

Paolo Vineis

Il rischio cancerogeno all'epoca della globalizzazione: il ruolo della ricerca epidemiologica e di laboratorio

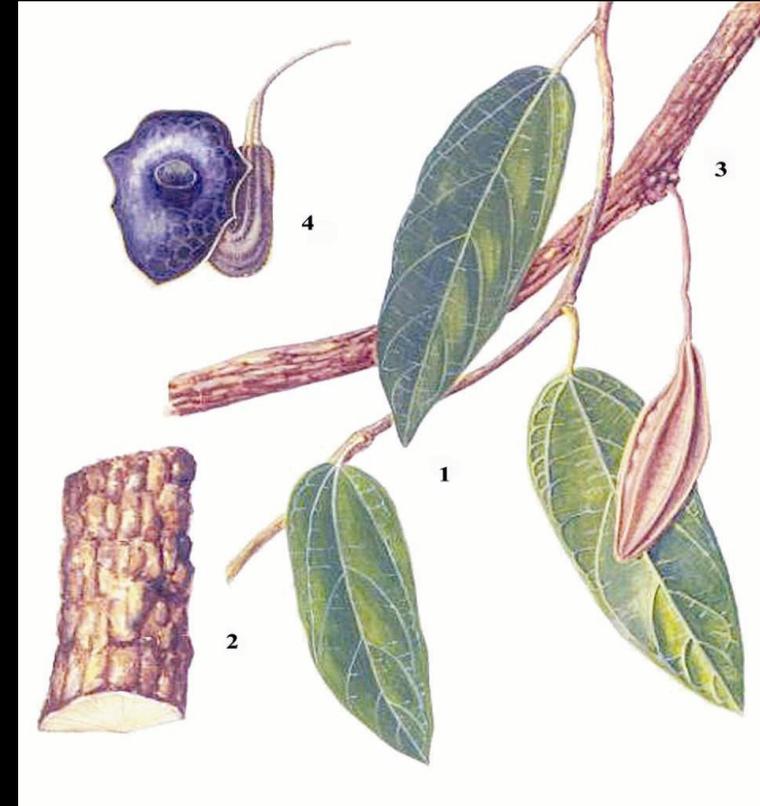
CANC TUM 2021

Relevance of study designs

Prevalence of Urothelial Cancers among Patients with Chinese Herb Nephropathy

- Case reports: 2 Belgium, 1 Taiwan, 1 U.K.
- Among 10 renal-grafted Chinese herb nephropathy patients 4 cases of multifocal carcinoma in situ
- Among 39 patients with end-stage renal disease 18 cases of urothelial carcinomas

IARC Monograph Vol 82, 2002



Arsenic in Drinking Water and Bladder and Kidney Cancer

Age-standardized mortality rate /100 000 by arsenic level

	General population	< 300 ($\mu\text{g/L}$)	300–590 ($\mu\text{g/L}$)	\geq 600 ($\mu\text{g/L}$)
Bladder				
Men	3.1	15.7	37.8	89.1
Women	1.4	16.7	35.1	91.5
Kidney				
Men	1.1	5.4	13.1	21.6
Women	0.9	3.6	12.5	33.3

Adverse effects may be easily underestimated

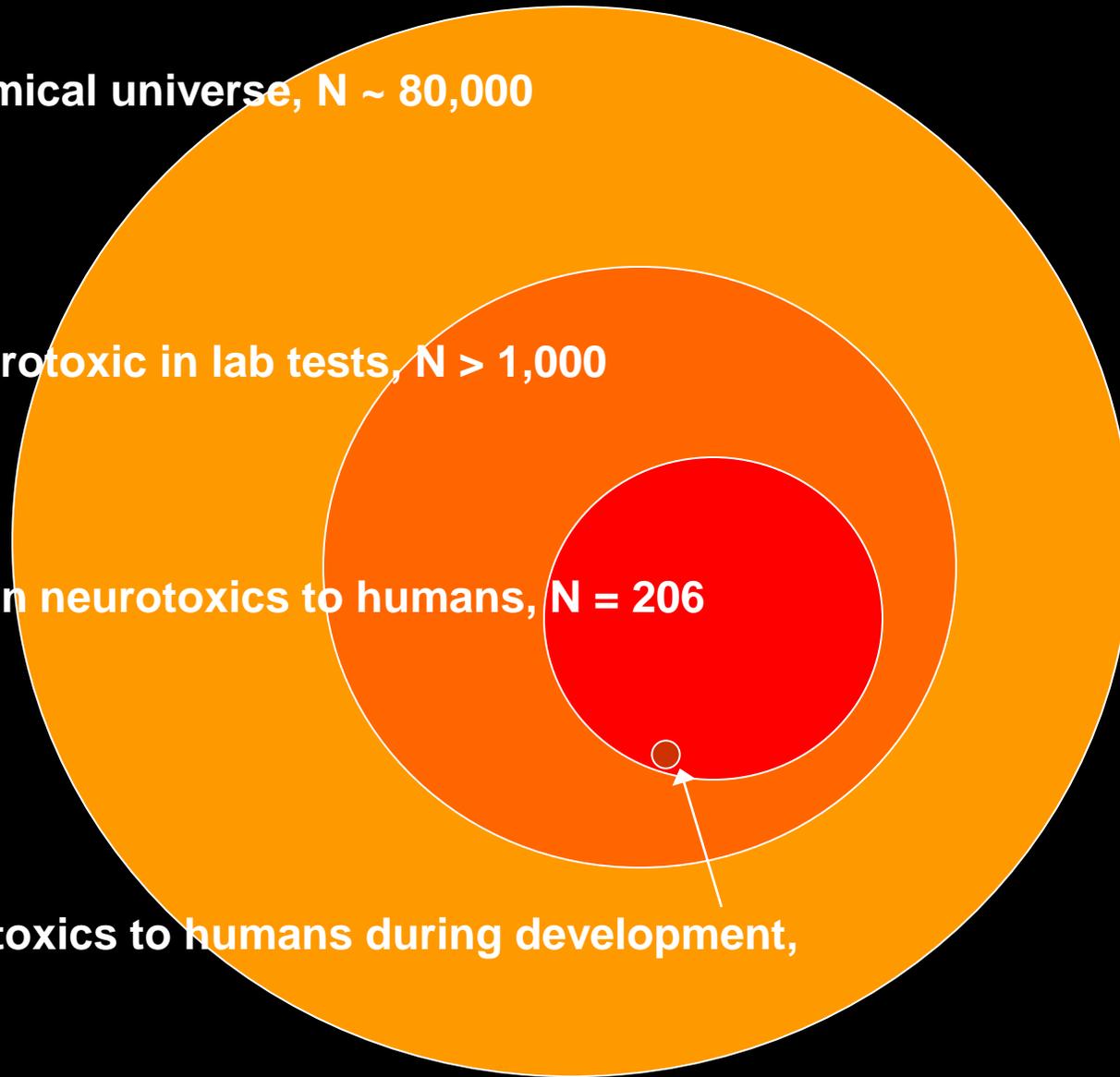
- Imprecise exposure assessment
- Outcome measures of limited validity
 - Sensitivity and specificity ('noise')
 - Appropriateness
 - Adjustment for confounders sometimes measured with better precision than the causative exposure
- Low statistical power

Chemical universe, $N \sim 80,000$

Neurotoxic in lab tests, $N > 1,000$

Known neurotoxics to humans, $N = 206$

**Known neurotoxics to humans during development,
 $N = 5$**



The environmental contribution to chronic disease

Familial and twin studies suggest that roughly 90% of cancer deaths cannot be explained by the genes and, therefore, point to environmental factors (broadly defined)

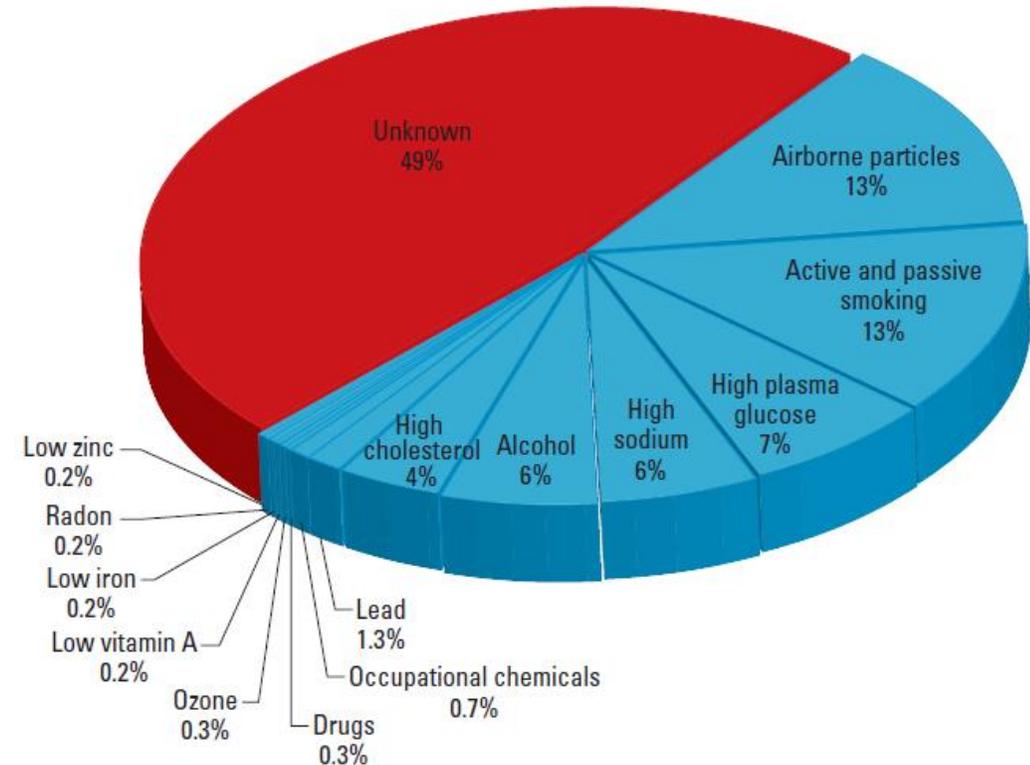


Figure 1. Risk factors for exposures that contribute to chronic-disease mortality. The chart was compiled from World Health Organization estimates of exposures affecting 50 million global deaths in 2010 (Lim et al. 2012). (Because some risk factors may be correlated, the indicated percentages are approximate.)

What are non-communicable diseases (NCD)?

Allen and Feigl (Lancet GH, 29017) have proposed a renaming/reframing as “socially transmitted diseases”

“The current list of NCDs describes a ragtag group of leftovers that do not satisfy Koch’s postulates”. Their attributes are:

- chronicity
- global burden
- preventable nature
- common proximal risk factors
(cholesterol, blood pressure, glucose, obesity)
- common behavioural risk factors (smoking, alcohol, diet, inactivity, air pollution)
- common distal risk factors (economic, social, environmental)
- common issues of inequality and injustice (“syndemic”)

In addition, risk factors for NCD often have a linear dose-response with risk (effects at low doses)

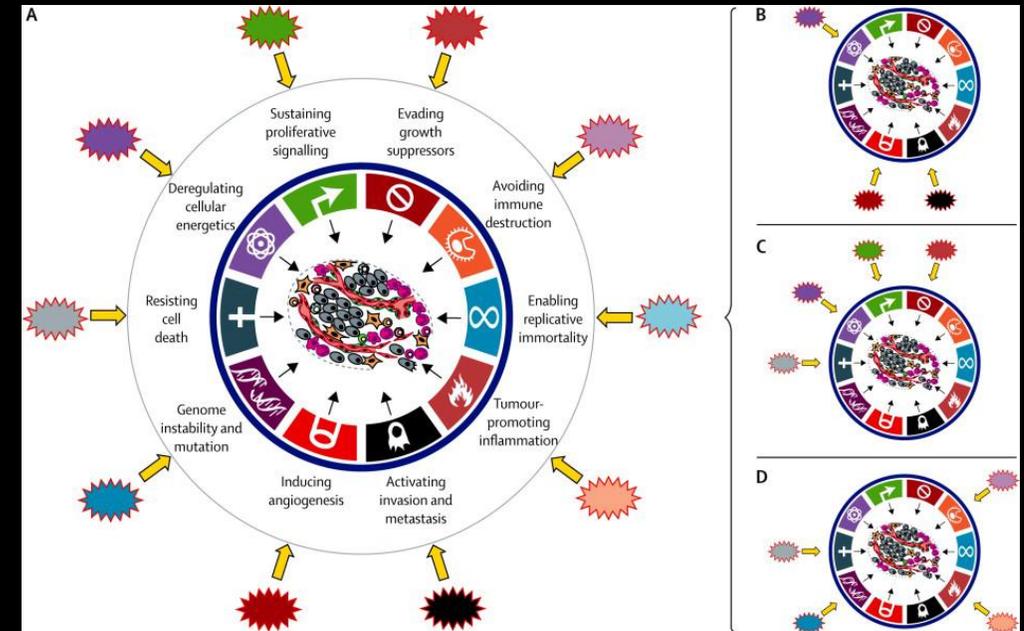
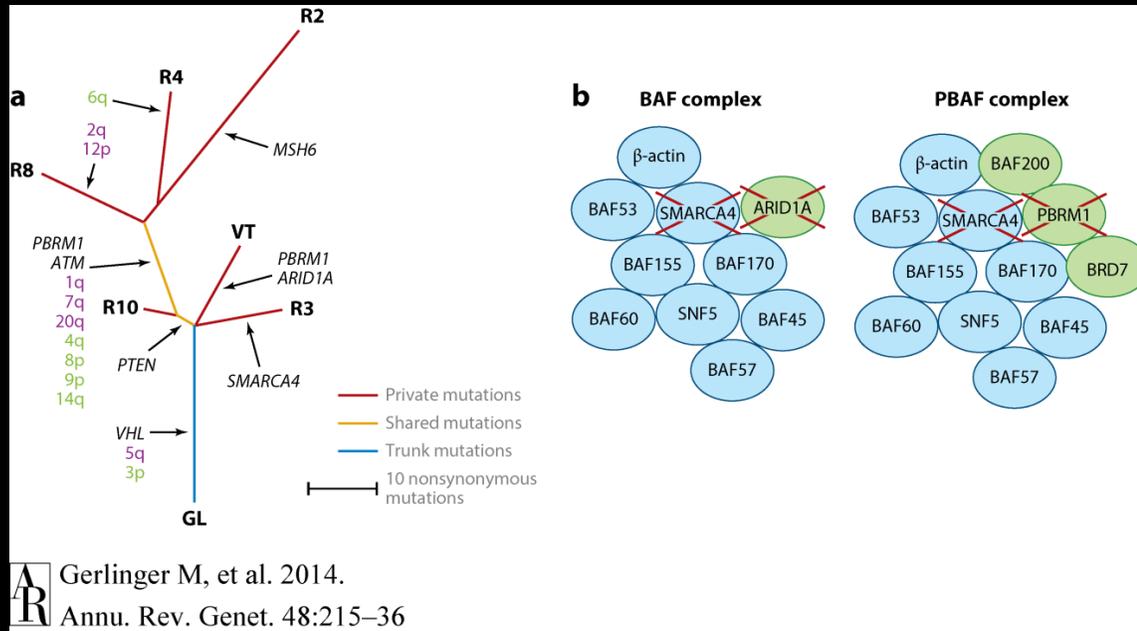
Hence the importance of:

- * Multifactoriality
- * Synergies
- * Mixtures and multiple exposures
- * Low doses
- * Early warnings (because of long latency periods)

Exposomics as the science of multifactoriality
How does it fit within the “attributable risk” paradigm?

The micro-environment perspective: mutagens and selectogens

Cancer genetic changes branch (branching evolution) since early stages, and the phenotype becomes more and more complex and individualized (even in the single metastasis) with time, leading to the «hallmarks of cancer» (Hanahan and Weinberg, 2011)



An **exposome** approach allows:

- Improvement of exposure assessment
- Enhancement of causal reasoning
- Improvement of mechanistic understanding (eg molecular signatures, pathways)
- Life-course approach to health
- Assessment of joint effects (mixtures)
- Revealing common roots of diseases (pathway perturbation)
- Agnostic/systematic analysis of environment-disease relationships

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

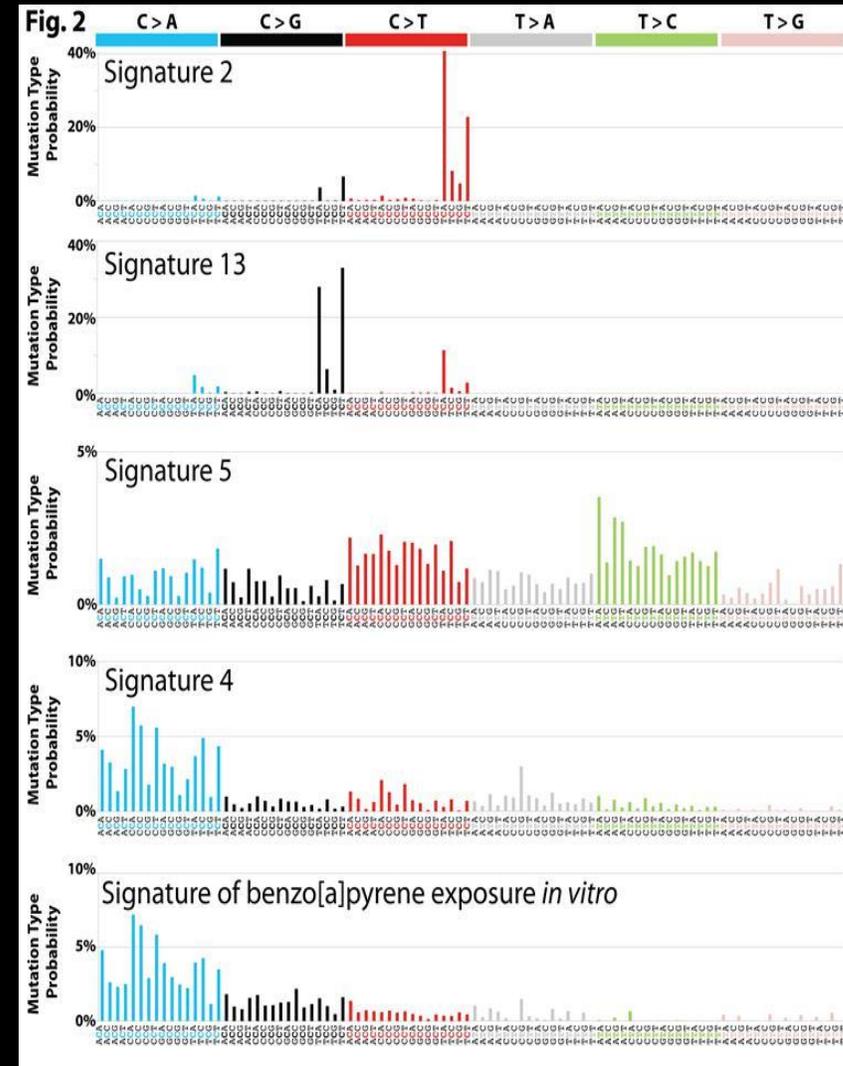
CANCER ETIOLOGY

Mutational signatures associated with tobacco smoking in human cancer

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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.

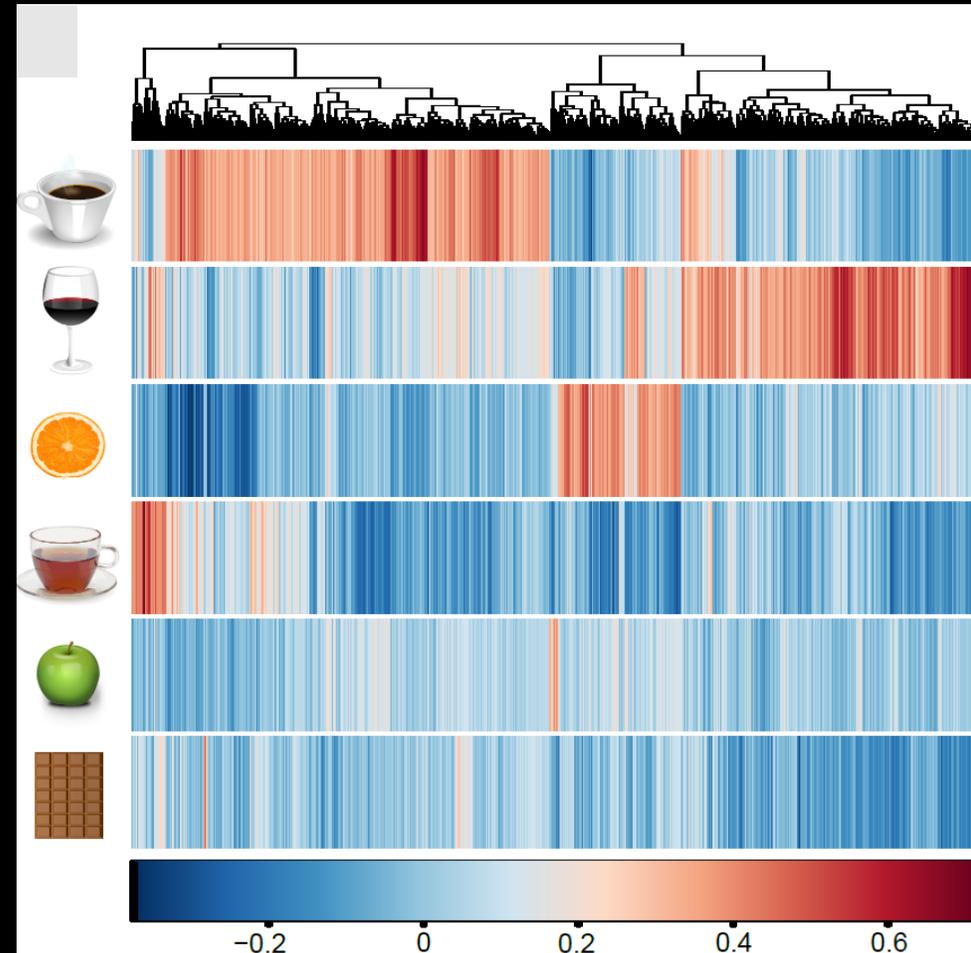
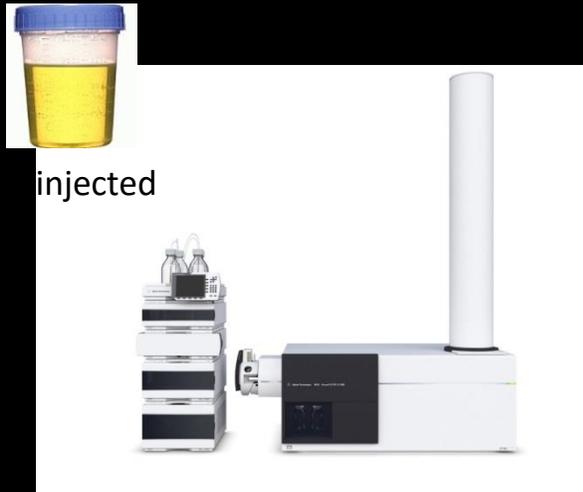
Tobacco smoking has been associated with cancer genome sequencing, we recently described



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

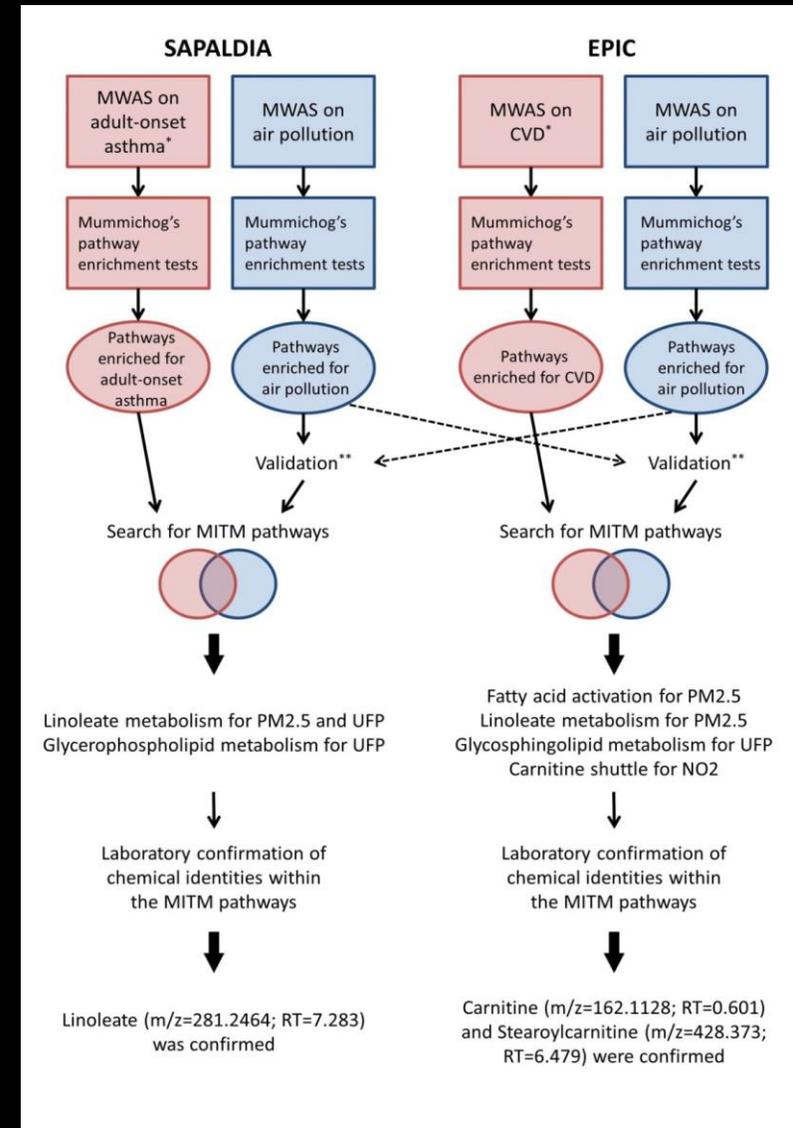
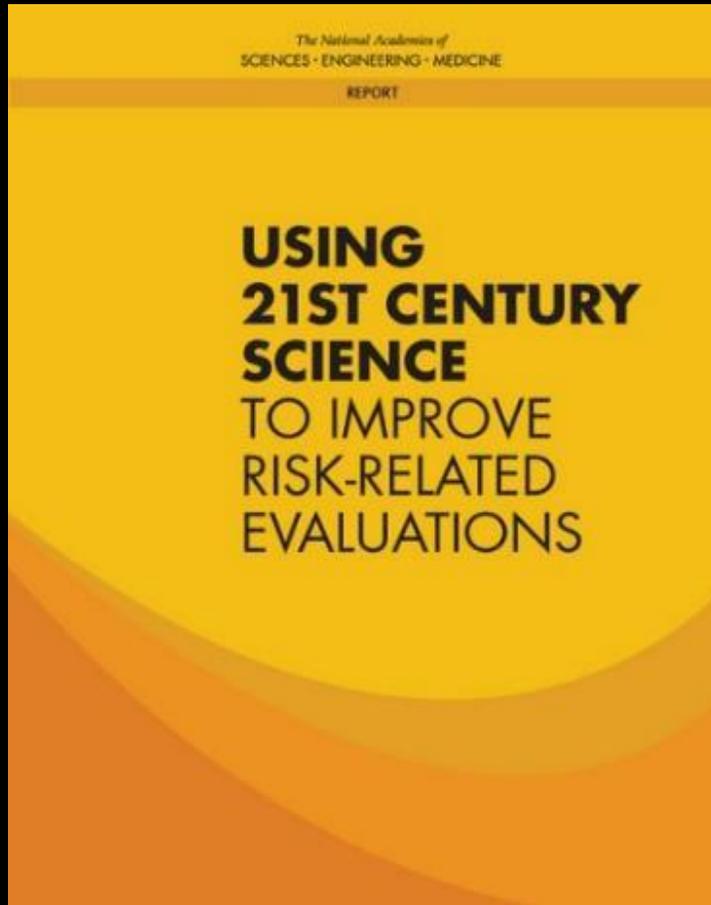
Exposure assessment: Metabolic signals associated with food intake

481 subjects from 4 countries
24-hr Dietary recalls
24-hr Urine samples
High-resolution mass spectrometry
(UHPLC-QToF-MS, neg ionization)
Iterative regression analyses



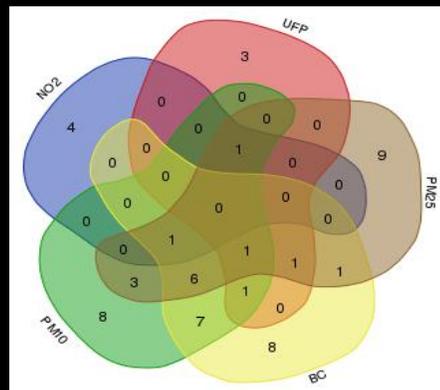
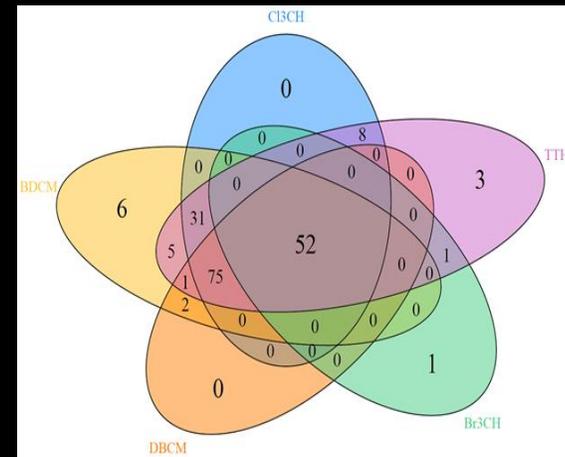
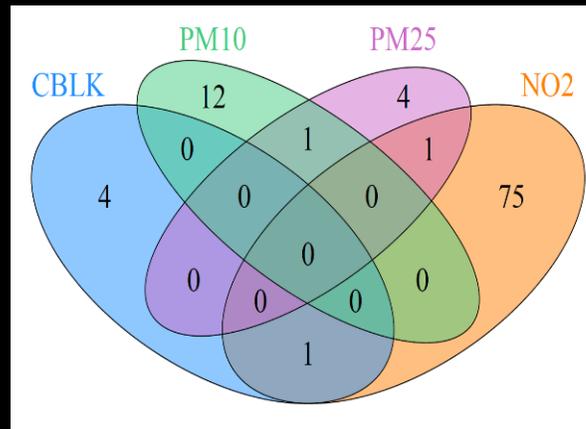
14,000 mass spectrometry features detected
2,272 features correlated to intake of six different foods

Pathways - «Meet-in-the-middle»



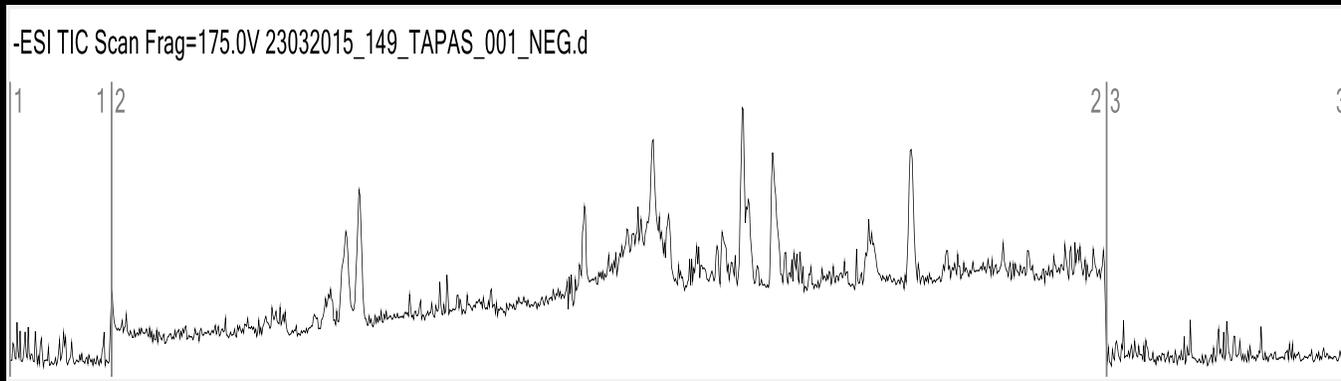
Mixtures

Metabolomic and miRNA signatures of different components of air pollution in the Oxford Street and TAPAS cross-over studies (Van Veldhoven et al, 2018; Krauskopf et al, 2018), and of disinfection by-products in swimming pool (Van Veldhoven et al, 2017)



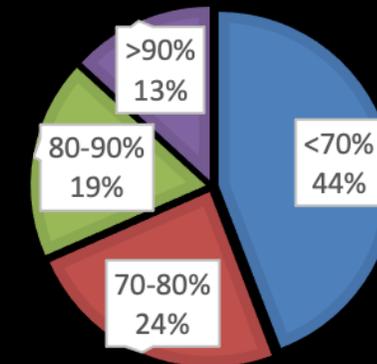
Untargeted data mining : preliminary findings in Exposomics (Dagnino, unpublished)

- ❑ Data-mining on 4 samples from TAPAS study (1 individual)
- ❑ Negative ionisation mode
- ❑ EPA Toxcast library



DATABASE MATCHING SCORE

■ <70% ■ 70-80% ■ 80-90% ■ >90%

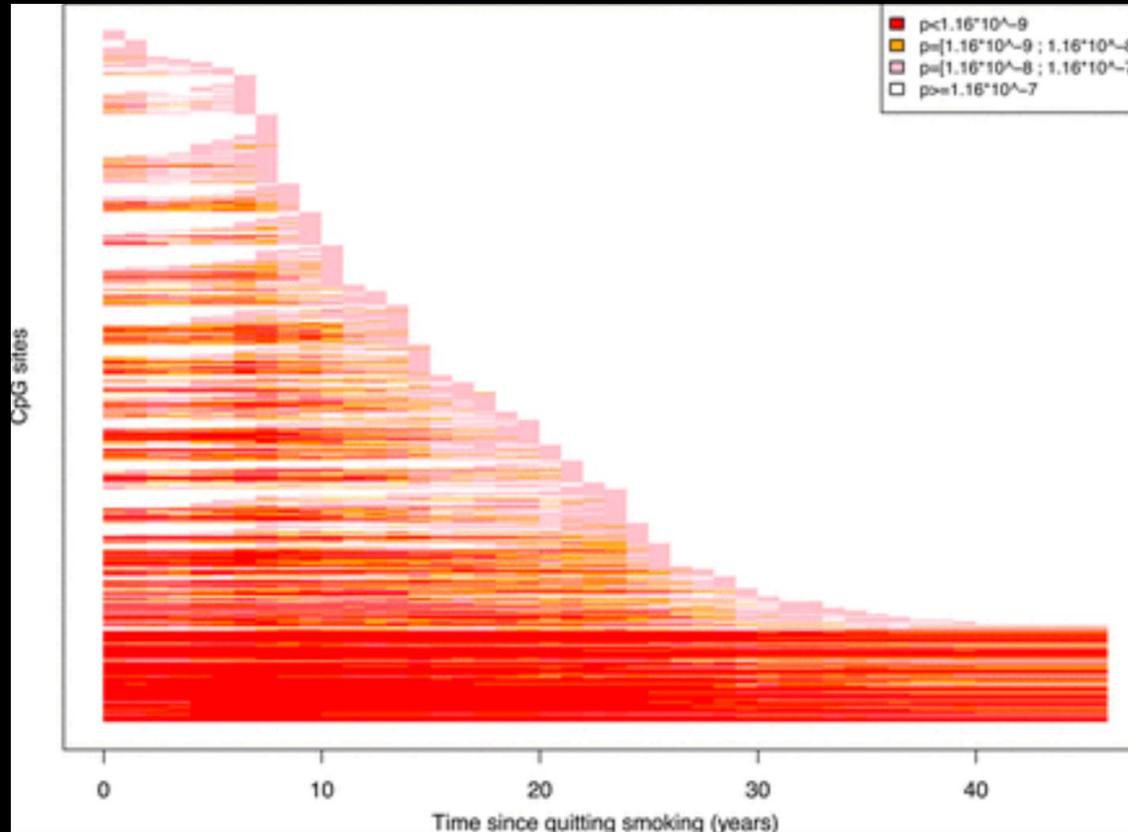


- ❑ Search for “compounds”: 1409 Compounds
- ❑ Database identification: 380 potential identifications
- ❑ Matching score: 49 with over 90% score match

Preliminary data: Snapshot of identification

Compound	Class	Database matching score
Diethyl Carbonate	Solvent	99%
PFOS	Perfluorinated compound	85%
PFOA	Perfluorinated compound	72%
Piperonyl sulfoxide'	Pesticide additive	92%
Pitavastin	Statin	71%
Lenperone	Antipsychotic	74%
4-Acetamidobenzoic acid'	Pharmaceutical excipient	99%
Morpholine	Food additive	94%
Gingerol	Food component/additive	99%

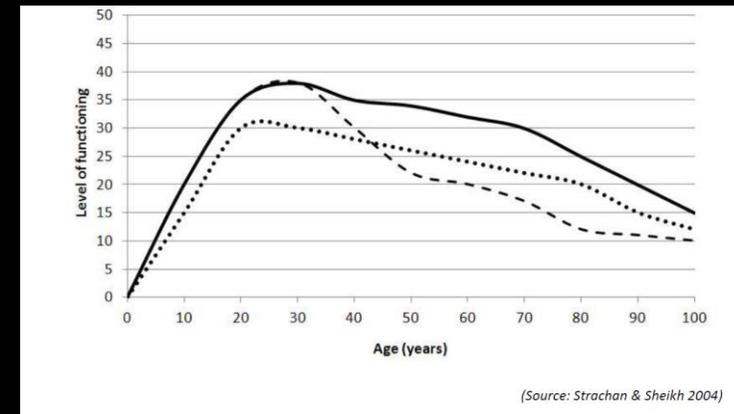
Epigenetics can profile long term exposure



From: Dynamics of smoking-induced genome-wide methylation changes with time since smoking cessation. Guida et al, Hum Mol Genet. 2015;24(8):2349-2359. doi:10.1093/hmg/ddu751

Complex indicators of life-long effects: biological clocks

- Ageing has been defined as the **“time-dependent decline of functional capacity and stress resistance, associated with increased risk of morbidity and mortality”**
- Lifestyle and environment can affect ageing rates at both the ‘build-up’ and ‘decline phase’
- Recently, molecular clocks have been developed to assess *biological age*, based on epigenetic and other ‘omic’ data



Risk factors of epigenetic age acceleration

- Meta-analysis of 16,000 people across 18 cohorts)
- Comparison of effects of leading NCD risk factors on epigenetic ageing
- Horvath, Hannum and Levine measures of epigenetic age acceleration and stochastic epigenetic mutations (SEMs) assessed
- SEMs are sites with extreme methylation levels, randomly distributed throughout genome, which accumulate with age (“epigenetic drift”)

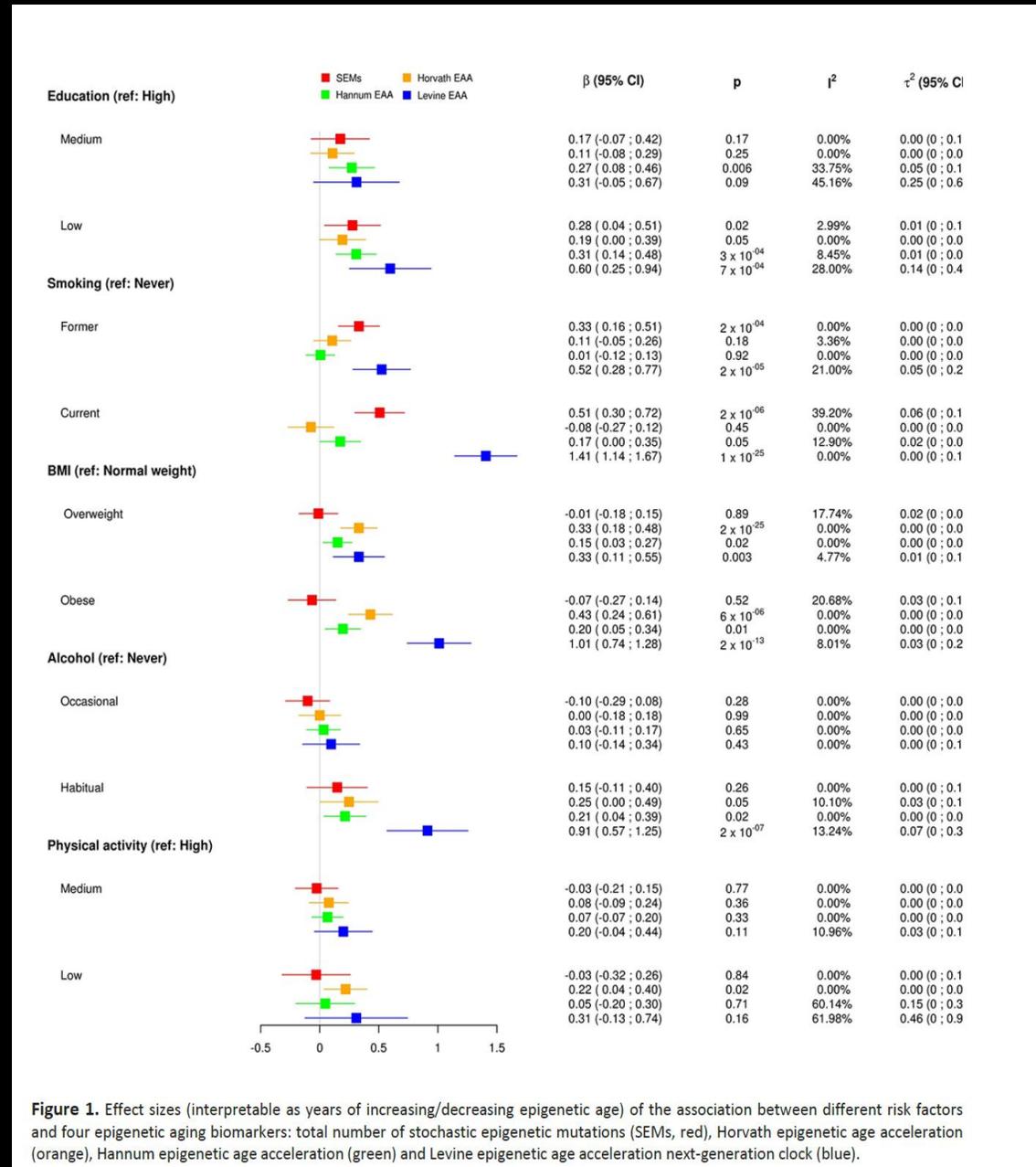
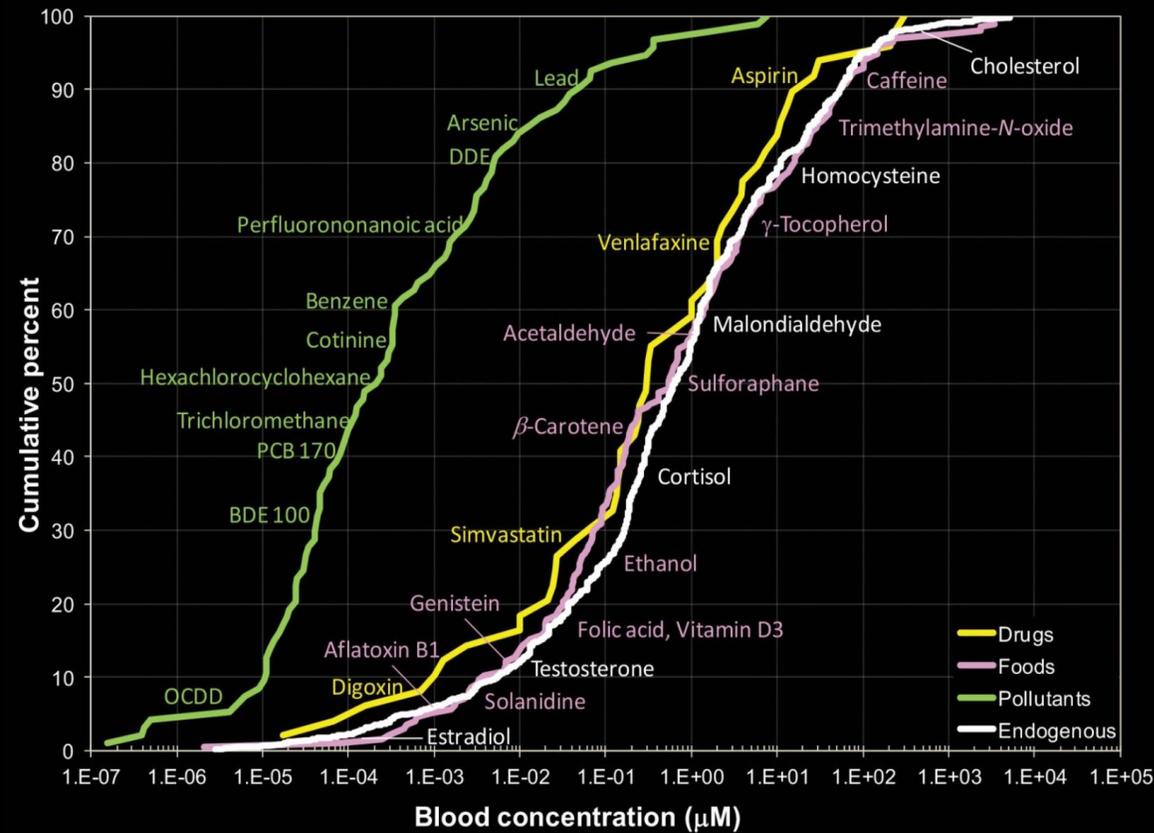


Figure 1. Effect sizes (interpretable as years of increasing/decreasing epigenetic age) of the association between different risk factors and four epigenetic aging biomarkers: total number of stochastic epigenetic mutations (SEMs, red), Horvath epigenetic age acceleration (orange), Hannum epigenetic age acceleration (green) and Levine epigenetic age acceleration next-generation clock (blue).

What are the gaps?

- Conceptual gaps, e.g. temporal sequence of hallmarks of disease, Rothman's paradigm, syndemics, ...
- What is the environment: not only biomedically relevant events!
- Lifecourse approach: only partially explored
- Agnostic approaches
- Omics: incomplete coverage (e.g. CpGs in Illumina platforms, annotation of metabolomics), sensitivity of assays (for low levels)
- Rapid developments in molecular technologies, e.g. RNA sequencing (ncRNA), high costs
- Sensors not yet developed for field use
- Good advancements in biostatistics, gaps in cross-omics
-

The blood exposome



- 1) Il termine *“esposoma”*, coniato nel 2005 da Christopher Wild (in giustapposizione a quello di *“genoma”*), indica l'insieme di tutto ciò a cui un essere umano viene esposto nel corso della propria vita, fin dal concepimento, attraverso l'ambiente sia esterno, sia interno
- 2) Il termine *“esposomica”* (che si inserisce nel contesto ampio delle cosiddette *“omiche”*) indica lo studio complessivo dell'esposoma tramite metodi di valutazione delle esposizioni sia esterne, sia interne (ad esempio, tramite l'uso di biomarke

Thank you