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The New World of Omics in Environmental Epidemiology

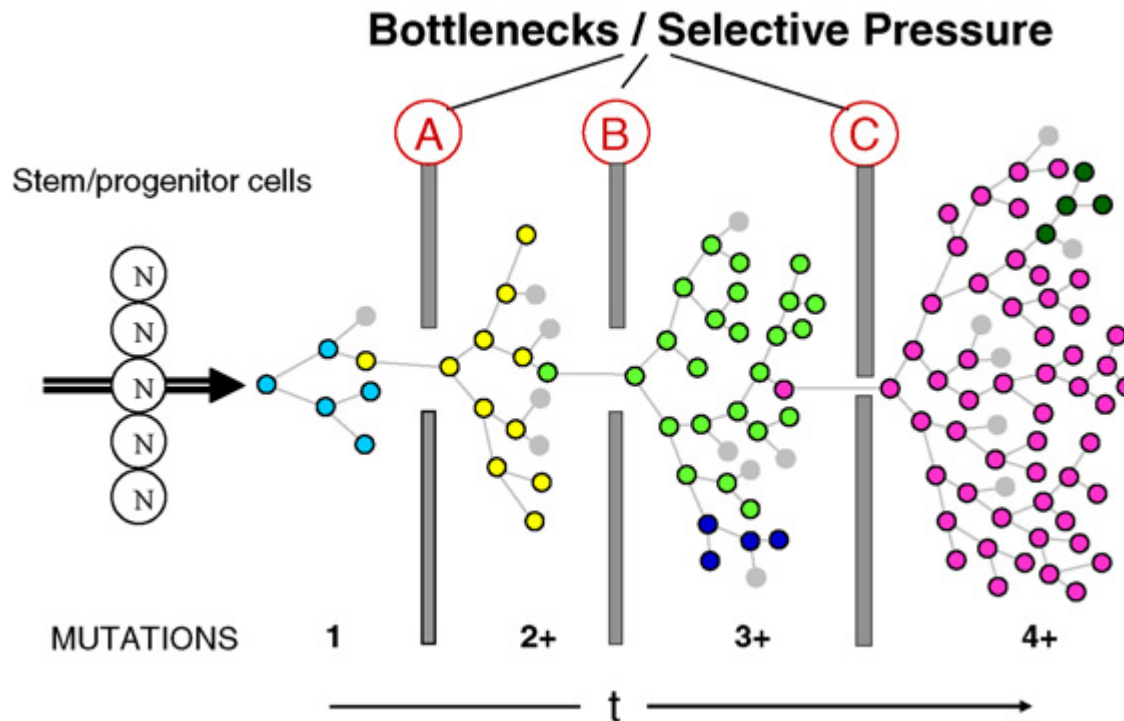
Zurich, June 21, 2018

MRC-PHE
Centre for Environment & Health

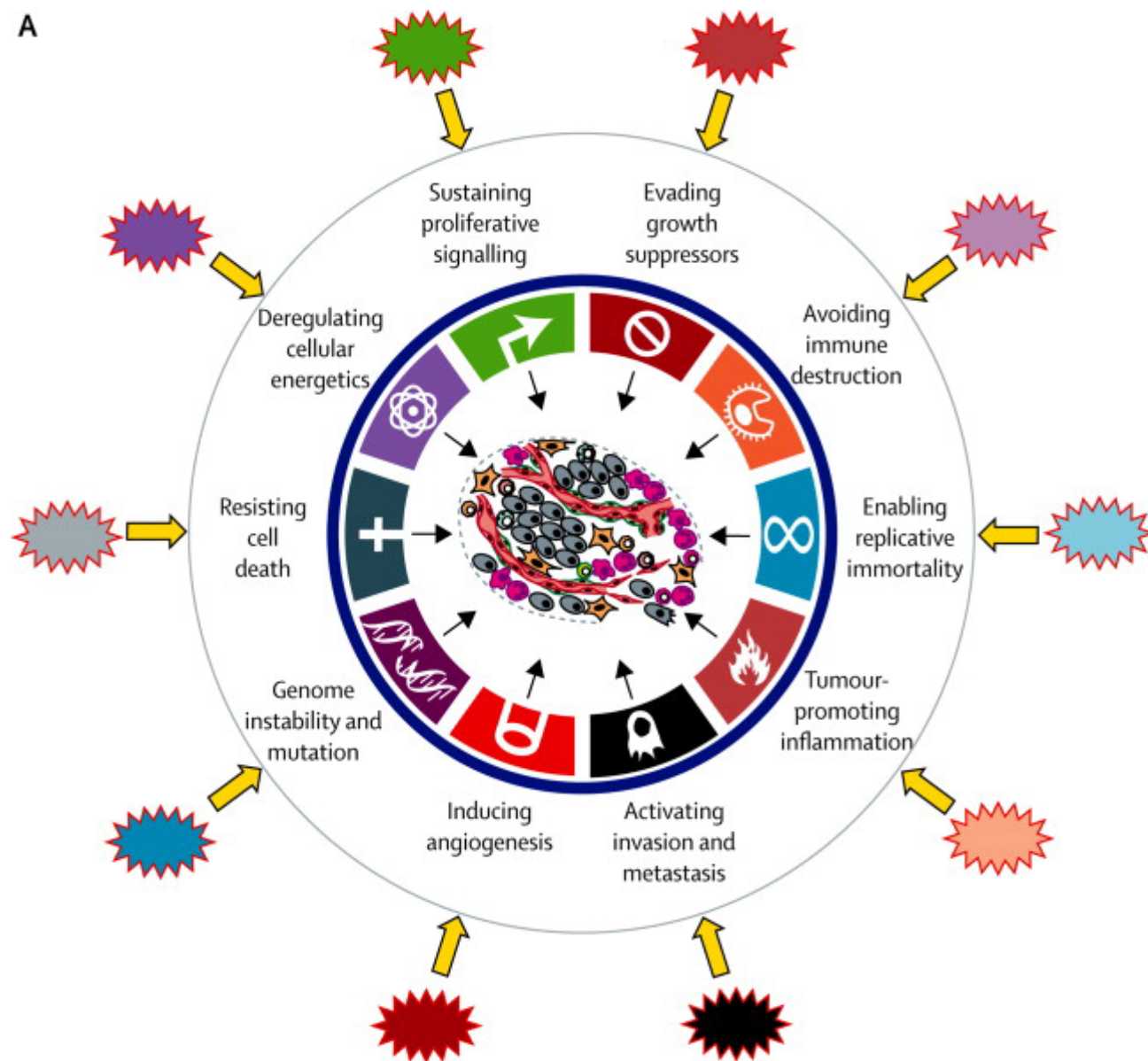


An evolutionary perspective

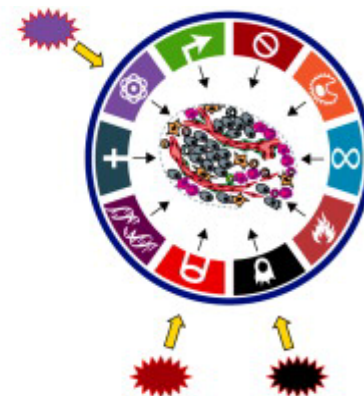
Cancer is the product of mutations, selection (**evolutionary branching**), and additional «**hallmarks of cancer**» that facilitate the growth and spread of cancer cells



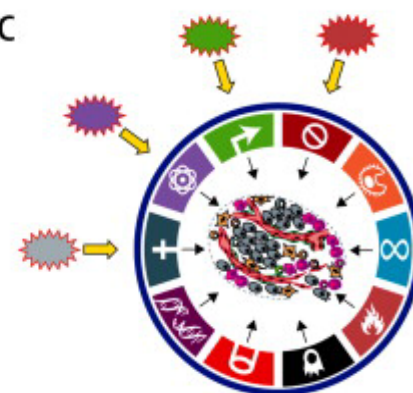
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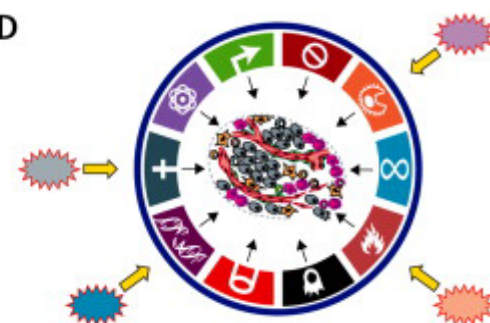
B



C



D



Exposome - the definition

- A potential measure of the effects of life course exposures on health. It comprises the totality of exposures to which an individual is subjected from conception to death, including those resulting from environmental agents, socioeconomic conditions, lifestyle, diet, and endogenous processes.
- Characterization of the exposome could permit addressing possible associations with health outcomes and their significance, if any, alone or in combination with genomic factors.

*Cited from the Dictionary of Epidemiology
MS Porta, 6th edition, OUP 2014*

The exposome

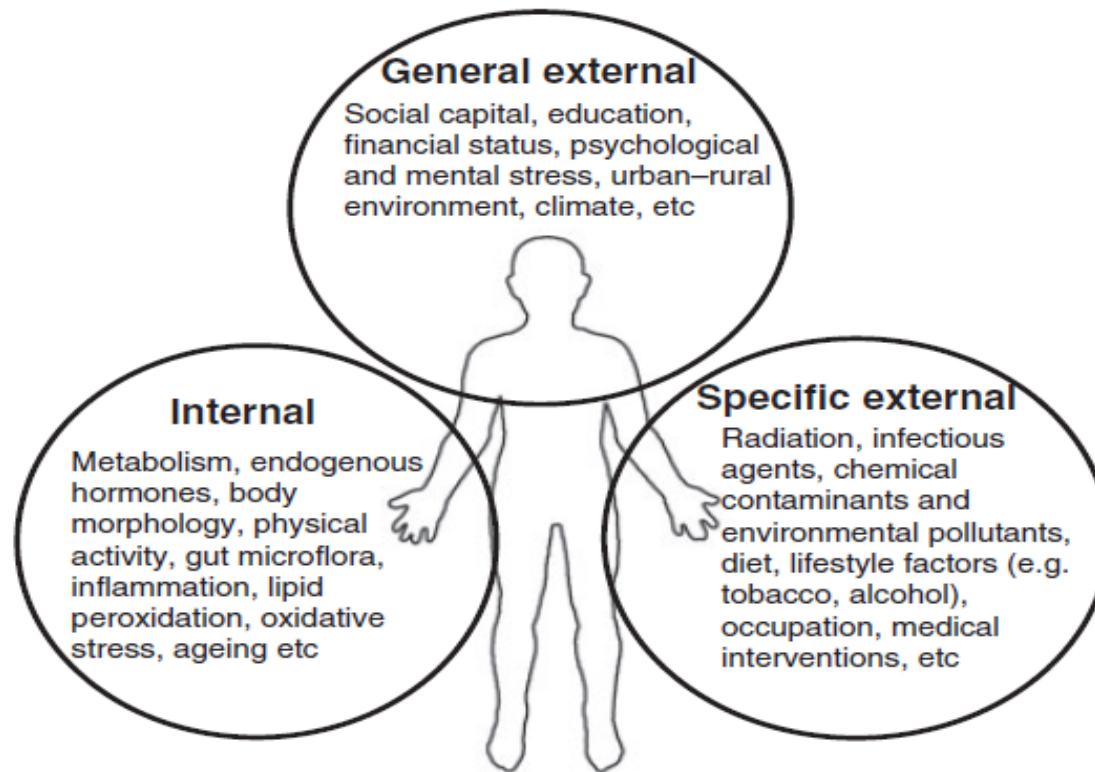
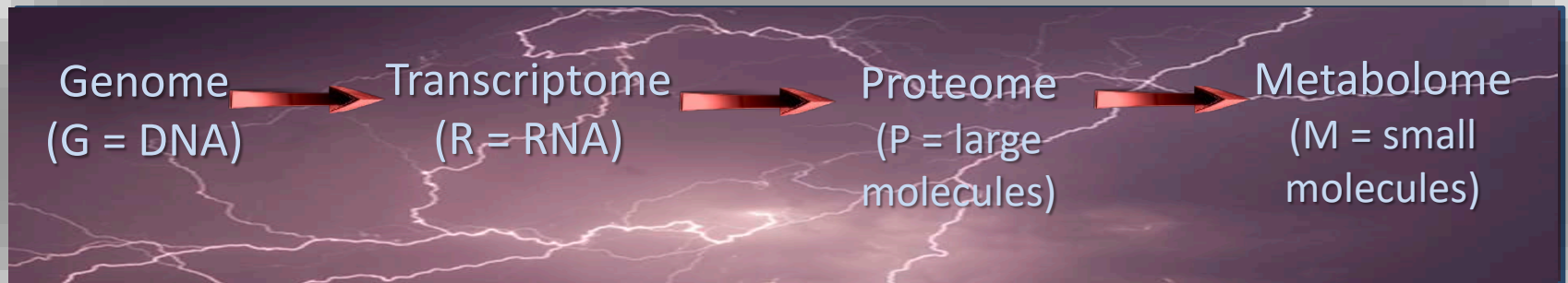


Figure 1 Three different domains of the exposome are presented diagrammatically with non-exhaustive examples for each of these domains

(C Wild, 2016)

Biomarker research supports causal reasoning by linking exposures with disease *via* mechanisms and emphasizing causality as a process

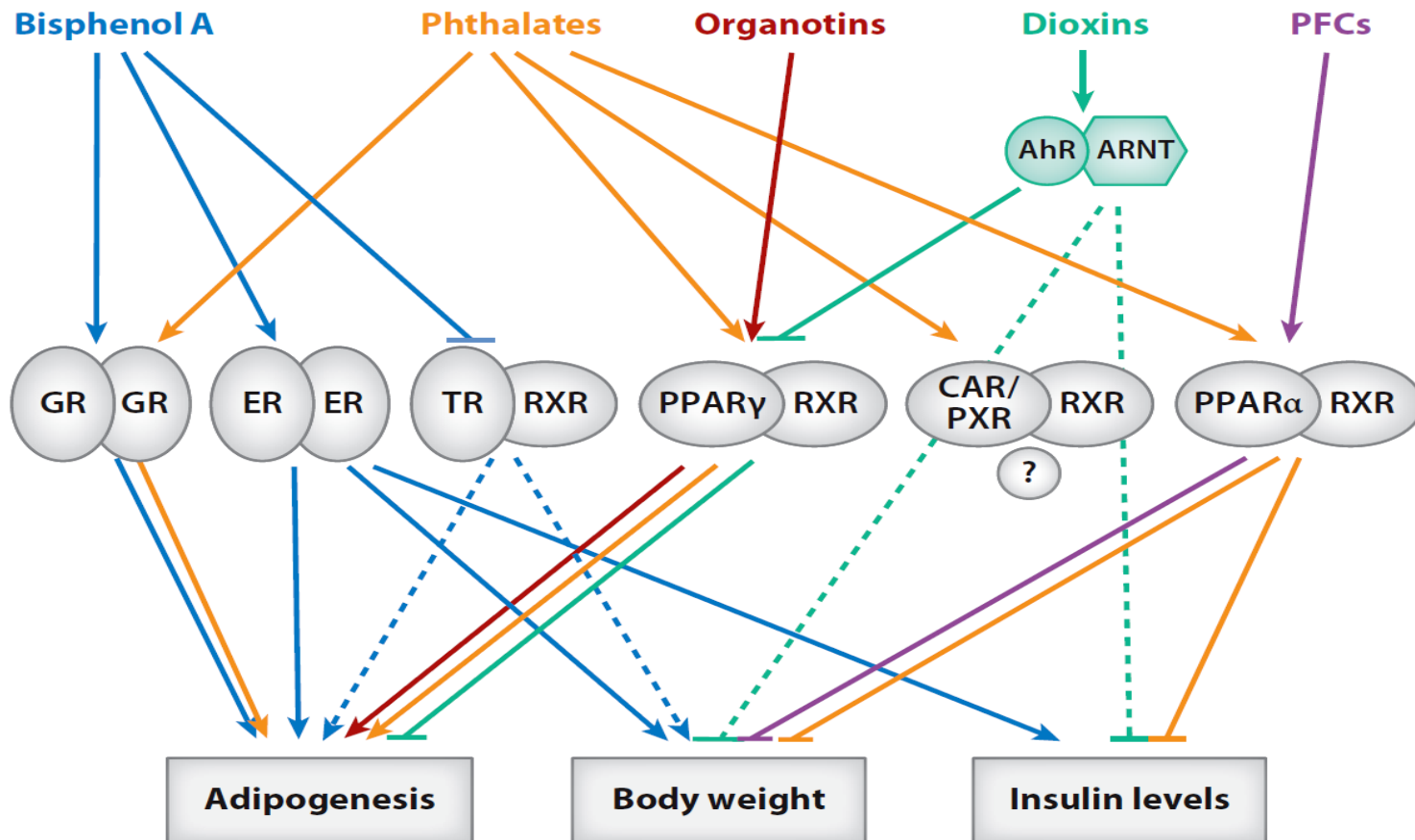
In the Salmon-Dowe causal approach (Salmon 1984, 1997; Dowe 1992, 2000), causal processes are capable of transmitting **conserved quantities**, such as mass-energy, linear momentum, or charge.



Transmission of conserved quantities is also transmission of information via molecules (=the internal exposome).

❖ «Pathway perturbation» - US National Academy of Sciences «Risk Assessment in the 21st century», 2017

- ❖ exposome research shows that the investigation of omics and molecular pathways (e.g. metabolomics, methylome, proteomics) can identify early signs of damage from environmental agents



EXPOsOMICS is a European Union funded project that aims to develop a novel approach to the assessment of exposure to high priority environmental pollutants, by characterizing the external and the internal components of the **exposome**.

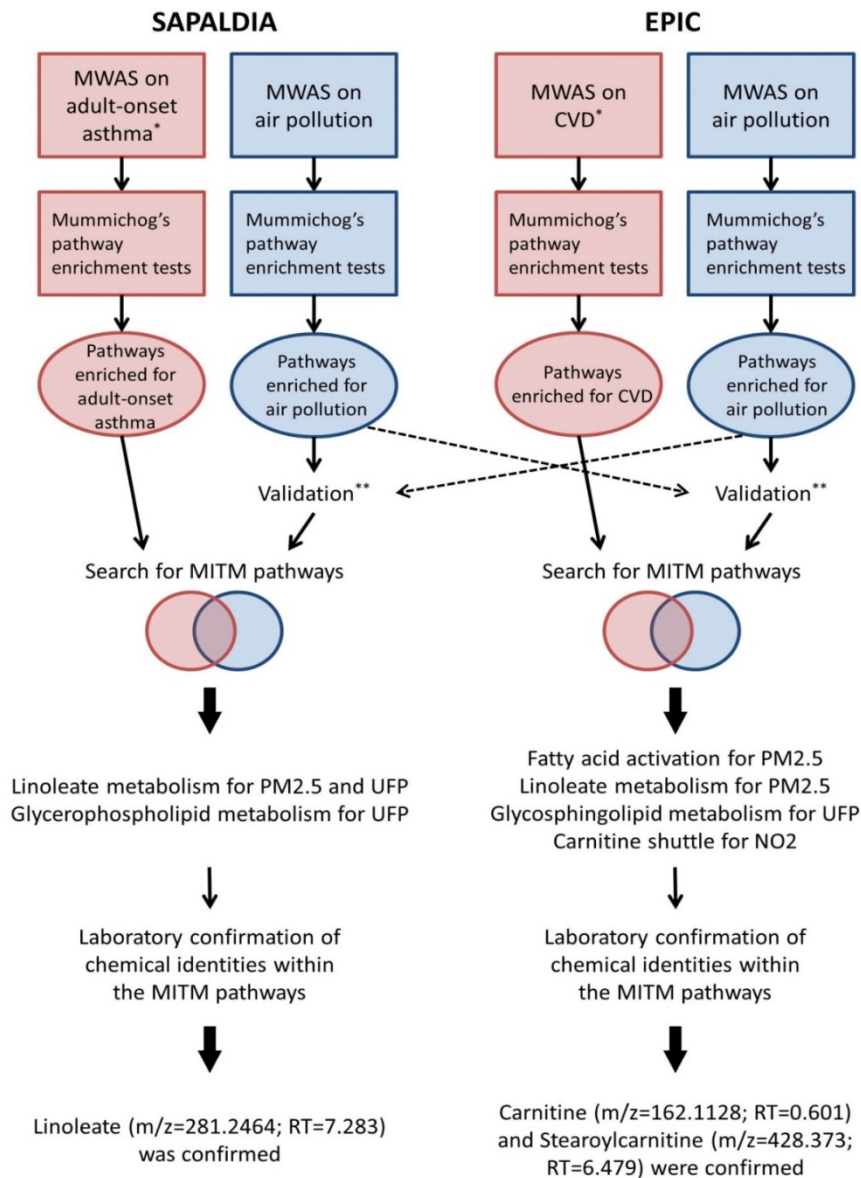
It focuses on air and water contaminants during critical periods of life. The project centres on 1) advanced exposure assessment at the personal and population levels within existing European short and long-term population studies; and 2) multiple “omic” technologies for the analysis of biological samples.

Oxford Street: 'active' exposure / Hyde Park: 'control' exposure



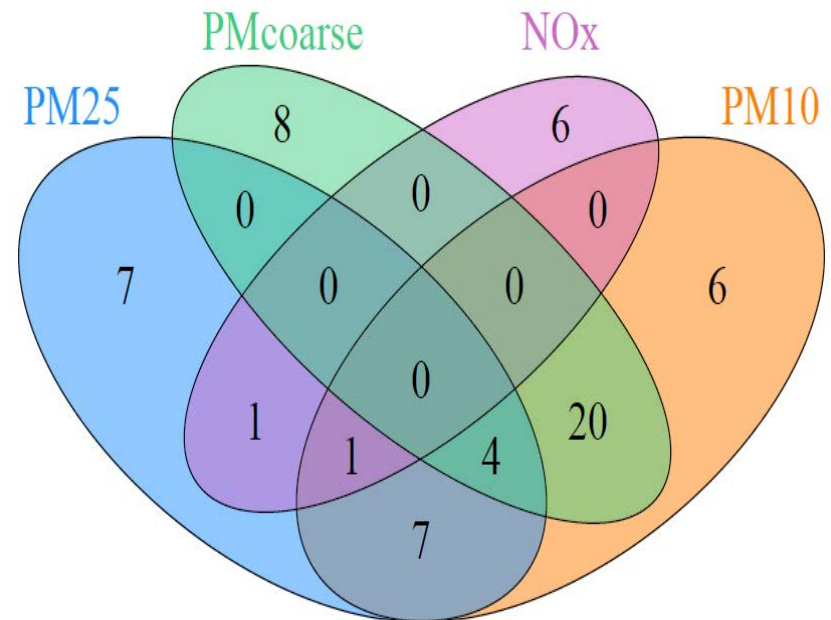
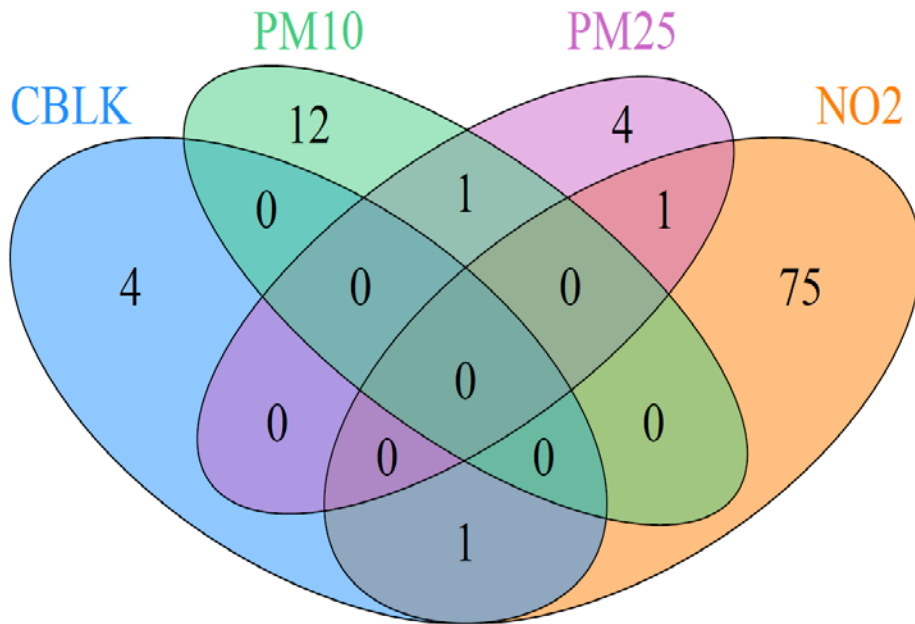
Study	Transcriptomics	Epigenetics	Proteomics	Metabolomics	Adductomics
PEM Basel	89 Raw	128 Raw/ Proc.	90 Raw/ Proc.	127 Raw/ Proc.	798 Raw
PEM Norwich	56 Raw	60 Raw/ Proc.	42 Raw/ Proc.	61 Raw/ Proc.	
PEM Turin	76 Raw	127 Raw/ Proc.	85 Raw/ Proc.	127 Raw/ Proc.	
PEM Utrecht	63 Raw	90 Raw/ Proc.	87 Raw/ Proc.	89 Raw/ Proc.	
ENVIRONAGE	193 Raw	200 Raw/ Proc.	198 Raw/ Proc.	204 Raw/ Proc.	N
Piccoli+	N/A	99 Raw/ Proc.	97 Raw/ Proc.	100 Raw/ Proc.	
Rhea	N/A	100 Raw/ Proc.	100 Raw/ Proc.	100 Raw/ Proc.	
INMA	N/A	600 Raw/ Proc.	97 Raw/ Proc.	100 Raw/ Proc.	
EPIC Turin	N/A	172 Raw/ Proc.	187 Raw/ Proc.	382 Raw/ Proc.	N
EPIC Varese	N/A	143 Raw/ Proc.	192 Raw/ Proc.		
MCC	N/A	406 Raw/ Proc.	405 Raw/ Proc.	591 Raw/ Proc.	N
Asthma SAPALDIA	N/A	604 Raw/ Proc.	402 Raw/ Proc.	405 Raw/ Proc.	566 Raw
Asthma ECHRS	298 Raw	80 Raw/ Proc.	80 Raw/ Proc.	80 Raw/ Proc.	
TAPAS	117 Raw	N/A	N/A	120 Raw/ Proc.	146 Raw
Oxford Street	316 Raw/ Proc.	N/A	N/A	360 Raw/ Proc.	404 Raw
PISCINA	86 Raw/ Proc.	N/A	120 Raw/ Proc.	120 Raw/ Proc.	134 Raw
TOTAL	1,294 (Raw) 402 Proc. (mRNA) 208 (Raw miRNA)	2,809 (Raw & Proc. samples)	2,182 (Raw & Proc. samples)	2,966 (Raw & Proc. samples)	1,914 (Raw files)

Metabolomics in asthma and CVD: meet-in-the-middle (Jeong et al, submitted)

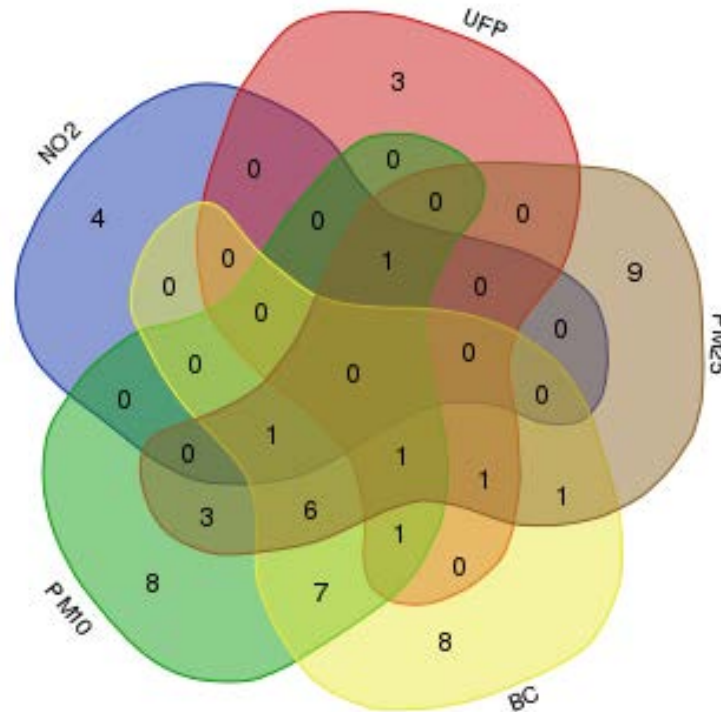


Effects of components in a mixture

Metabolomic signatures of different components of air pollution
(Oxford Street study, left, and TAPAS, right) (Bonferroni
significance)(van Veldhoven, submitted)

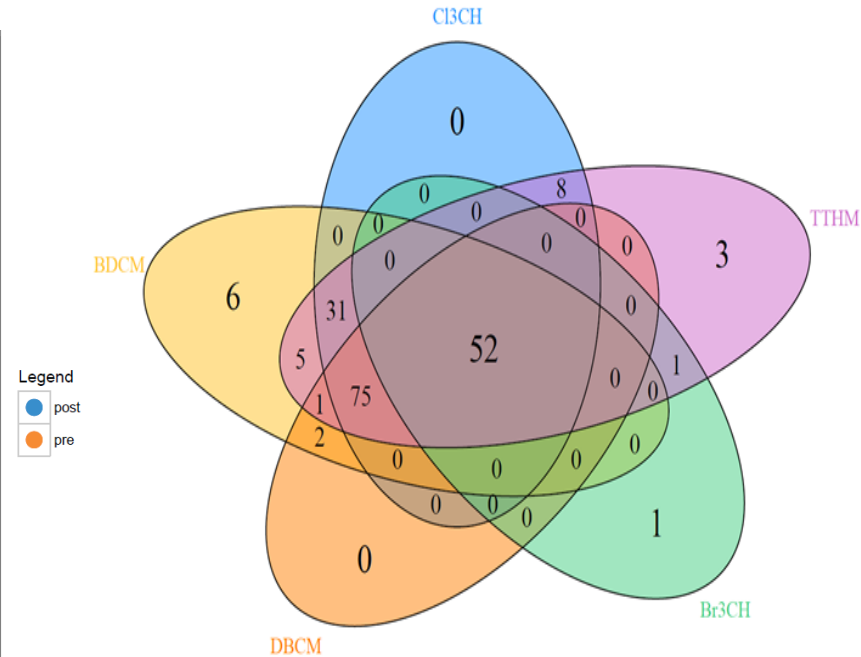
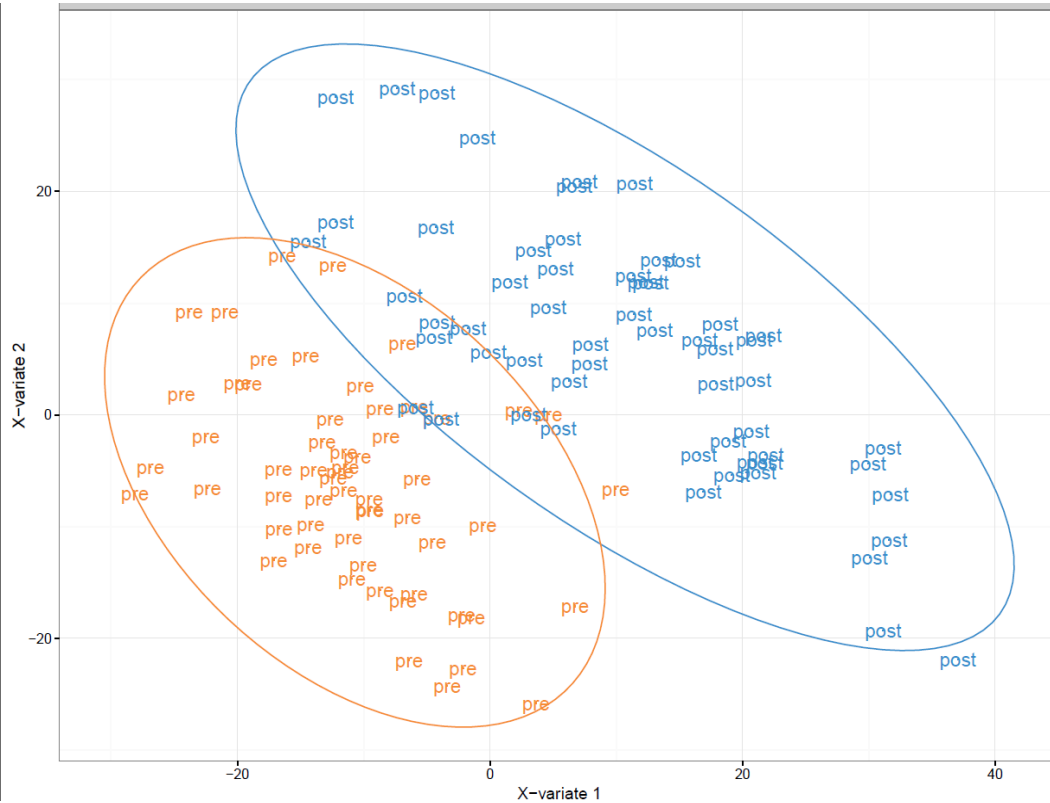


miRNA work in relation to air pollution shows that air pollutants impact several pathways via miRNA activation that in turn are relevant to the multi-organ toxicity of air pollution



Pollutant-specific cmiRNAs associated with TRAP exposure. The figure shows the overlap as well as the specificity of the pollutant-specific cmiRNAs associated with exposure to NO₂, UFP, PM_{2.5}, BC and PM₁₀ of the included subjects in Hyde Park and Oxford Street. **Julian Krauskopf et al, 2018**

Water quality in a swimming pool: metabolites from metabolomics show overlap, unlike for air pollutants (Van Veldhoven et al, 2017)



Fingerprints of exposures: certain exposures may leave characteristic fingerprints in DNA

CANCER ETIOLOGY

Mutational signatures associated with tobacco smoking in human cancer

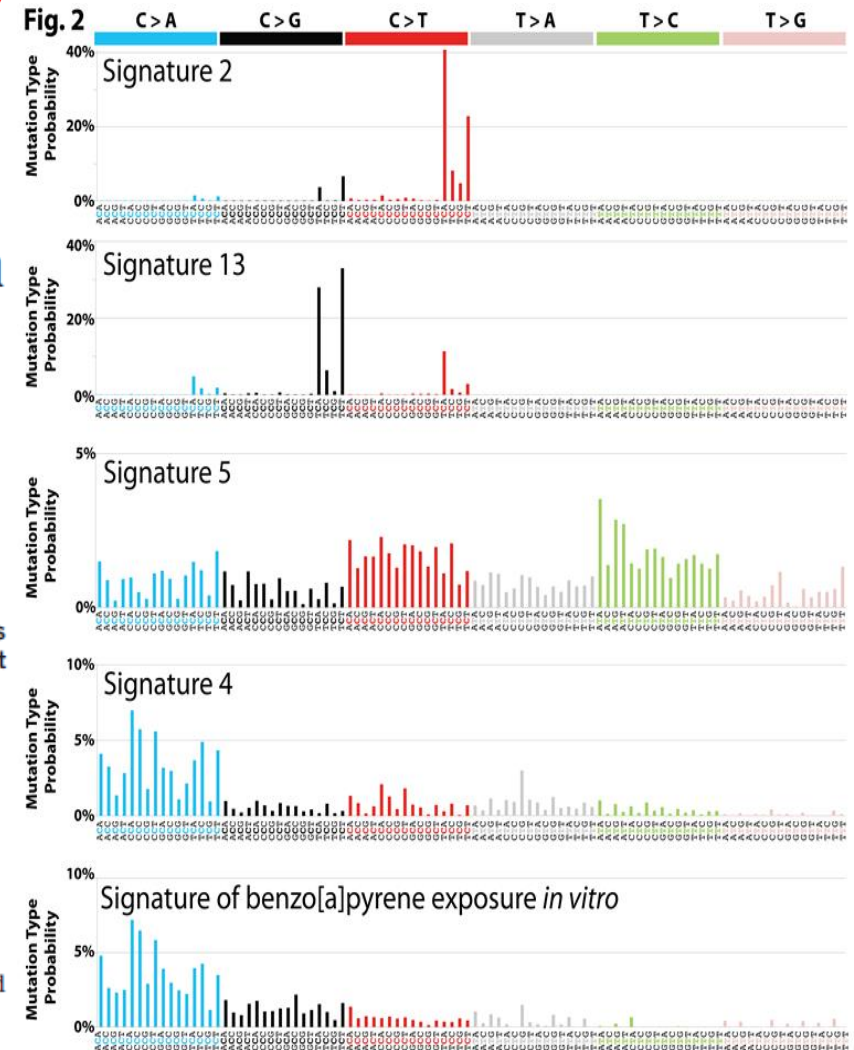
Ludmil B. Alexandrov,^{1,2,3*} Young Seok Ju,⁴ Kerstin Haase,⁵ Peter Van Loo,^{5,6} Iñigo Martincorena,⁷ Serena Nik-Zainal,^{7,8} Yasushi Totoki,⁹ Akihiro Fujimoto,^{10,11} Hidewaki Nakagawa,¹⁰ Tatsuhiro Shibata,^{9,12} Peter J. Campbell,^{7,13} Paolo Vineis,^{14,15} David H. Phillips,¹⁶ Michael R. Stratton^{7*}

Tobacco smoking increases the risk of at least 17 classes of human cancer. We analyzed somatic mutations and DNA methylation in 5243 cancers of types for which tobacco smoking confers an elevated risk. Smoking is associated with increased mutation burdens of multiple distinct mutational signatures, which contribute to different extents in different cancers. One of these signatures, mainly found in cancers derived from tissues directly exposed to tobacco smoke, is attributable to misreplication of DNA damage caused by tobacco carcinogens. Others likely reflect indirect activation of DNA editing by APOBEC cytidine deaminases and of an endogenous clocklike mutational process. Smoking is associated with limited differences in methylation. The results are consistent with the proposition that smoking increases cancer risk by increasing the somatic mutation load, although direct evidence for this mechanism is lacking in some smoking-related cancer types.

Tobacco smoking has been associated with | cancer genome sequencing, we recently described

Tobacco smoke as a mixture that leaves different signatures depending on the cancer site and possibly on the chemicals involved – e.g. PAH for lung cancer: signature 4

Science, 4 November 2016



Integrating socio-economic status and omics



Goals of **H2020 Lifepath**

To improve the understanding of the mechanisms through which healthy ageing pathways diverge by SES, by investigating **life-course biological pathways using omic technologies**.

Numbers involved in Lifepath

Subjects included in mortality analysis (adults)(Stringhini et al Lancet 2017)=1.7 million

Functional outcomes (paper in preparation)=108,261

Already available methylome (EPIC, MCCS, TILDA)>5,000

New measurements (Airwave, G21, TILDA, Whitehall II) >3,000

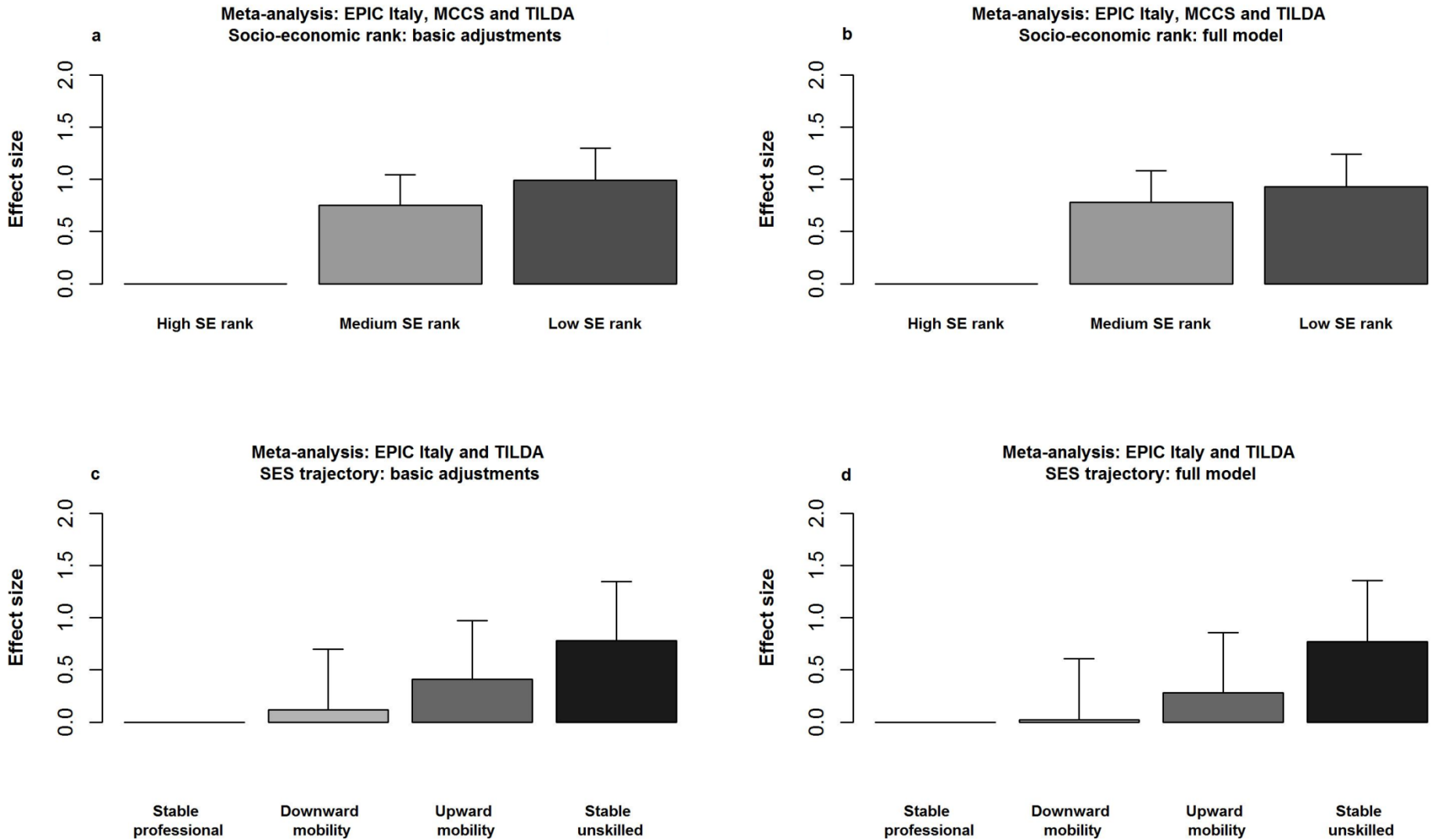
Already available inflammatory markers>5,000, new measurements 1,000

Metabolomics in 35,000 subjects (UCLEB consortium)

Epigenetics: biological clocks in Lifepath

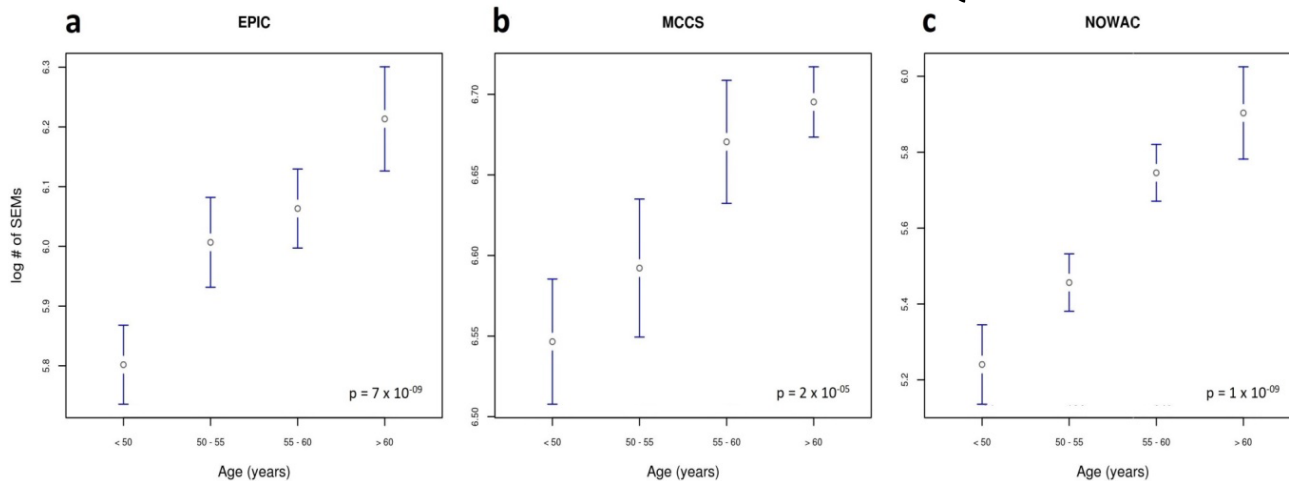
- Horvath developed the DNA methylation clock to predict age with high accuracy using 353 CpG sites
- From this Age Acceleration may be derived as a discrepancy between methylation age and chronological age

Age acceleration based on DNA methylation in three cohorts (G Fiorito, 2017)



Stochastic epigenetic mutations (SEMs) - Stochastic epigenetic mutations (SEMs) appear randomly in the genome and are not shared among subjects (Gentilini et al. Aging 2015).

Epimutation --> $\text{DNAm} < Q1 - 3 \text{ IQR}$ or $\text{DNAm} > Q3 + 3 \text{ IQR}$, where $\text{IQR} = Q3 - Q1$



The number of SEMs increases exponentially during aging.

High inter-individual variability in the rate of accumulation.

- Is associated with alcohol drinking, betel quid chewing, and cigarette smoking (Yamashita et al. PNAS 2018).
- Is higher in breast cancer tissue compared with adjacent non-cancerous tissue (Teschendorff et al. Nat. Comm. 2016).
- Correlates with Hepatocellular carcinoma tumor staging (Gentilini et al. Oncotarget 2017).
- Is associated with X chromosome inactivation skewing in women (Gentilini et al., Aging 2015).



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