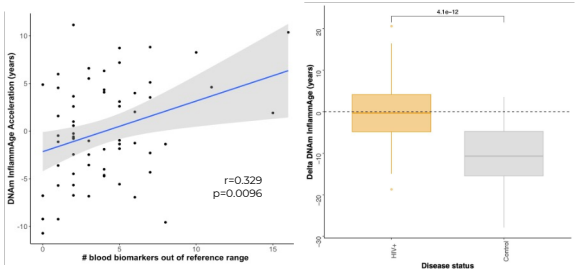


Higher accessibility and scalability

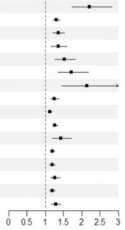
Trained age predictor ML model
using 42 SCI saliva DNAm proxies: novel InflammAge biomarker
N=338, MAE=3.8337



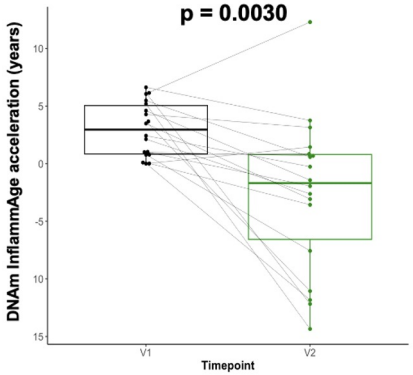
InflammAge acceleration is associated with:
- Blood markers out of clinical reference ranges (N=61)
- Chronic pro- inflammatory disease (HIV, N=46control+142HIV)
- Inflammatory conditions in GS biobank (N= c.20,000)



Predictor	n_event	Prop Female	mean_age_case	sd_age_case
alc_problems	1101	0.542	53.7	12.4
benign_colon	793	0.482	62.5	8.35
bronchiectasis	144	0.59	67.2	8.56
cholecystitis	401	0.688	58	12.7
cholelithiasis	655	0.728	57.9	12.6
COPD	566	0.602	63.8	9.68
GORD	1466	0.666	56.5	12.1
IDA	452	0.692	59.9	14.8
leukaemia	35	0.457	66.5	12.2
MDS	21	0.381	71.2	9.03
oth_anaemia	625	0.656	61.3	14.6
peripheral_arterial_disease	213	0.455	66	8.2
peritonitis	132	0.561	60.9	13.8
pulm_fibrosis	64	0.359	72.1	7.98
sec_pulm_htn	34	0.529	71.6	8.41
splenomegaly	14	0.5	57.6	9.14
AKI	370	0.484	72.8	10
bacterial	1217	0.565	61.1	15.1
lrti	956	0.559	66.6	12.4
mycoses	90	0.6	63.6	9.69
oth_organisms	1427	0.57	63.1	13.8
oth_organs	722	0.575	61.9	13.8
sepsis	258	0.496	68.4	11.1
uti	661	0.623	66	13.9
covid	334	0.581	63.2	13.8



We demonstrated actionability
with InflammAge reduction in a nutraceutical interventional trial
(N=18)



Images: 1. Stevenson *et al.* 2021, *J. Gerontol A Biol*;

Preventive healthcare and epigenetics

Prevention/risk

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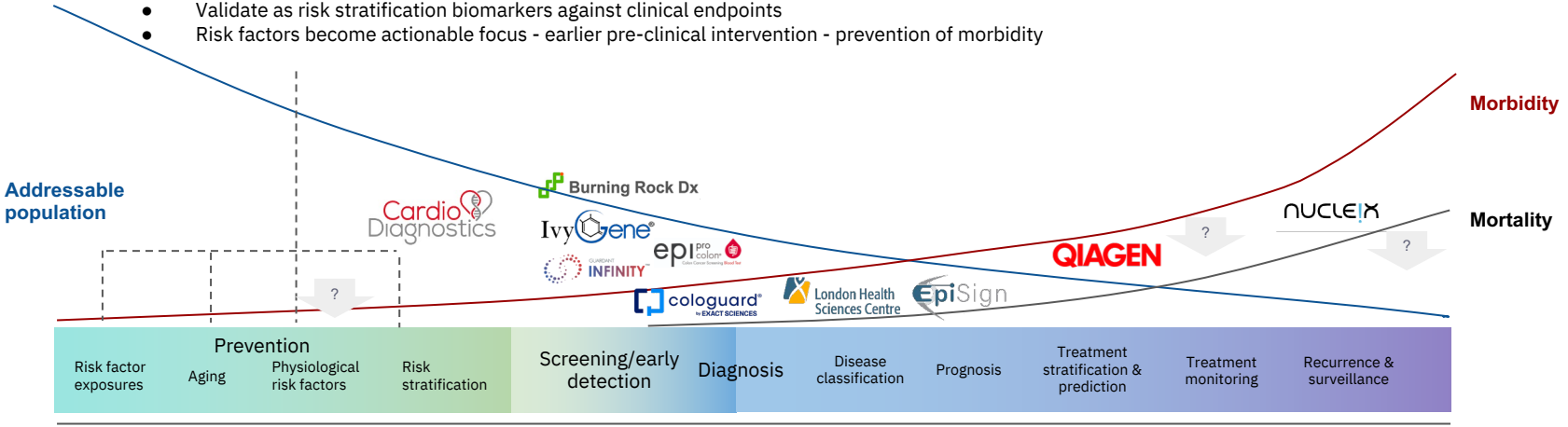
- AI/ML models for risk factor quantification - 1000s of DNAm sites
- Integrate environmental risk exposures, aging, physiological stress with genetics
- Classified as wellness test by FDA - faster to market + wider reach

- Validate as risk stratification biomarkers against clinical endpoints
- Risk factors become actionable focus - earlier pre-clinical intervention - prevention of morbidity



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Deconvoluting epigenetic biological age for preventative healthcare

	1 Prevention	2 Screening and early detection	3 Diagnosis	4 Treatment selection and monitoring
Cardiovascular disease		Polygenic risk score for cardiovascular disease. Lipids and cholesterol test.	ECG and troponin blood test (myocardial infarction). CT or MRI (stroke).	Lipids and cholesterol test. Coagulation screening to monitor antiplatelet and anticoagulant therapies.
Type 2 diabetes		HbA1c test	HbA1c test	HbA1c and glucose test
Cancer		FIT stool test (colorectal cancer) Mammography (breast cancer) Galleri test (multi-cancer)	Colonoscopy (colorectal cancer) Tissue biopsy	Companion diagnostic to select drug. cfDNA test to monitor recurrent or residual disease.
And much, much more...				

HURDLE

Summary

1. Epigenetics can **integrate** genetics and environment to quantify complex traits like aging and disease risk

2. DNA methylation is an **accessible, dynamic data source** for next gen AI/ML built biomarkers

3. Biological age biomarkers such as **InflammAge** can track the effect of interventions
4. DNA methylation biomarkers could link **prevention, risk stratification, and early detection** for tomorrow's population-health screening strategies

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BAYER

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for an exclusive discount code on our Biological Age test!

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Epigenetic Scientist

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R&D Manager

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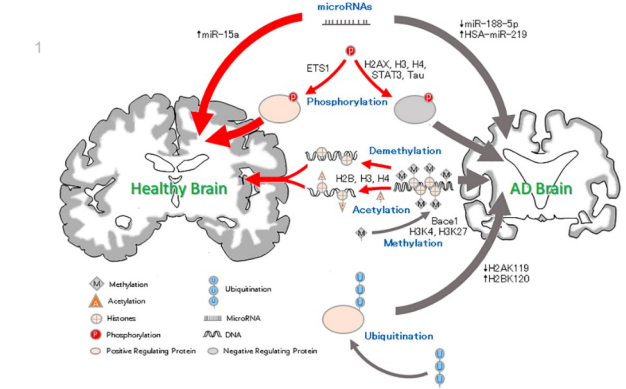
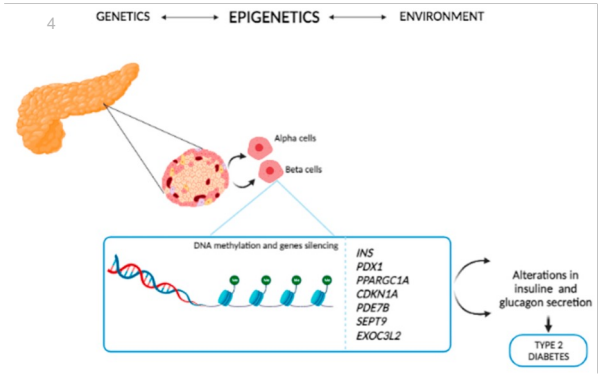
Epigenetic drivers and fingerprints of disease

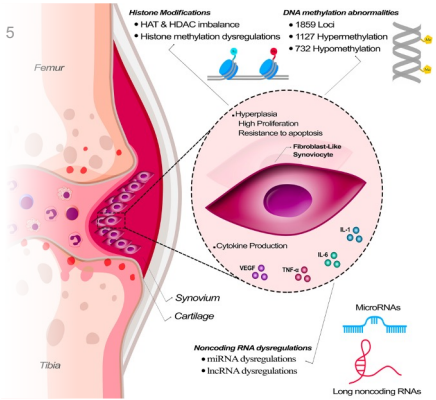
Neurodegenerative disease



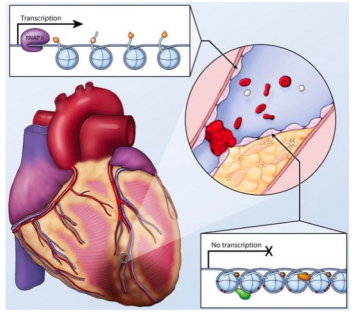
T2D/metabolic disease



Inflammatory/autoimmune disease



Cardiovascular disease



Cancer

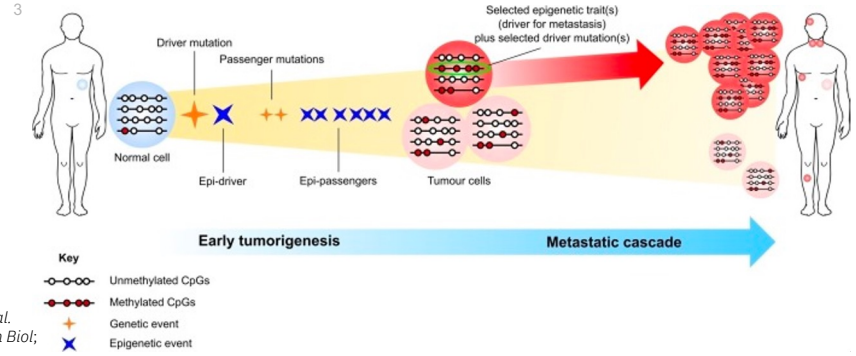


Image: 1. Gao *et al.* 2022, *Aging NeuroSci*; 2. Turgeon *et al.* 2014, *Med Epi*; 3. Caparelli *et al.* 2021, *Biomed*; 4. Karami *et al.* 2019, *Immunol Cell Biol*; 5. Chatterjee *et al.* 2018, *Sem Can Biol*;

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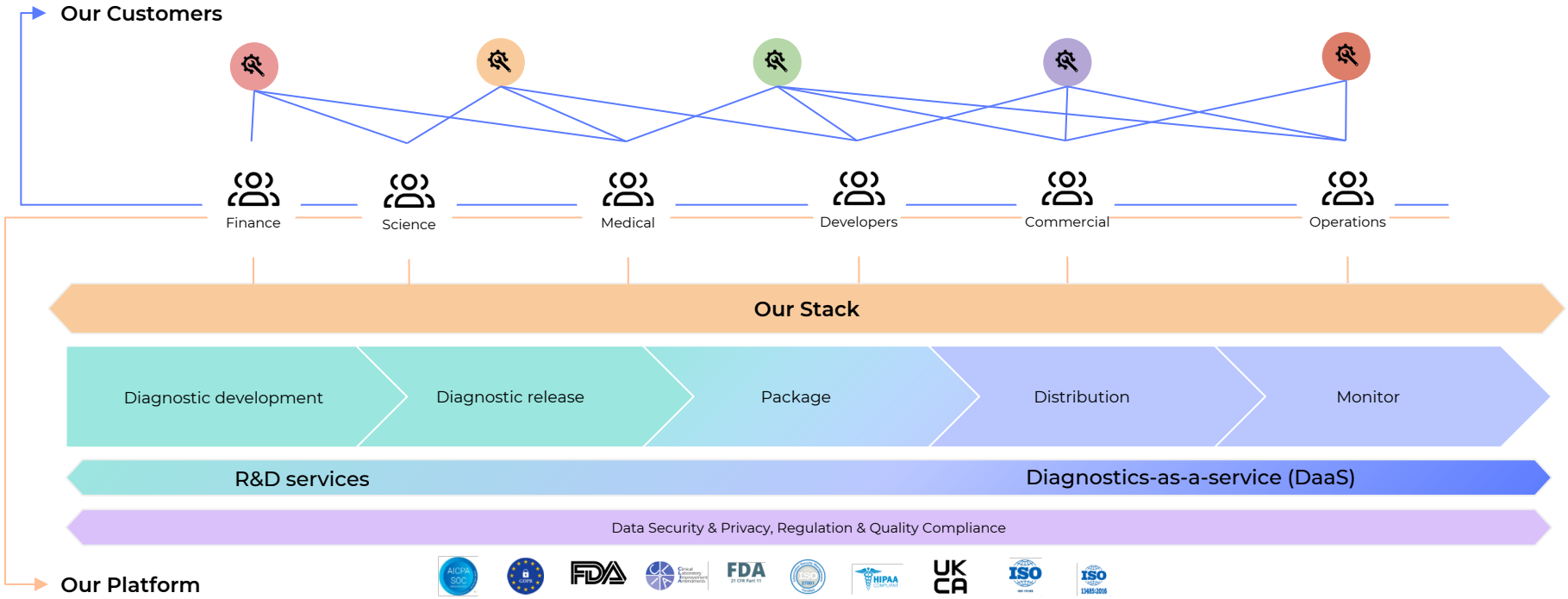
Deploying the biomarker in Hurdle's DaaS platform for global scale



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