Icahn School of Medicine at Mount Sinai

Department of Environmental Medicine and Public Health

A Multi-Platform Non-Targeted Framework for Measuring the Human Exposome

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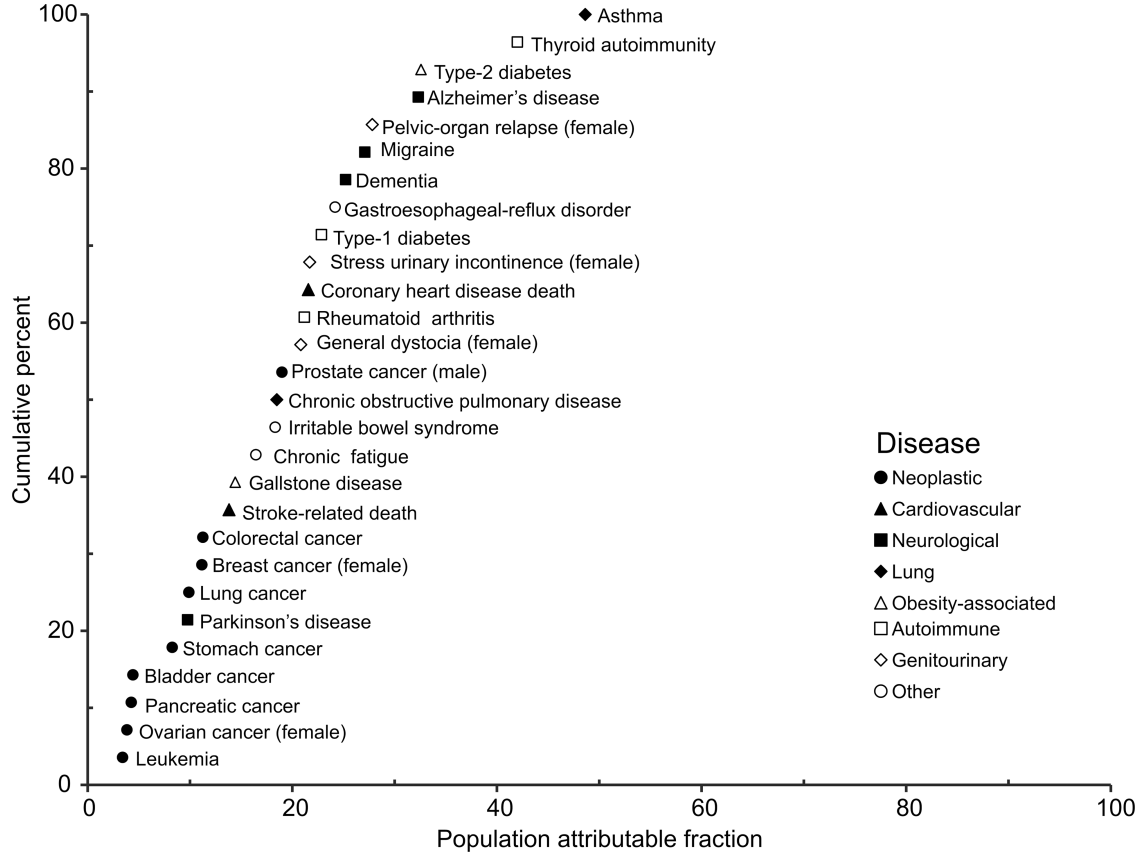
Overview

1. A critical role for untargeted assays in characterizing the human exposome
2. High-resolution mass spectrometry: New insight into (old) exposures
3. Incorporating untargeted assays to study emerging environmental health concerns

Molecular classification of disease risk in the post-genomic era: Reality

Population attributable fractions for 28 disease phenotypes estimated from studies of monozygotic twins.



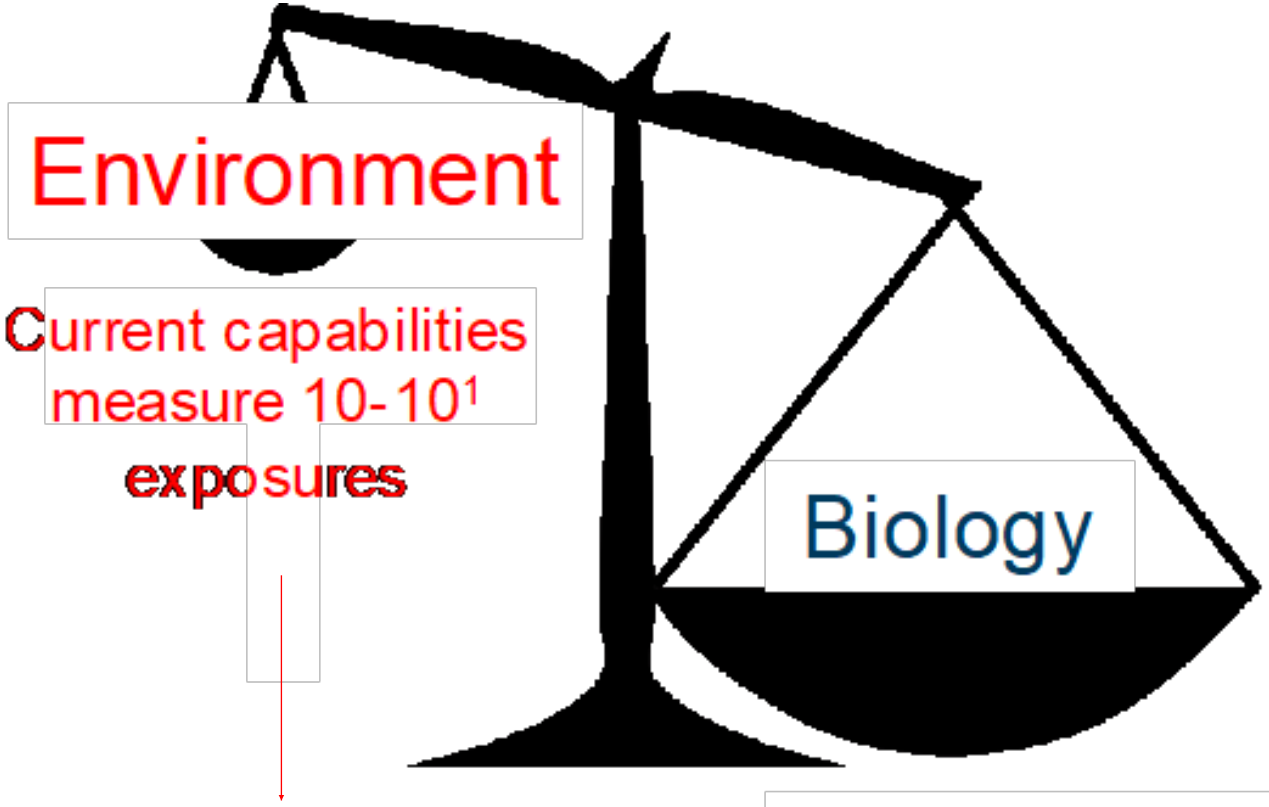
Proportion reduction in disease if G or GxE risk factors removed

Rappaport SM (2016) Genetic Factors Are Not the Major Causes of Chronic Diseases. PLOS ONE 11(4): e0154387.

Heritability provides an unbalanced view of human health and disease

Rappaport SM et al. (2014) The blood exposome and its role in discovering causes of disease. EHP. 122(8); Wild CP. (2005) Complementing the genome with an “exposome”: the outstanding challenge of environmental exposure measurement in molecular epidemiology. Cancer Epidemiol. Biomarkers Prev.14(8):; Vineis P et al. (2001) Misconceptions about the use of genetic tests in populations. Lancet. 357(9257)

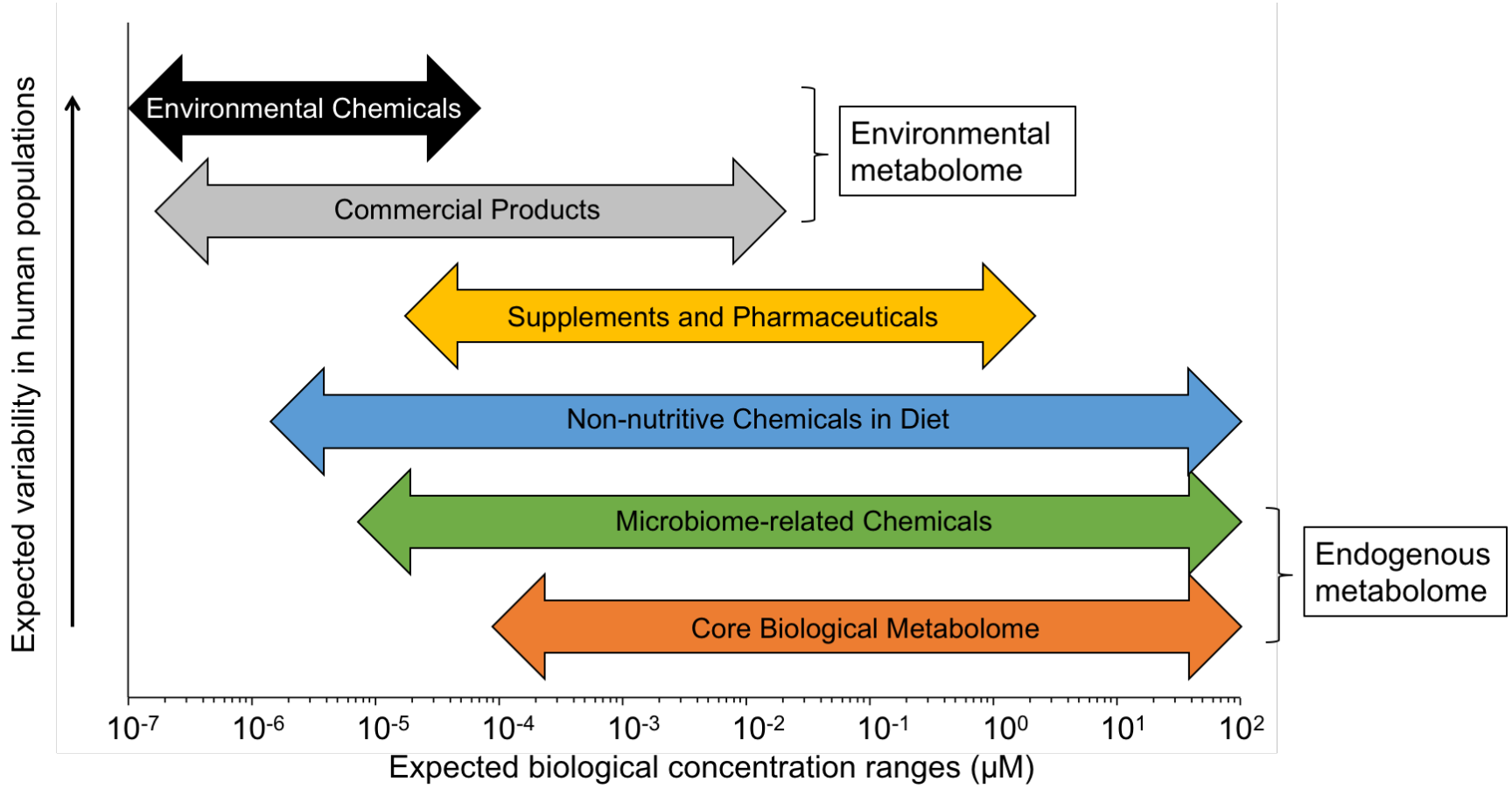
Measurement of environment limited relative to health importance and availability of genetic information



Critical need to develop analytical frameworks for universal screening to provide measure of the exposome

WGS
Genotyping (10^5-10^6 genes)
Transcriptomics (>50k)
Methylation (>10^5)
Proteomics (>10^4)

The human metabolome can be defined as the complete collection of small molecule metabolites found in the human body



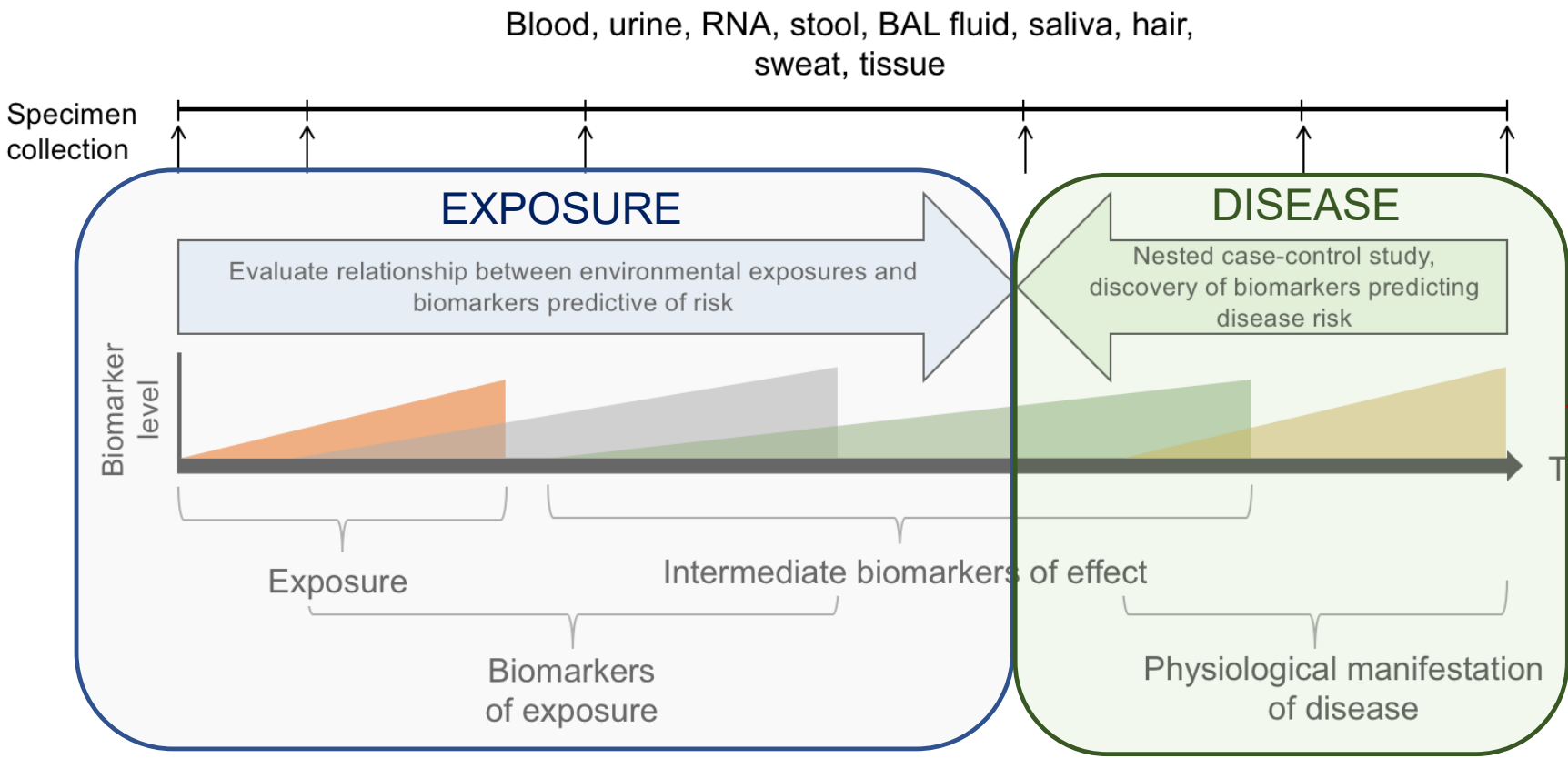
https://en.wikipedia.org/wiki/Metabolomics#/media/File:Human_metabolome_project.png
Walker et al (2016), Chapter 7 in E. Holmes, J.K. Nicholson, A.W. Darzi & J.C. Lindon (Eds): Metabolic Phenotyping in Personalized and Public Healthcare.
Wishart, D. S., T. Jewison, A. C. Guo, M. Wilson, C. Knox, Y. Liu, A. Scalbert (2013). "HMDB 3.0--The Human Metabolome Database in 2013." Nucleic Acids Res **41**(Database issue): D801-807.

To measure the exposome, we need to expand beyond traditional environmental health and analytical chemistry approaches

The human metabolome contains >1 million chemicals
Human exposure is likely to exceed 400,000 chemicals

To understand the complexity of the human exposome, we must adopt **analytical strategies and study designs** that incorporate **untargeted measures of exposure**

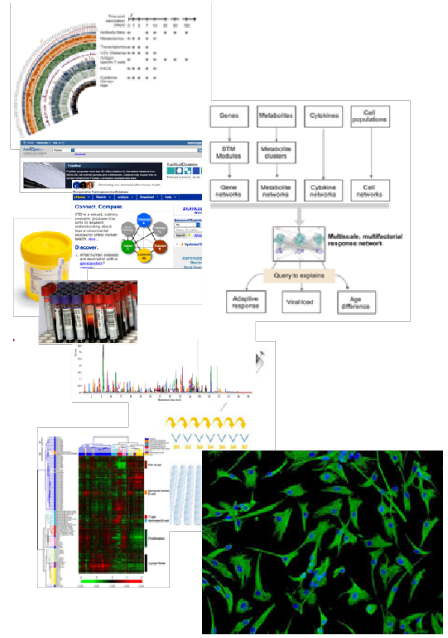
Comprehensive measure of the metabolome provides biomarkers throughout the continuum from exposure to disease



Exposure phenotyping and biological effects

Adverse outcome phenotyping and early biological effects of disease manifestation

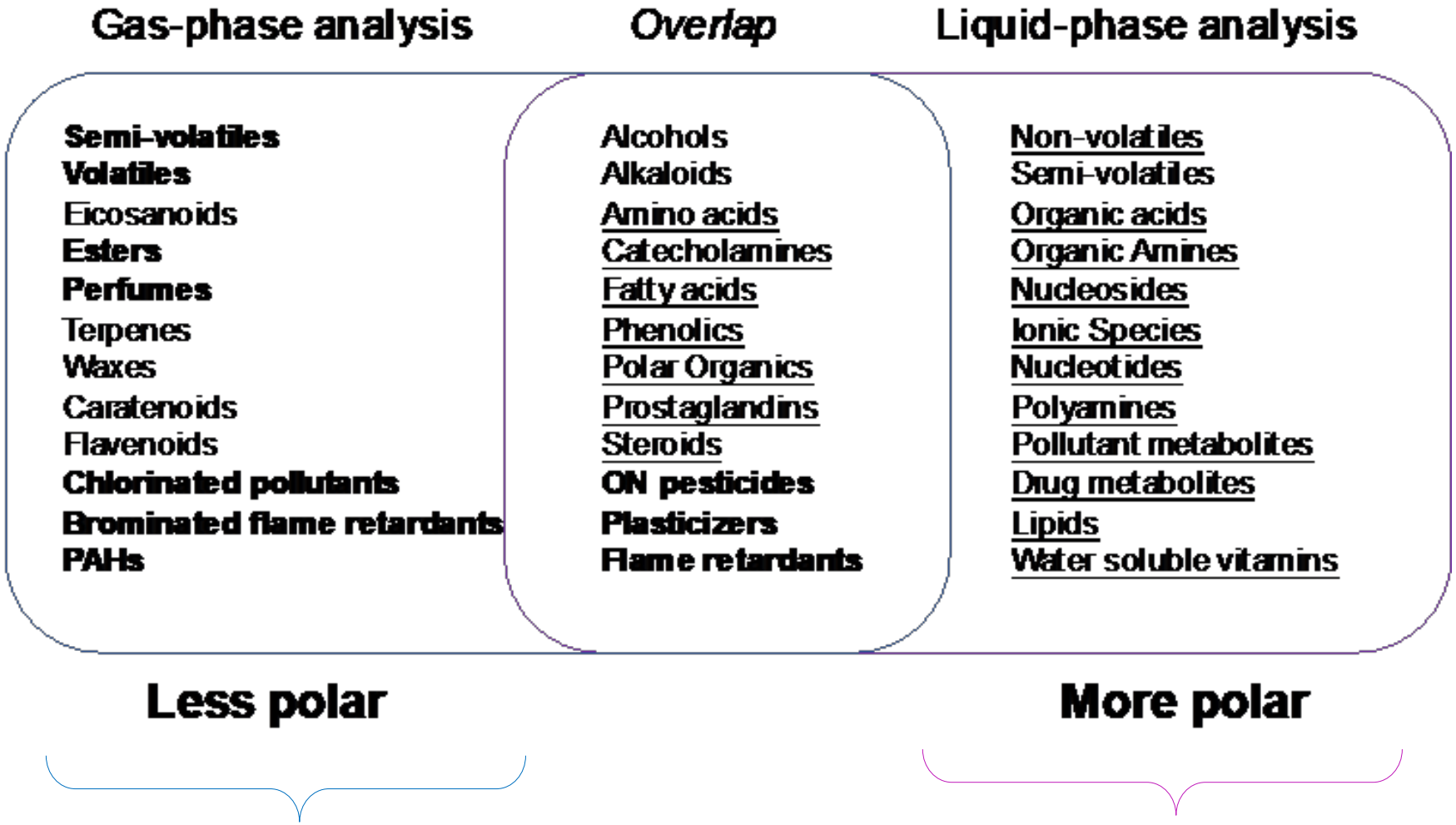
MECHANISMS



Informed model systems for identifying environment-disease mechanisms

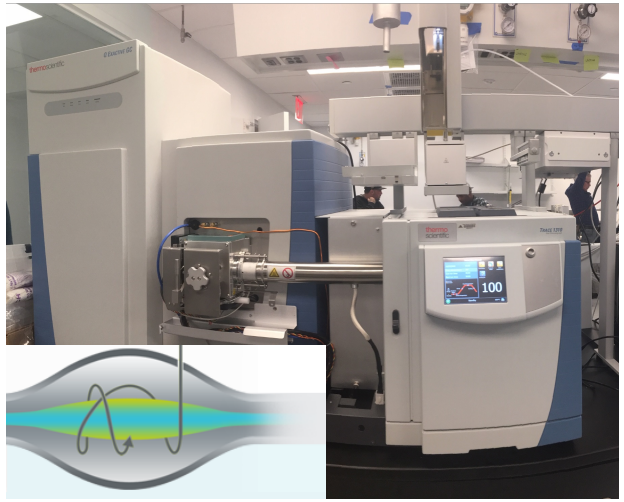
- *In vitro*
- *C. elegans*
- *Animal models*

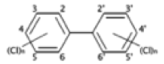
Operationalizing untargeted assays for the Exposome: GC-HRMS and LC-HRMS for EWAS x MWAS of disease



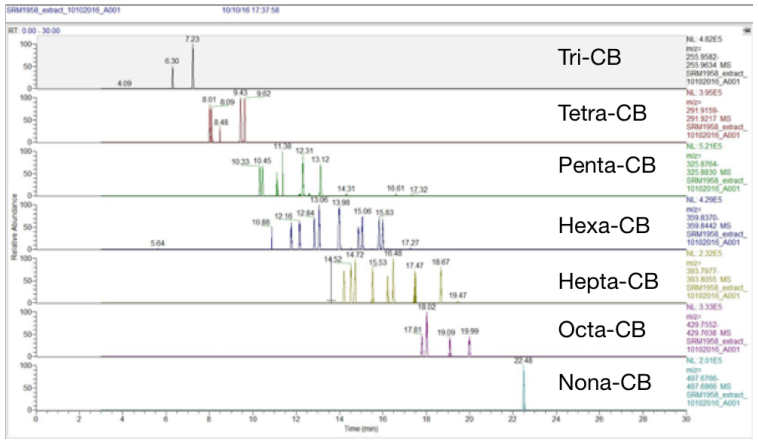
GC-HRMS: Volatile and semi-volatile exposure biomarkers

Q Exactive GC Orbitrap

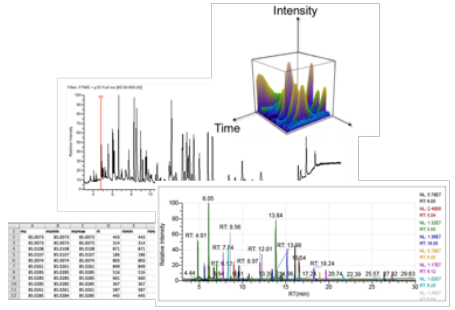




Polychlorinated biphenyls at 0.5-5 nM

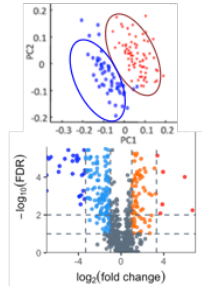


Peak Picking

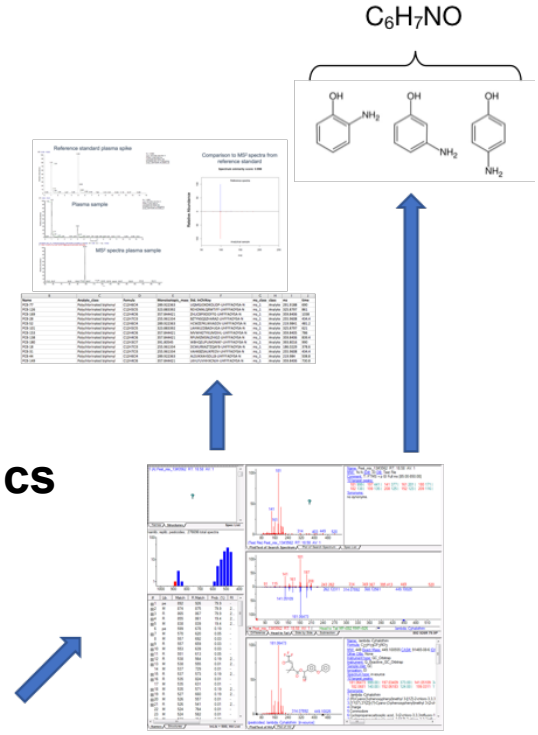


Deconvolution

Bioinformatics

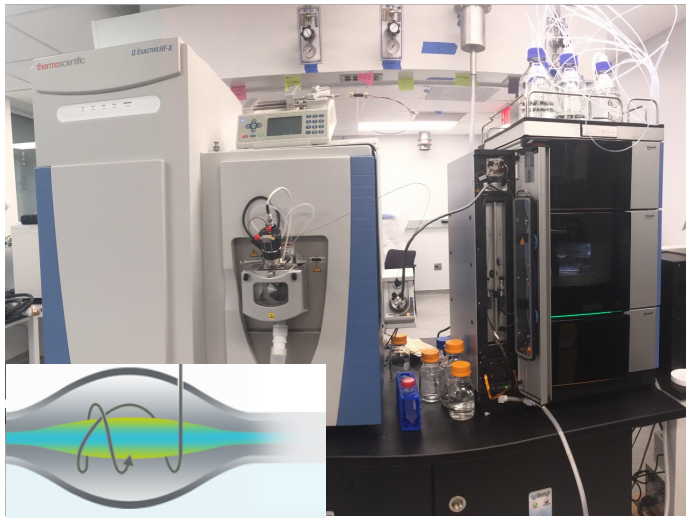


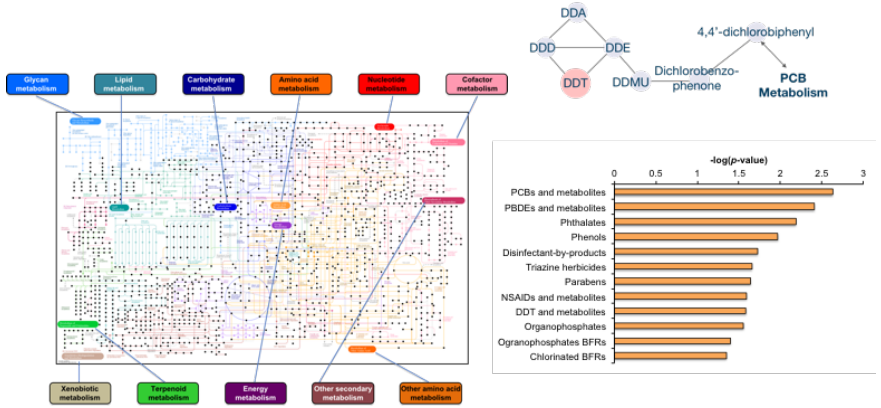
Identification + Annotation

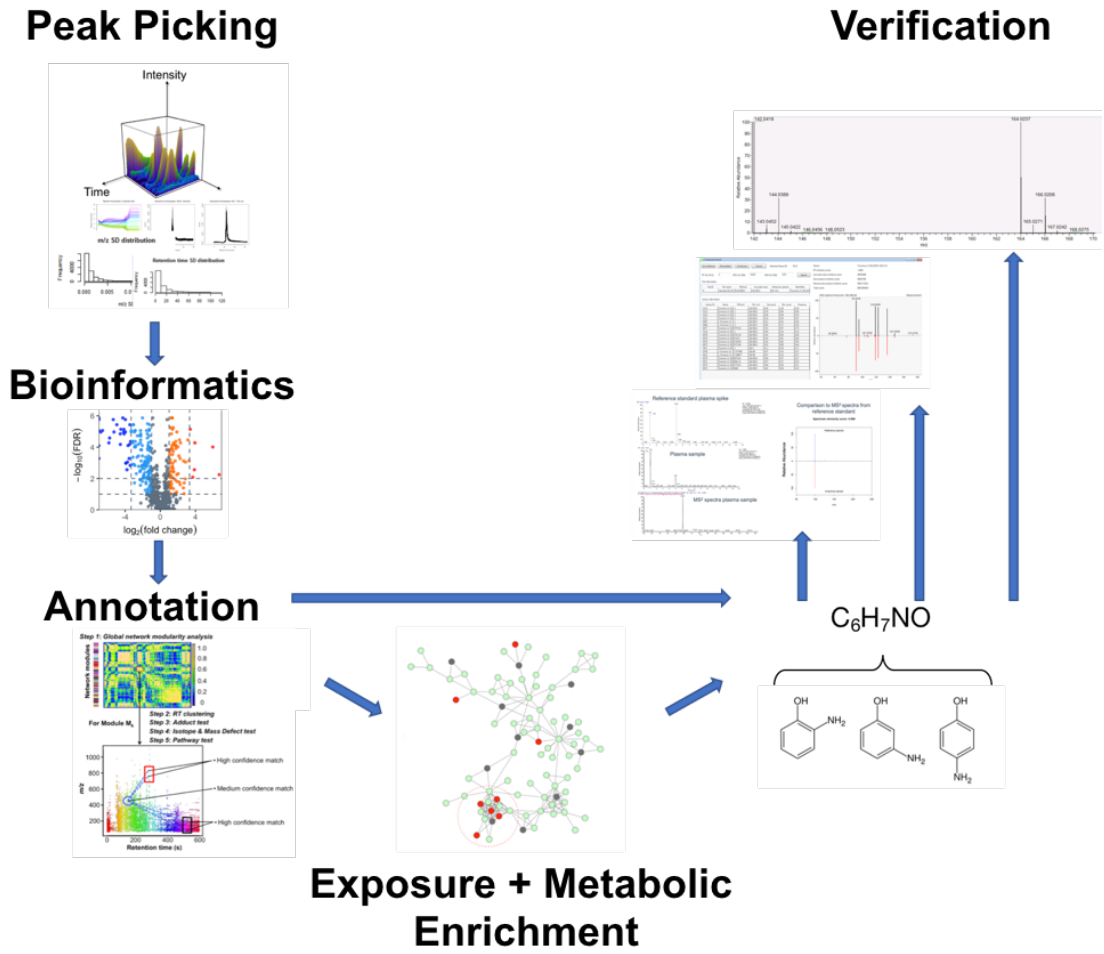


LC-HRMS: Exposure biomarkers and biological response

Thermo Vanquish Duo + Q-Exactive HFX

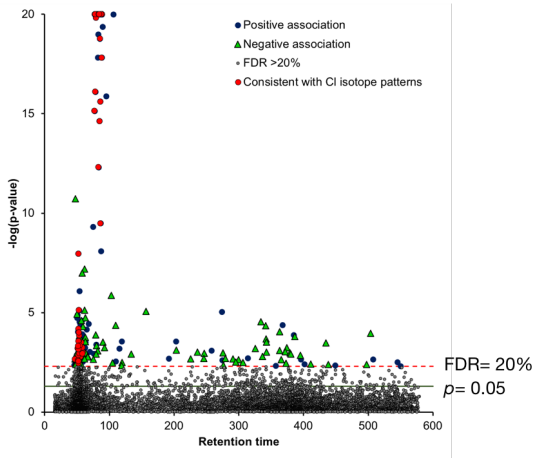




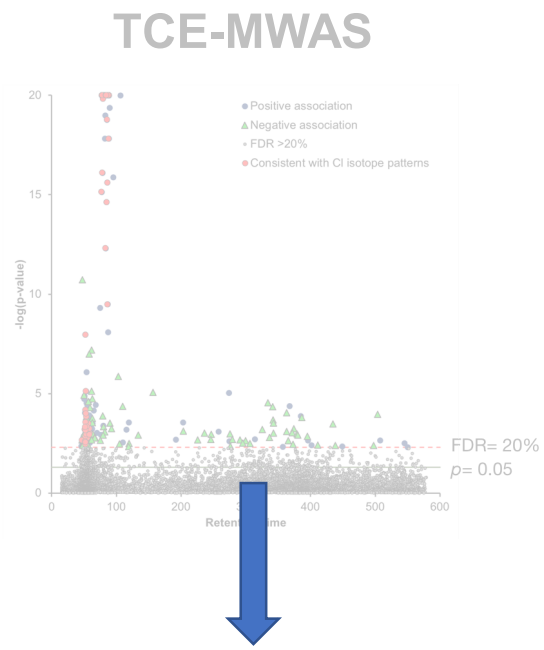


MWAS of occupational trichloroethylene exposure

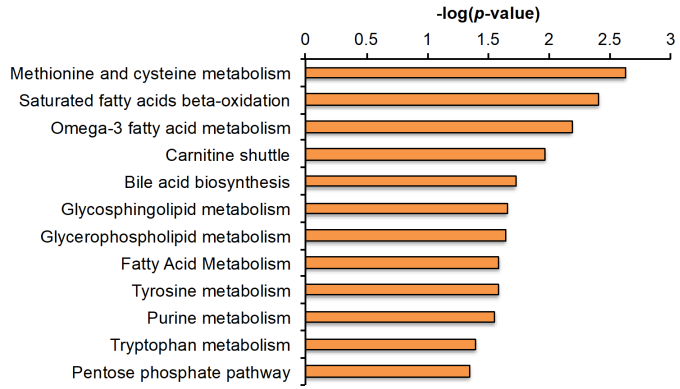
TCE-MWAS



MWAS of occupational trichloroethylene exposure

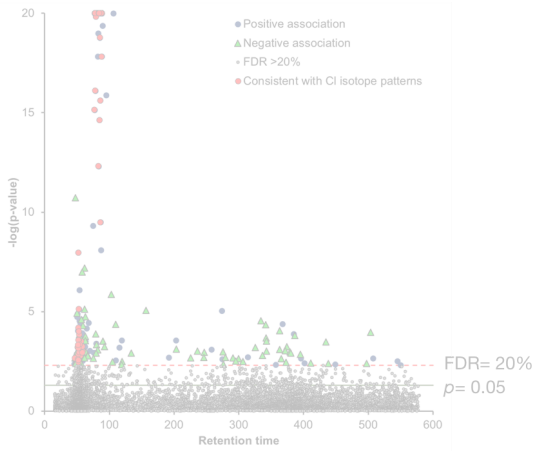


Biological Response

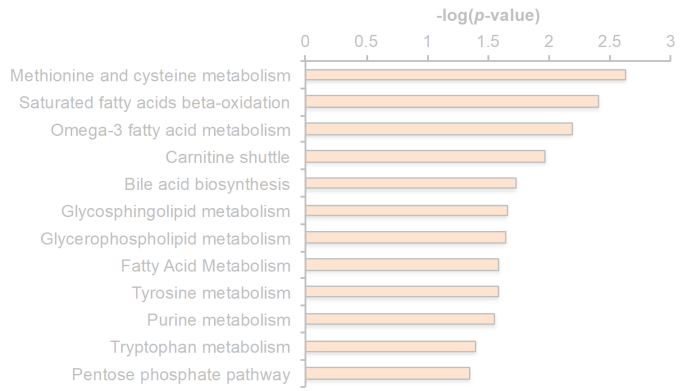


MWAS of occupational trichloroethylene exposure

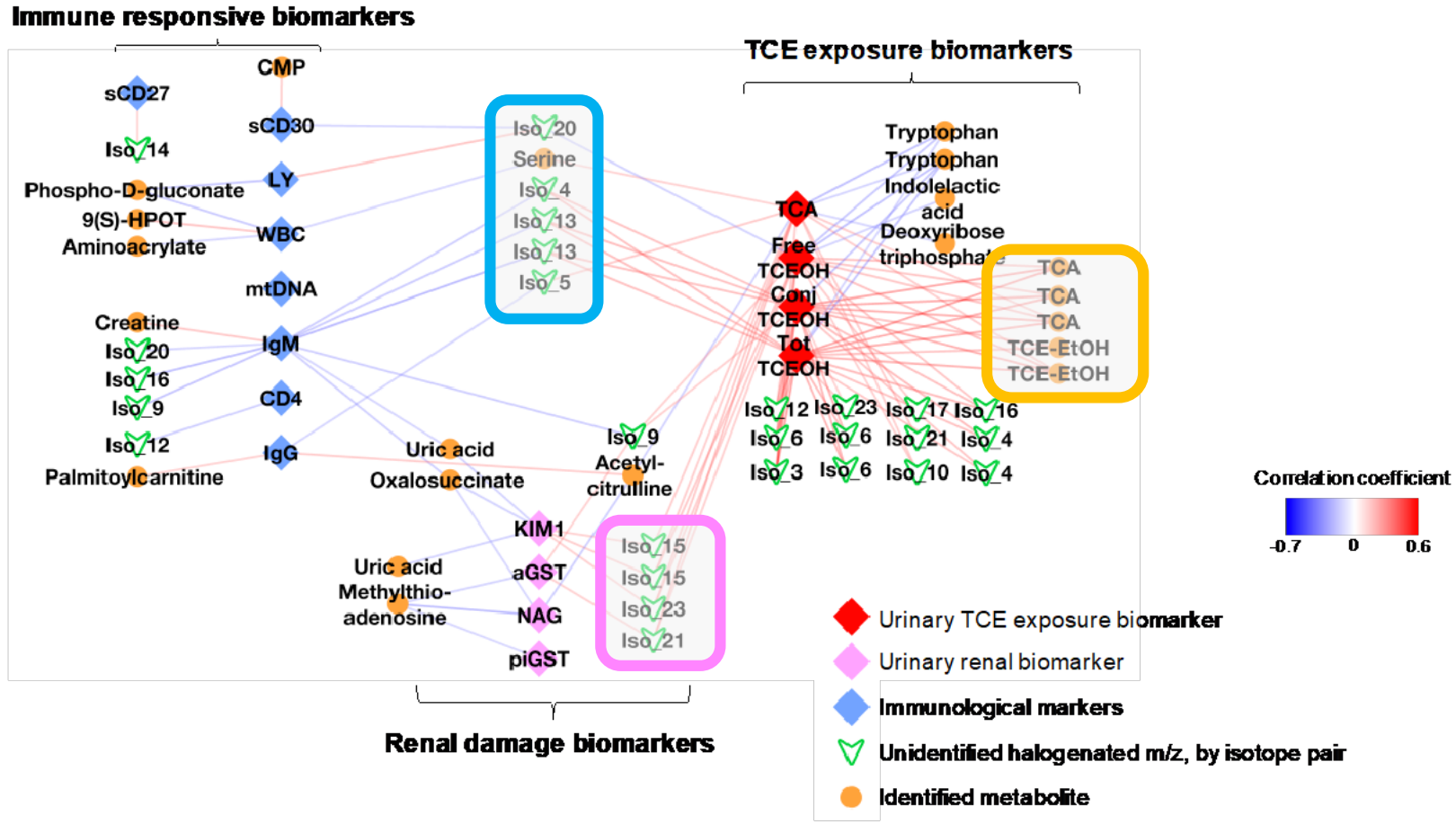
TCE-MWAS



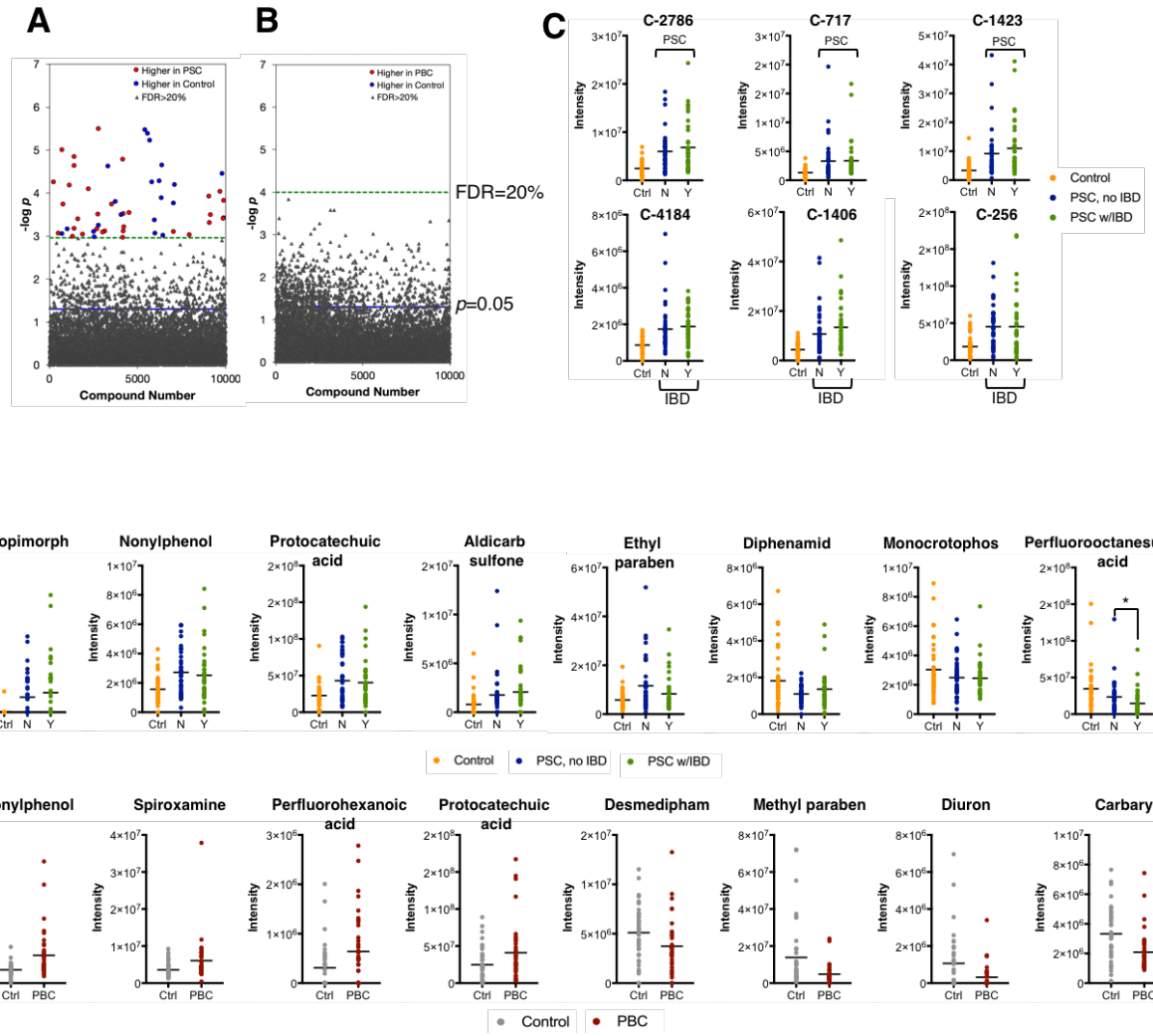
Biological Response



Linking exposure to disease risk biomarkers



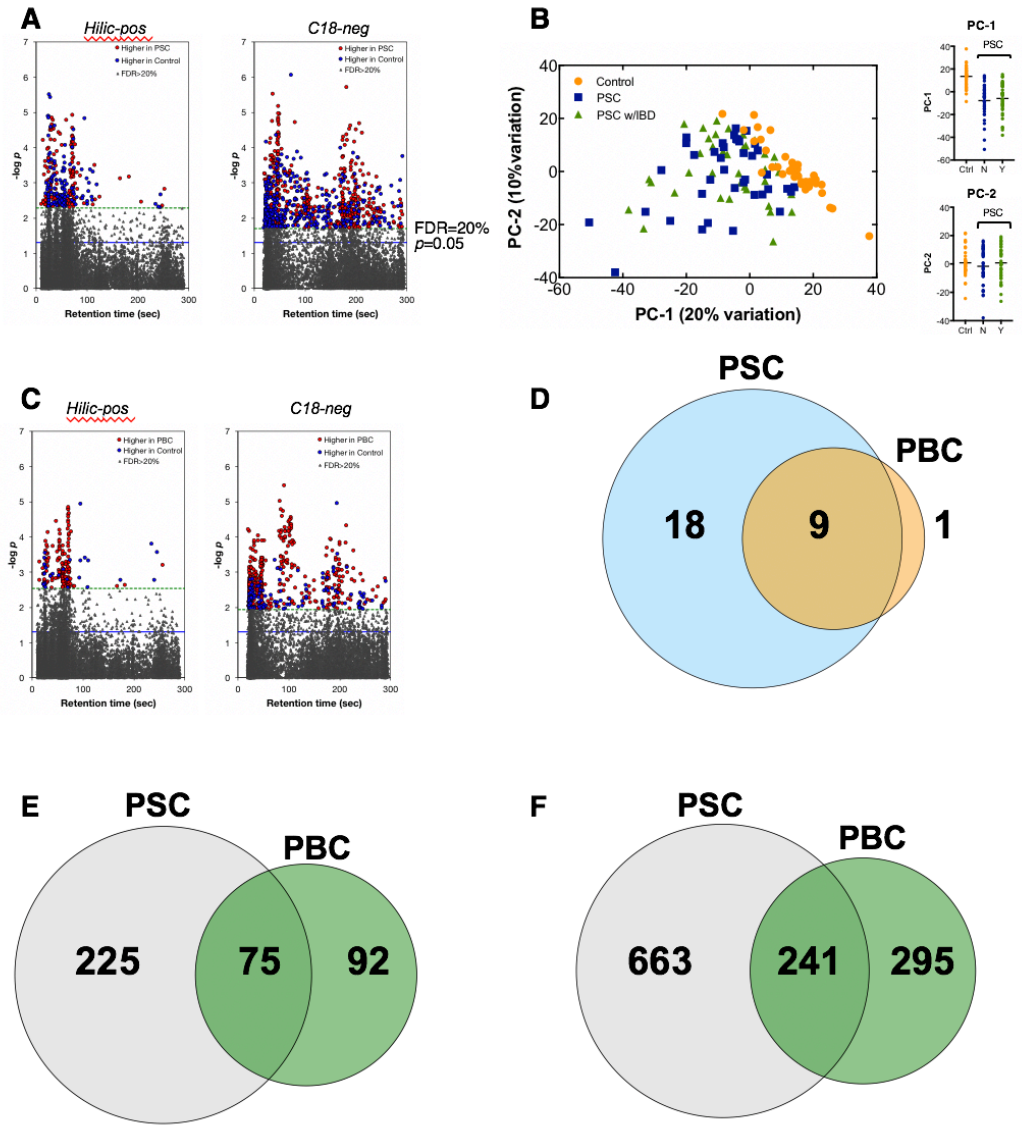
Exposome-wide association study: PSC and PBC



- Untargeted EWAS (>10,000 compounds) using state-of-the-art high-resolution mass spectrometry detected uncharacterized compounds associated with PSC, independent of IBD status
- Targeted EWAS (>600 chemicals) using known, confirmed exposure biomarkers identified pesticides, preservatives and industrial chemicals associated with both diseases

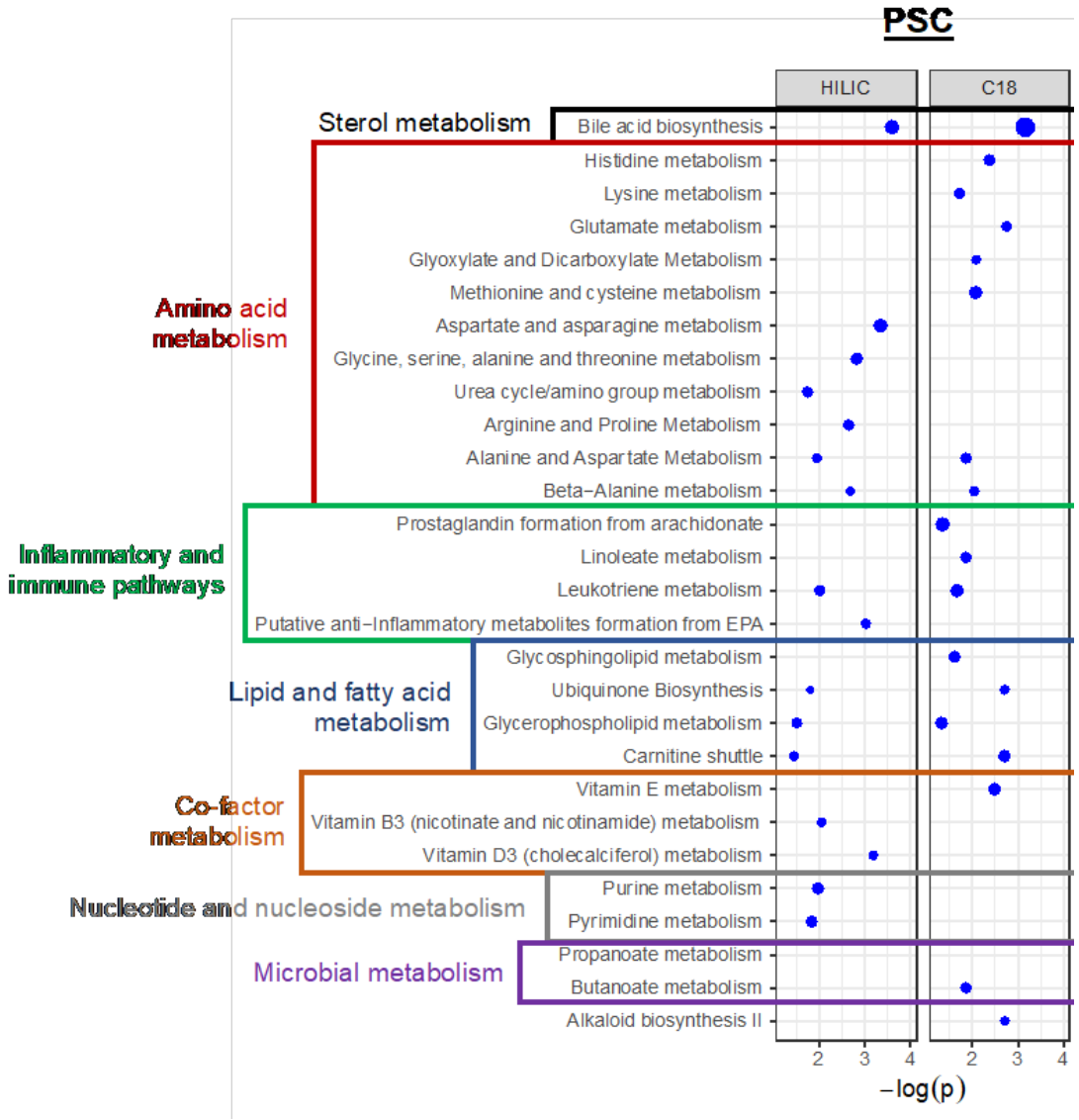
Walker D, Cheung A, Juran B, Jones D, Miller G, Lazaridis K. *Manuscript in preparation*

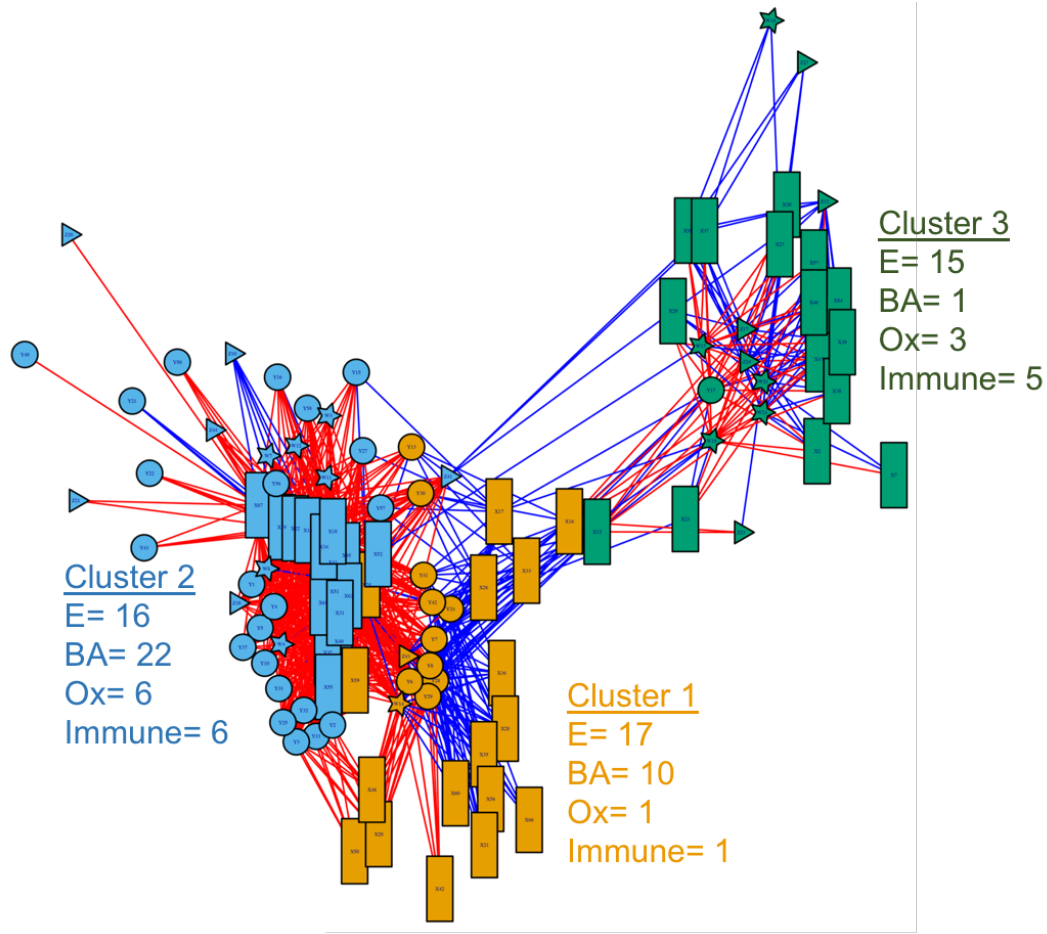
Metabolome wide association study: PSC and PBC



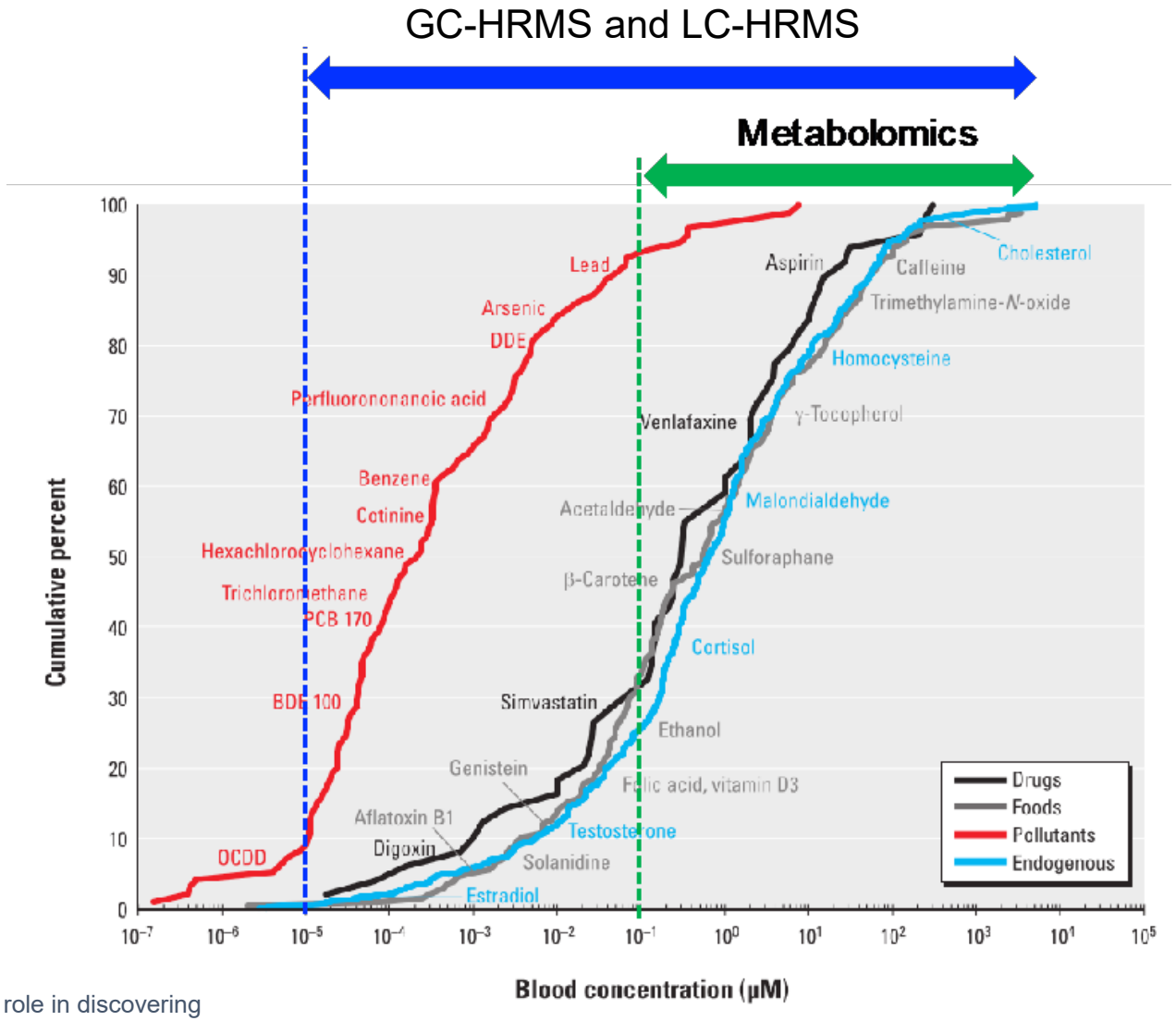
- Metabolome-wide association study (MWAS) of PSC identified 1,204 metabolic features associated with the disease at FDR<20%.
- Comparison of all metabolic features associated with PSC at FDR<20% using principal component analysis (PCA) showed no differences between PSC patients and those with IBD.
- Metabolic pathway enrichment identified 27 and 10 pathways associated with PSC and PBC, respectively. Nine pathways were associated with both diseases.

Linking exposure and biological response: Big data methods for integrating EWAS and MWAS

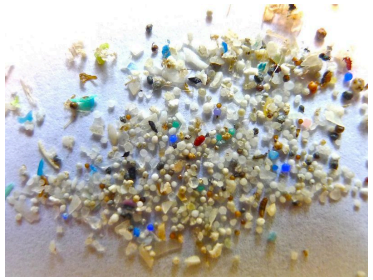




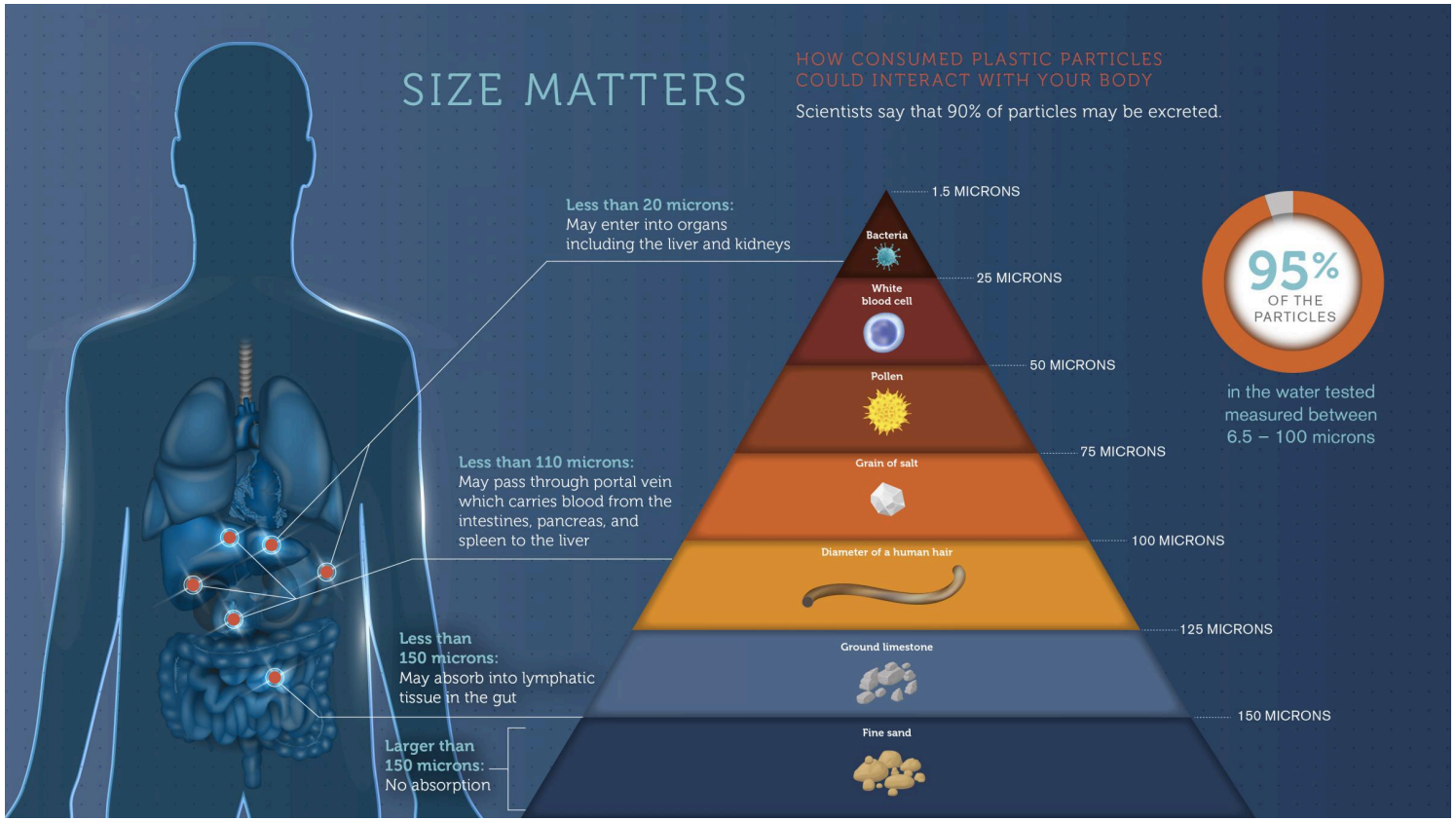
Linking exposure and biological response: Big data methods for integrating EWAS and MWAS



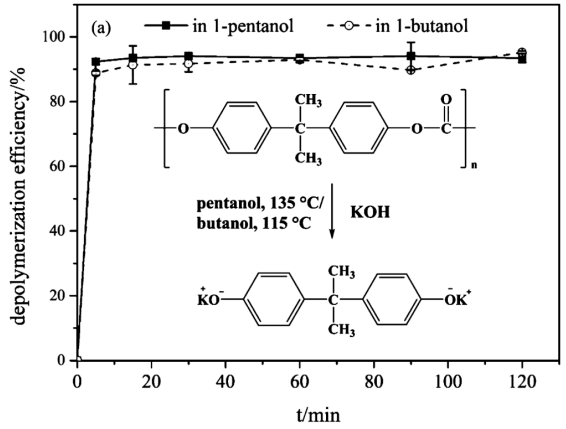
Rappaport SM et al. The blood exposome and its role in discovering causes of disease. Environ. Health Perspect. 2014;122(8):769–74.

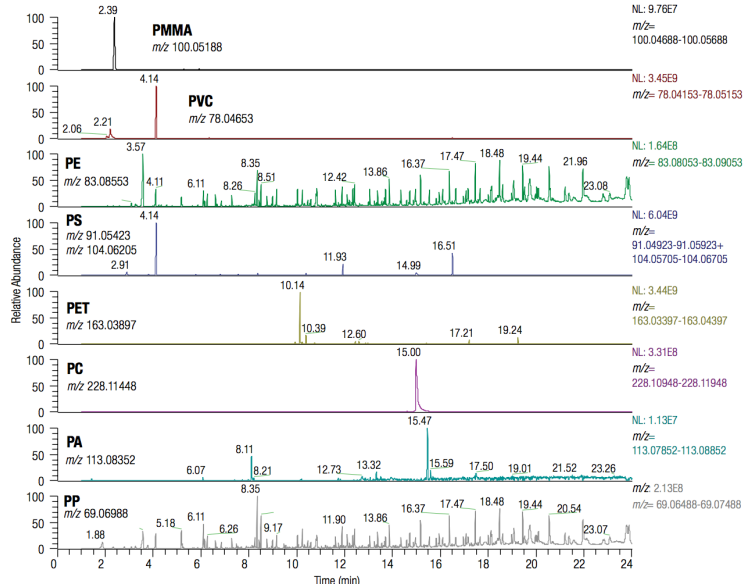


Expanding powerful analytical strategies available from HRMS to measure new exposures in biological samples: Microplastics



https://orbmedia.org/stories/plus-plastic/

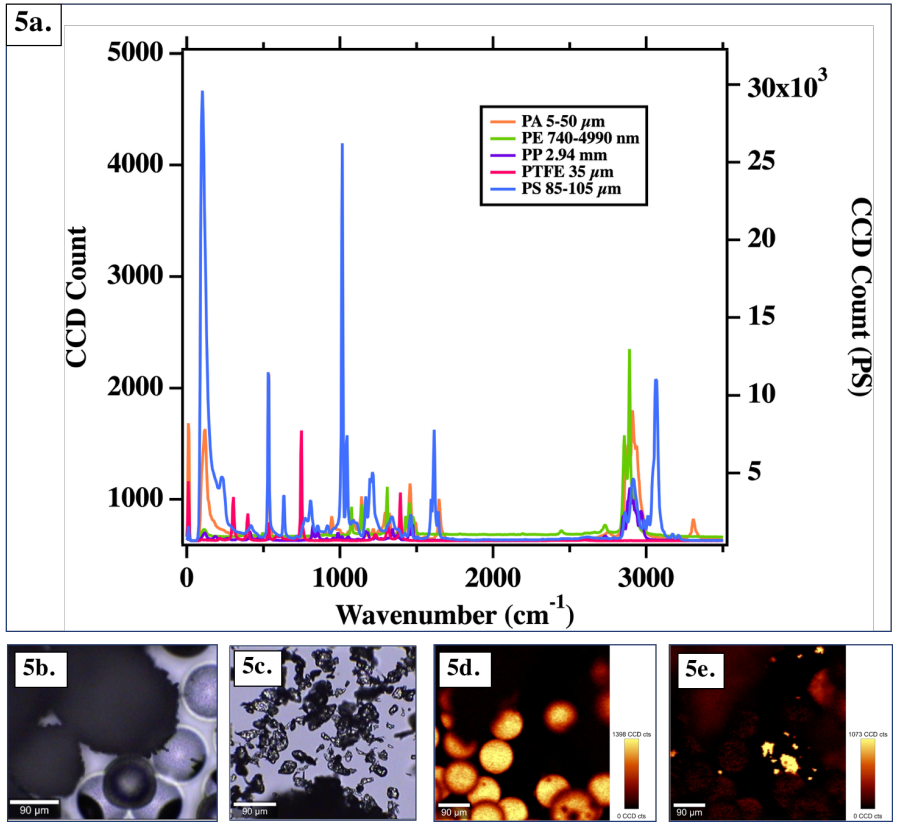


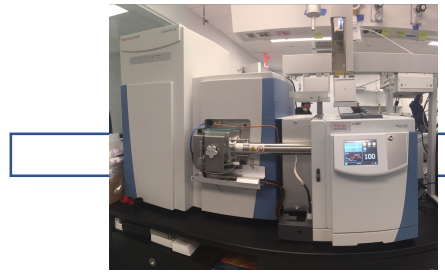


Wang, L., Zhang, J., Hou, S., & Sun, H. (2017). A Simple Method to Quantify PC and PET Microplastics in the Environmental Samples by LC-MS/MS. Environmental Science & Technology Letters, acs.estlett.7b00454.

Logemann J, Oveland E, Bjorøy O, Peters W, Cojocariu C, Kögel T. Application note 10643, Pyrolysis-GC-Orbitrap MS - a powerful analytical tool for identification and quantification of microplastics in a biological matrix. Thermo Scientific

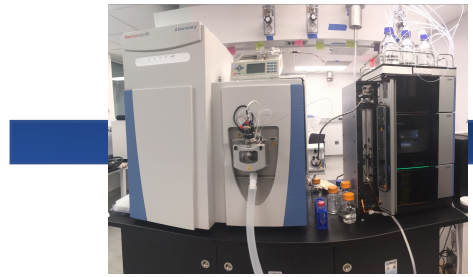
A role key for untargeted HRMS assays in microplastic exposure assessment





<u>Pyrolysis HRMS</u>

- Quantification of known particles
- Screening for >15,000 polymers
- Sample volatiles and semi-volatiles



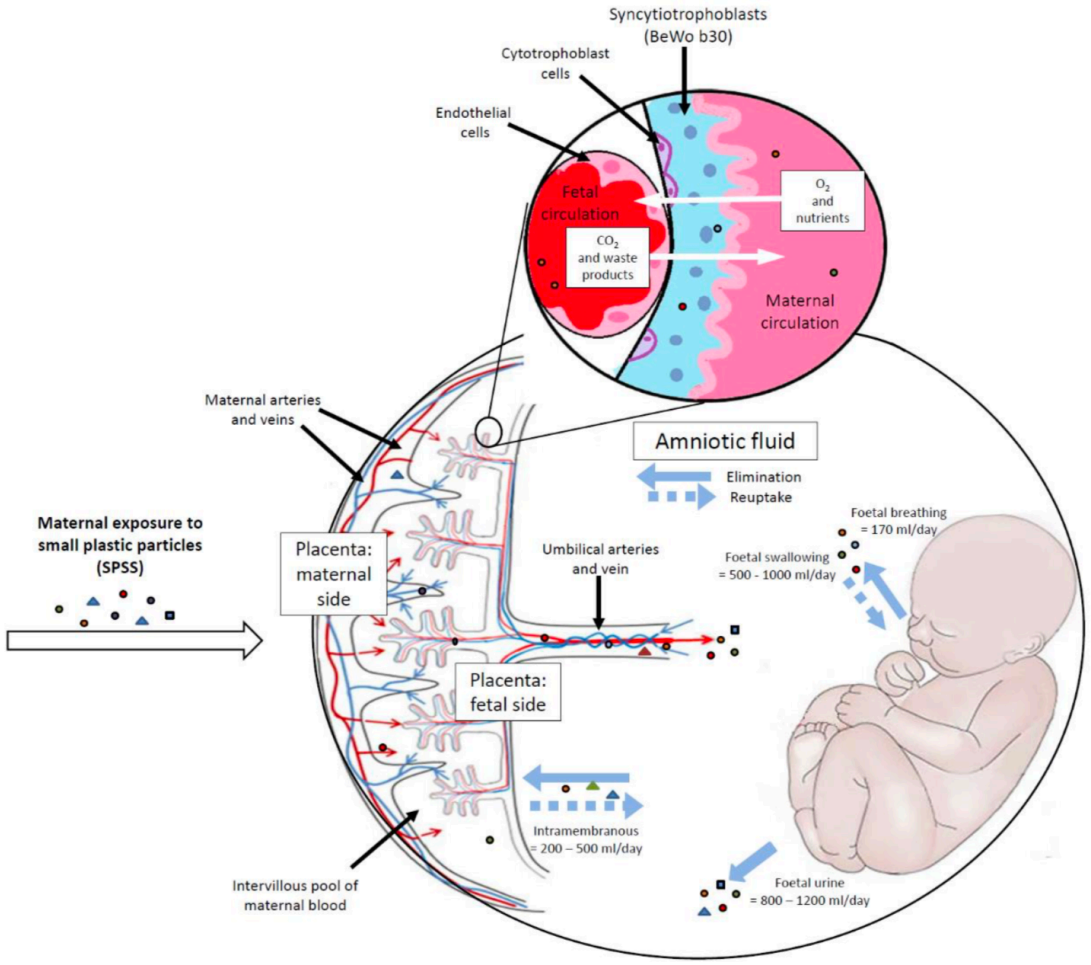
<u>Depolymerization and LC-HRMS</u>

- Quantification of known particle monomers
- Bound additives
- Polymer screening

<u>Small molecule profiling LC-HRMS</u>

- Free plastic additives
- Adsorbed and co-transported contaminants
- Biological response

Small plastic particles (SPPs) in the human fetal environment: Novel studies on exposure and hazard



Research questions:

- What is the exposure of SPPs in the low µm and nm range in the human fetal environment?
- What is the potential hazard of SPPs and associated chemicals in the placenta?

Research Team (J. Legler, PI):

- Utrecht University: J. Legler, H. Dusza, R. Vermeulen
- Westfriesgasthuis: G. ten Tusscher
- Vrije Universiteit Amsterdam: M Lamoree
- Deltares: D. Vethaak
- Mount Sinai: D. Walker

Funding Agency: Netherlands Organization for Health Research and Development (ZonMw)

Conclusions

- Untargeted assays profiling the human metabolome provide key insight into exposure and associated biological response
- Combined GC-HRMS and LC-HRMS establishes a unified platform for EWAS × MWAS of disease
- HRMS technologies provide a powerful basis for developing new approaches to study exposure of emerging environmental health concern

Acknowledgments

High Resolution Exposomics Group (L to R):
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National Cancer Institute
- Nathaniel Rothman, Qing Lan, Bryan Bassig

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