Audience participation in the panel discussions

Go to www.menti.com
and use the code
86 98 50

Social media

Relevant hashtags:
#**Exposome**
#EUHealthResearch
#H2020
#HumanExposome

EC Twitter tags:
@EUScienceInnov
@EU_H2020

European Commission

The EU Framework Programme for Research and Innovation

HORIZON 2020

Launch of the European Human Exposome Network

Understanding the health impacts of a lifetime of environmental exposures

Research and Innovation

11 February 2020

Welcome by the European Commission

- **Irene Norstedt**
  Acting Director, People Directorate,
  DG Research and Innovation
- **Veronica Manfredi**
  Director, Quality of Life Directorate,
  DG Environment
- **Philippe Roux**
  Head of Unit, Country knowledge and scientific committees,
  DG Health and Food Safety

Christopher Wild

On the Origins of the Exposome

Christopher Paul Wild, PhD

Emeritus Director, International Agency for Research on Cancer, Lyon, France

On the Origins of the Exposome

- the prompt
- the past
- the promise
- the perspective

....the prompt

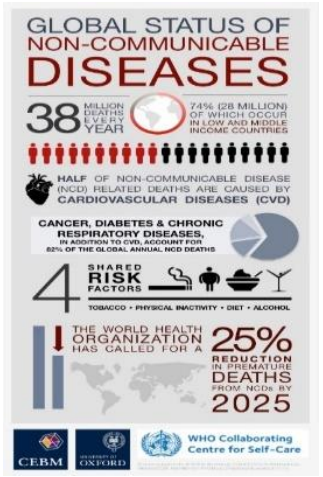
The global cancer burden: necessity is the mother of prevention

- Growing burden of cancer (and other NCDs) predominantly caused by environmental and behavioural risk factors
- No country can afford to treat its way out of the cancer problem
- Prevention must be central to an integrated approach including early detection, treatment and care, but is neglected
- Preventive interventions are impossible without knowledge of the causes and preferably the underlying mechanisms

Wild CP (2019) Nature Reviews Cancer 19: 123-124

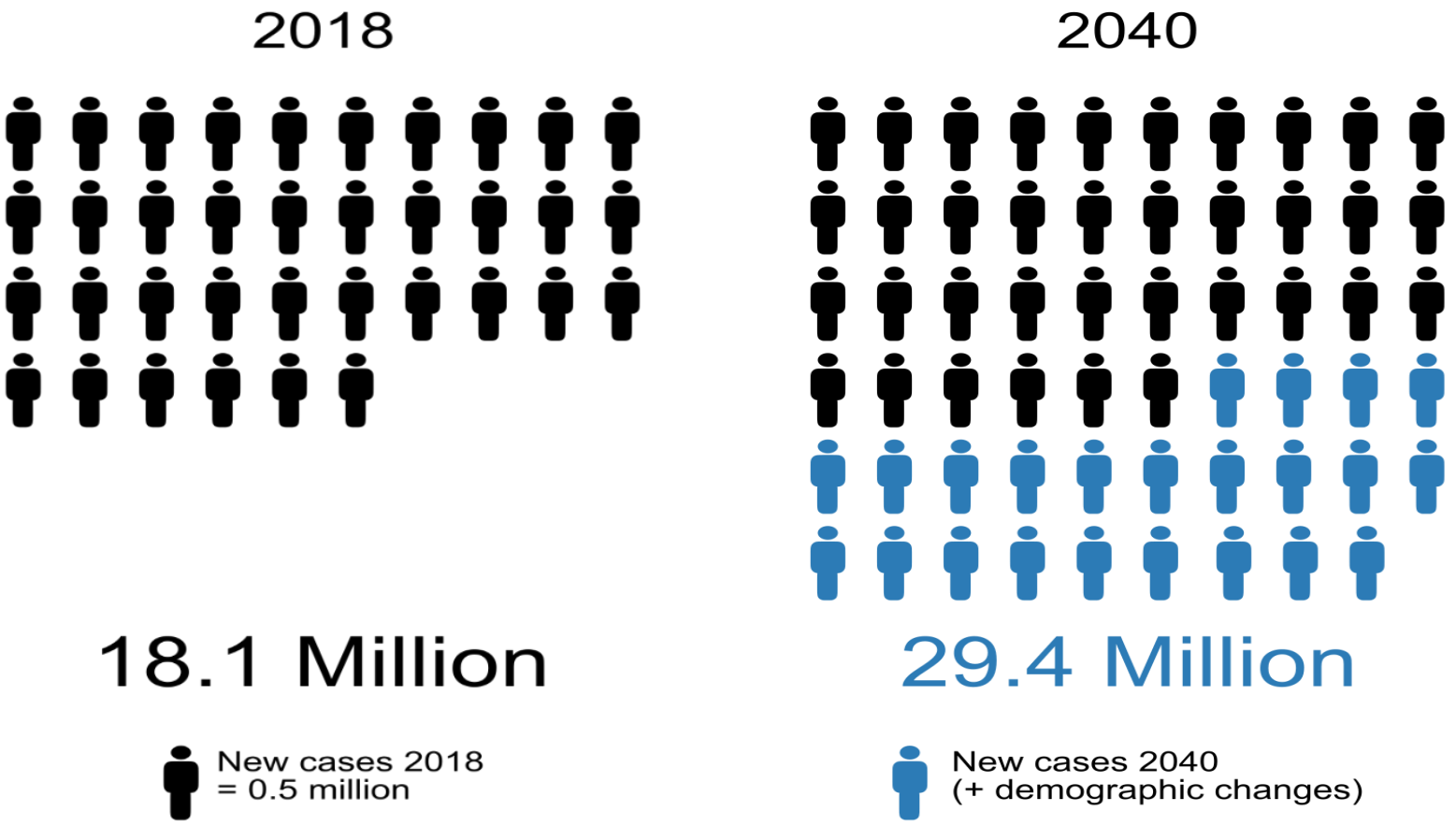
Cancer is a disease of uncontrolled growth

Magnitude: the increasing burden of cancer



Pattern: the changing pattern of cancer

Cancer is a disease of uncontrolled growth: no. of new cases 2018 and 2040 worldwide



Projections based on demographic change alone

The economic costs of cancer add to the suffering

- Productivity loss in 30 European countries in 2008 due to cancer-related mortality[1]:
  - €75 billion in total;
  - average €219,000 per cancer death;
  - 0.58% of European GDP, up to 1.05% in central-Eastern Europe
- Economic burden in the 27 EU countries in 2009[2]:
  - €126 billion in total
  - Health care €51 billion; Productivity losses and lost working days €52 billion; Informal care €23 billion

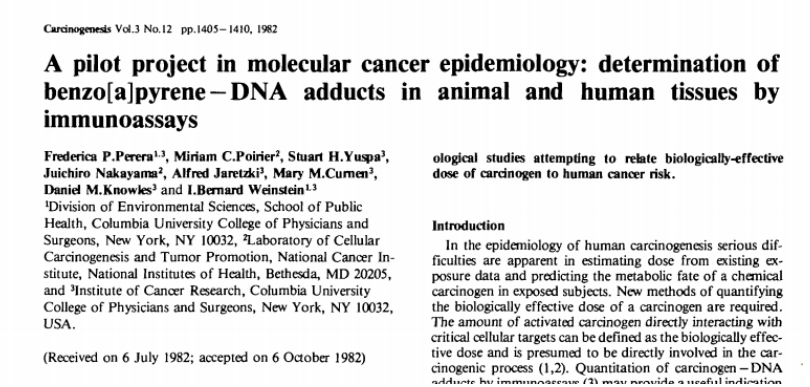
[1]Hanly P et al., (2015) Int. J. Cancer 136: E136-145

[2]Luengo-Fernandez R., et al., (2013) Lancet Oncol., 14: 1165-74

….the past

On the Origins of the Exposome

- 1982: during my PhD studies - international meeting at Paterson Labs, Manchester, UK on immunoassays to measure DNA damage
- 1982-1985: First examples of DNA adducts in human tissues to measure exposure
- 1980s: molecular epidemiology focused on improvement of exposure assessment
- 1990s: following PCR invention, major shift to candidate gene SNPs in case-control studies; less emphasis on exposure assessment



Carcinogenesis Vol.3 No.12 pp.1405–1410, 1982

A pilot project in molecular cancer epidemiology: determination of benzo[a]pyrene–DNA adducts in animal and human tissues by immunoassays

Frederica P.Perera[1,3], Miriam C.Poirier[2], Stuart H.Yuspa[3], Juichiro Nakayama[2], Alfred Jaretzki[3], Mary M.Curnen[3], Daniel M.Knowles[3] and I.Bernard Weinstein[1,3]

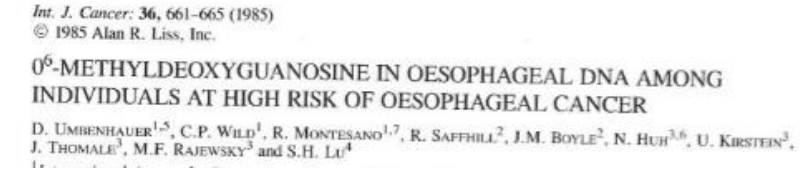
[1]Division of Environmental Sciences, School of Public Health, Columbia University College of Physicians and Surgeons, New York, NY 10032, [2]Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, National Institutes of Health, Bethesda, MD 20205, and [3]Institute of Cancer Research, Columbia University College of Physicians and Surgeons, New York, NY 10032, USA.

(Received on 6 July 1982; accepted on 6 October 1982)

ological studies attempting to relate biologically-effective dose of carcinogen to human cancer risk.

Introduction

In the epidemiology of human carcinogenesis serious difficulties are apparent in estimating dose from existing exposure data and predicting the metabolic fate of a chemical carcinogen in exposed subjects. New methods of quantifying the biologically effective dose of a carcinogen are required. The amount of activated carcinogen directly interacting with critical cellular targets can be defined as the biologically effective dose and is presumed to be directly involved in the carcinogenic process (1,2). Quantitation of carcinogen–DNA

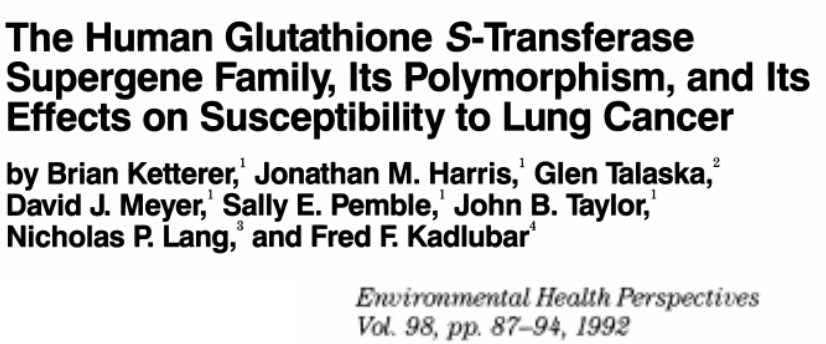


Int. J. Cancer: **36,** 661–665 (1985)

© 1985 Alan R. Liss, Inc.

O^6-METHYLDEOXYGUANOSINE IN OESOPHAGEAL DNA AMONG INDIVIDUALS AT HIGH RISK OF OESOPHAGEAL CANCER

D. Umbenhauer[1,5], C.P. Wild[1], R. Montesano[1,7], R. Saffhill[2], J.M. Boyle[2], N. Huh[3,6], U. Kirstein[3], J. Thomale[3], M.F. Rajewsky[3] and S.H. Lu[4]



The Human Glutathione *S*-Transferase Supergene Family, Its Polymorphism, and Its Effects on Susceptibility to Lung Cancer

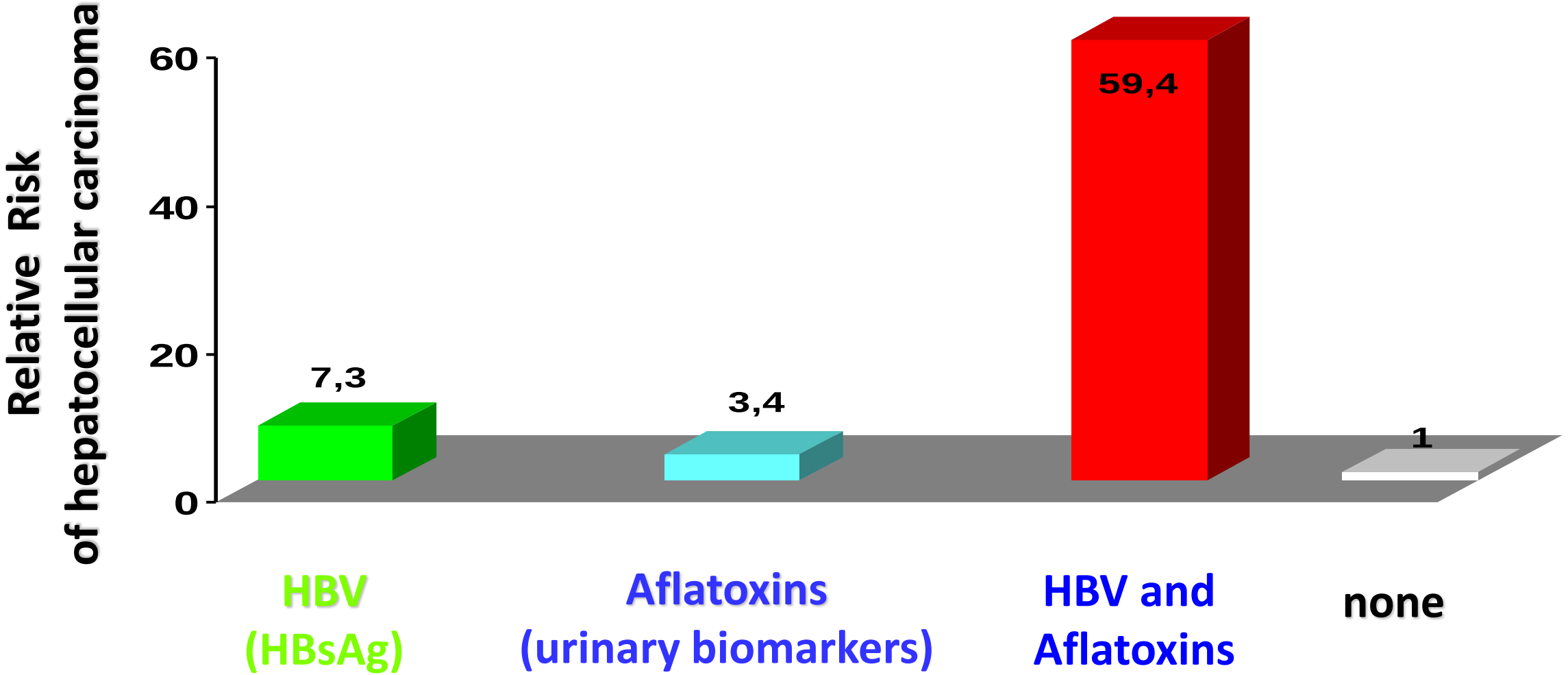
by Brian Ketterer,[1] Jonathan M. Harris,[1] Glen Talaska,[2] David J. Meyer,[1] Sally E. Pemble,[1] John B. Taylor,[1] Nicholas P. Lang,[3] and Fred F. Kadlubar[4]

Environmental Health Perspectives
Vol. 98, pp. 87–94, 1992

Experiencing success: the case of aflatoxins

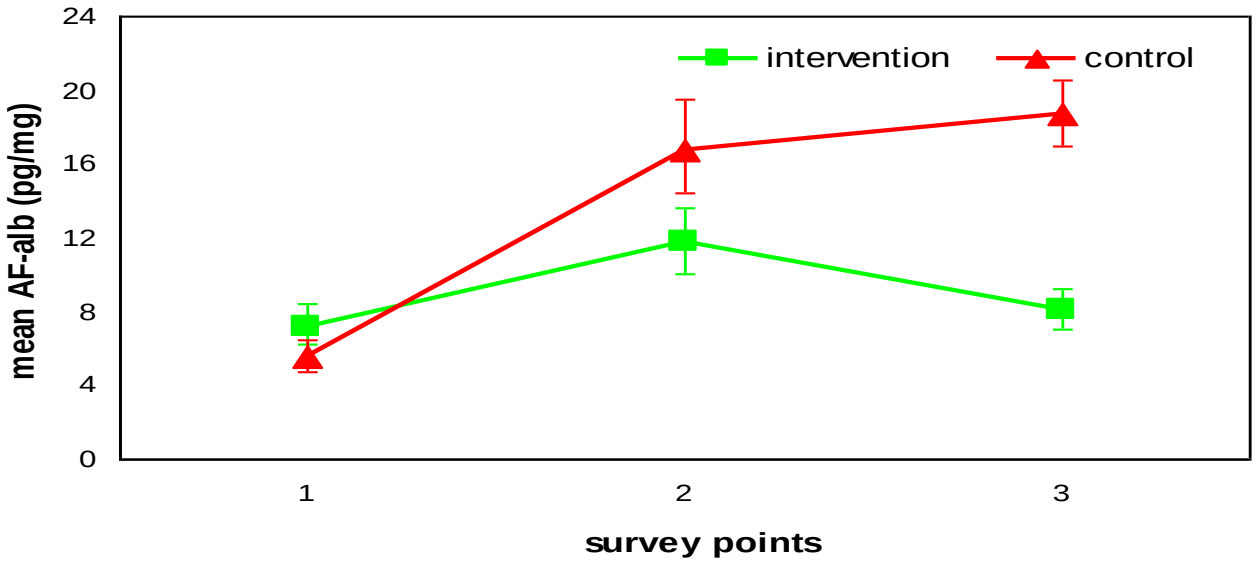
- Produced by *Aspergillus spp*; aflatoxins are common contaminants of dietary staples in sub-Saharan Africa and parts of Asia
- Potent mutagens and liver carcinogens in animals
- Epidemiological studies limited by poor exposure measurement
- Biomarkers of aflatoxin-DNA and protein adducts in blood and urine led to major research advances

Aflatoxin biomarkers: interaction between HBV infection and aflatoxins in liver cancer in China



adapted from Qian et al, CEBP 1994, following Ross et al., Lancet 1992

Aflatoxin biomarkers: primary prevention in subsistence farmers Guinea



Turner et al., (2005) *The Lancet*, **365**, 1950-1956

Origins of the exposome: a difficult birth

The landscape

- Diseases: the causes of NCDs are mainly non-genetic
- Genetics: huge investment yielding exquisite measurement precision at the individual level
- Environment: relative paucity of investment and limited improvement in exposure assessment
- Cohorts: major investment in large prospective cohort studies with biobanks e.g. UK Biobank
- Science and technology: exciting advances in cancer biology with analytical tools applicable to human biospecimens

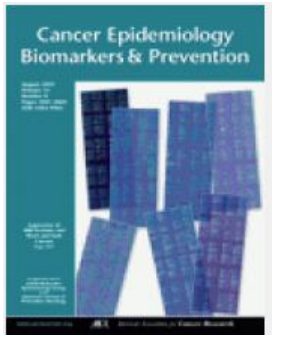
The image

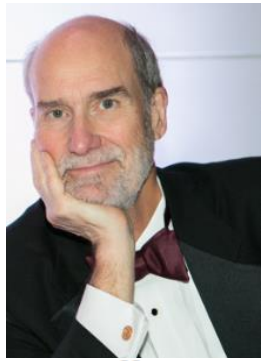
male Fiddler Crab

Wild CP (2005) CEBP,14: 1847-1850

Wild CP (2012) Int. J. Epi, 41: 24-32

Origins of the exposome: a struggle for life





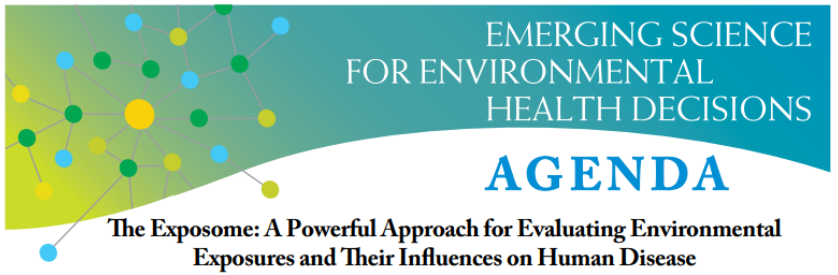
- Paper turned down by a number of leading journals – not reviewed
- Submitted in my role as co-editor-in-chief of CEBP. Dr John Potter comment: *"this is out there"*
- An anonymous childhood – no citations or follow-up for 5 years
- Resuscitated by the US National Academy of Sciences, Engineering and Medicine with support of Dr Steve Rappaport

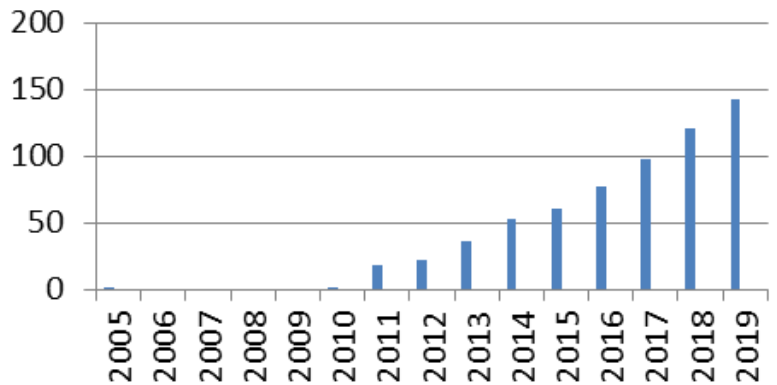
Editorial

Complementing the Genome with an "Exposome": The Outstanding Challenge of Environmental Exposure Measurement in Molecular Epidemiology

Christopher Paul Wild

Molecular Epidemiology Unit, Centre for Epidemiology and Biostatistics, Leeds Institute of Genetics, Health and Therapeutics, Faculty of Medicine and Health, University of Leeds, Leeds, United Kingdom



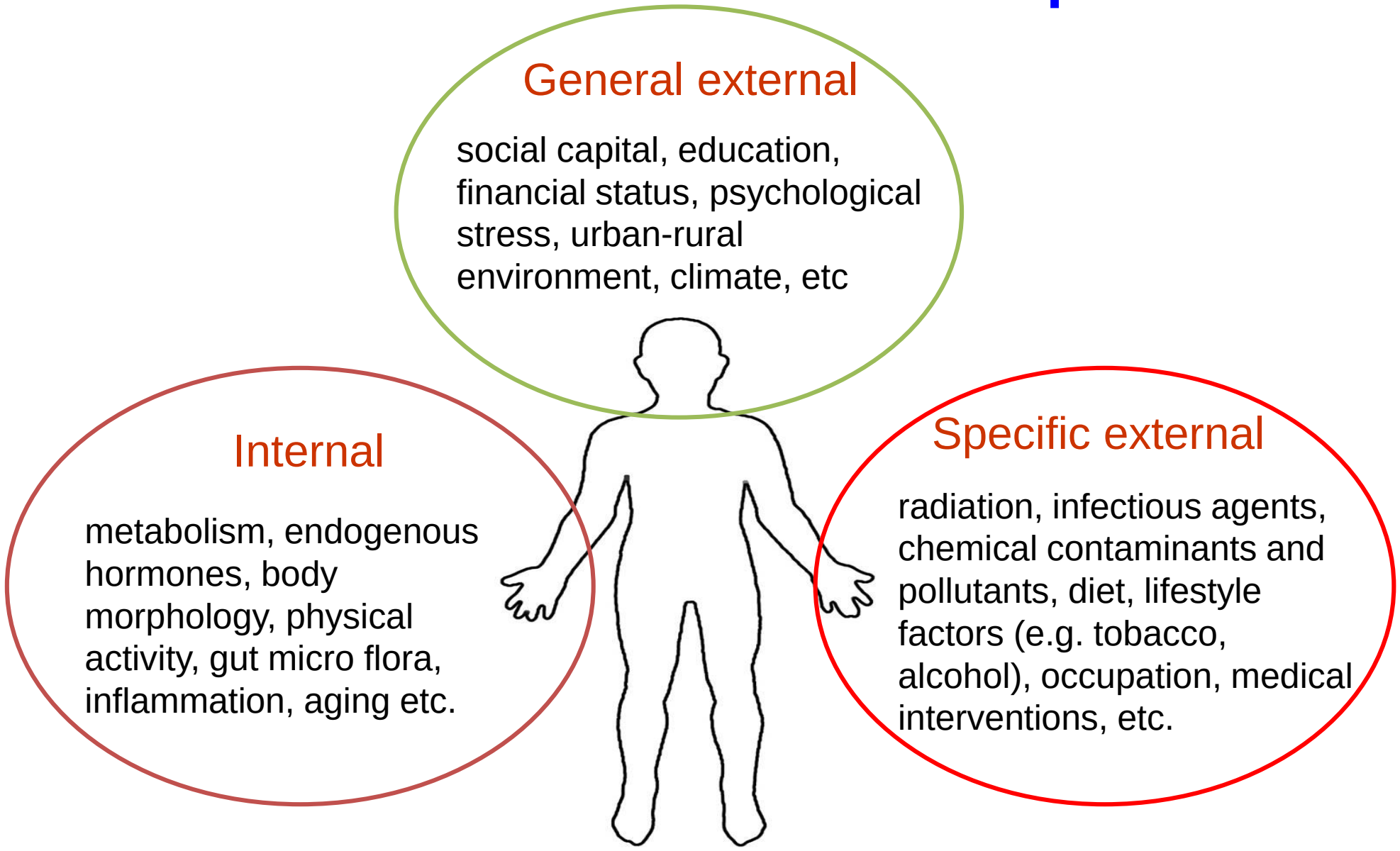


Exposome - the definition

- 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.

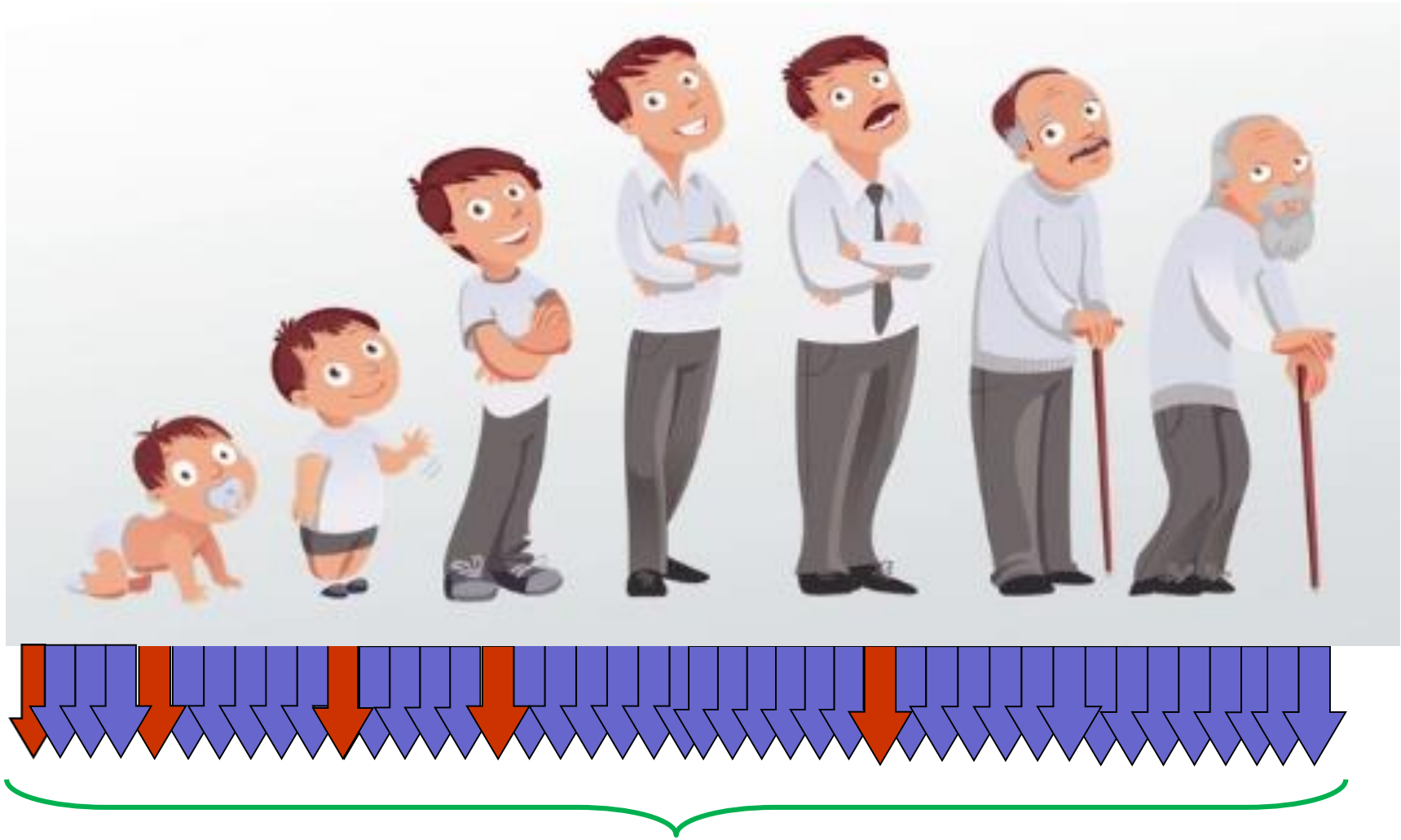
Cited from the Dictionary of Epidemiology
MS Porta, 6th edition, OUP 2014

Exposome: the breadth of exposures



Wild CP (2012) Int. J. Epidemiol, 41: 24-32

Exposome: the timing of exposures



Wild CP (2012) Int. J. Epidemiol, 41: 24-32

The challenges in characterising the exposome are inherent to the strengths

- Scale and complexity: characterization of many categories of quite different types of exposure *e.g. gut microbiome through to the built environment*
- Dynamic: the exposome changes markedly over time – possibility of critical windows of exposure *e.g. in early life; major lifestyle changes e.g. moving residence, changing jobs*
- Technical and data analysis: complex and evolving, requiring innovative informatics and statistical methods
- However, even partial characterisation can bring major benefits

The exposome complements, but does not mirror, the genome

- The exposome *(in its pure sense, in its entirety)* is unlikely to be characterized for a given individual; it will be partially characterized across many individuals
- While application of the genome to health may be at the individual level, individual level application is unlikely for the exposome; the application will be at a population, or sub-population level
- Therefore, the value of the exposome is likely to be found primarily in public health benefits rather than clinically

….the promise

The exposome: the challenges of growing-up

2005: newborn baby

2020: the teenage years

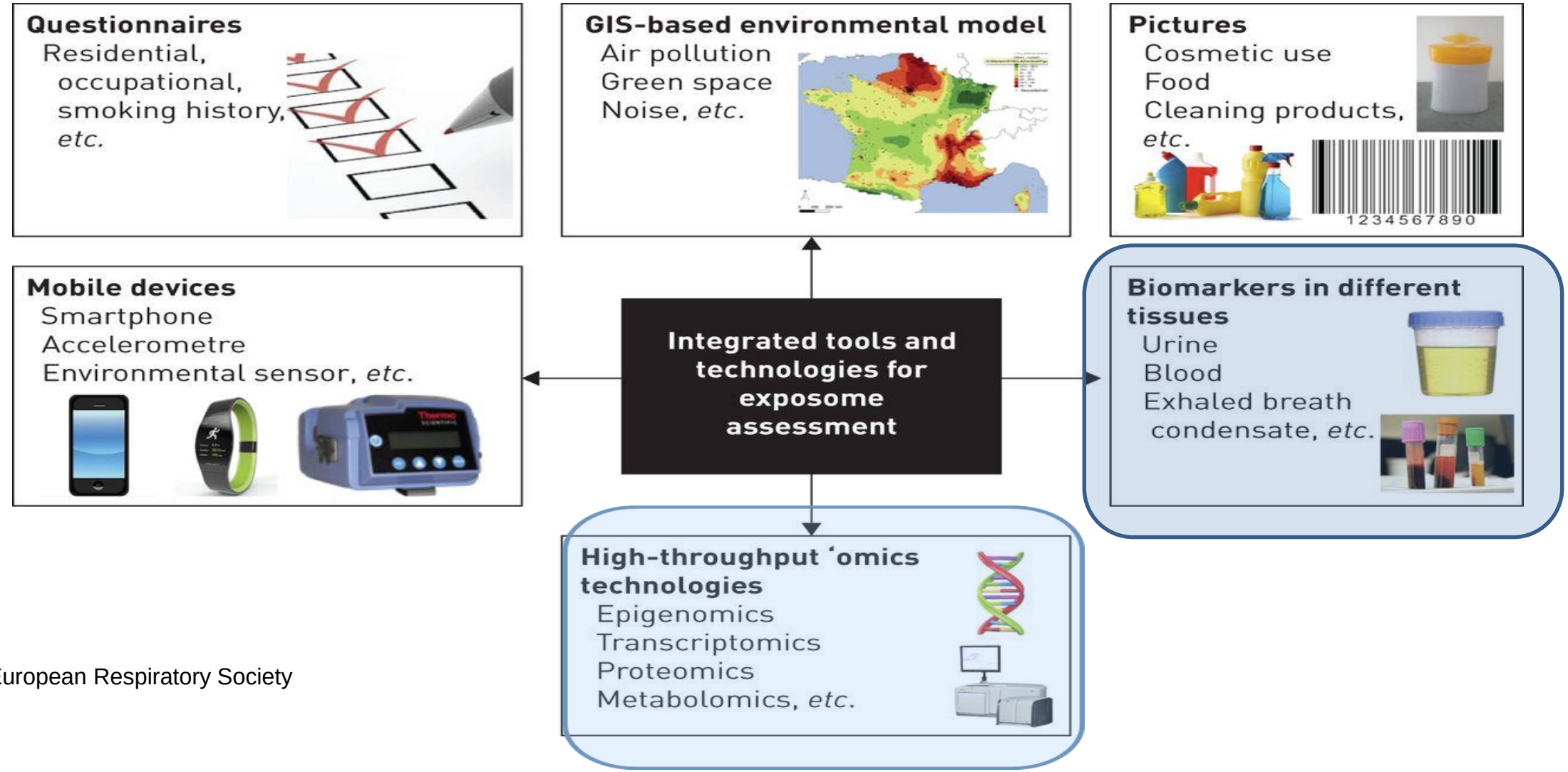
An opportunity for scientific innovation: in the questions framed

- A paradigm shift: to capture a far greater breadth of exposures for a given person
  - including agnostic approaches to generate new hypotheses e.g. environment-wide association studies
  - to permit analysis of mixtures: co-occurrences, interactions, synergies etc.
- To explore the timing of exposures and their differential effects over a life-course
- Exemplar for studying the causes and prevention of a wide range of diseases through an inter-disciplinary approach

An opportunity for scientific innovation: in the tools applied

- Common soil of biology – "two-way" translational research from basic science to both the clinic and the population *(see Wild CP et al., (2013) Env. Molec. Mutagen.54: 480-499; Wild CP et al., (2015) JNCI 107 (1); dju353)*
- Common research platforms - prospective cohort studies, biobanks, analytical platforms, databases
- Common goals: engenders multi-sectoral collaboration from the molecular to the socio-political ; "causes of the causes"; policy research

Exposome: the new array of tools

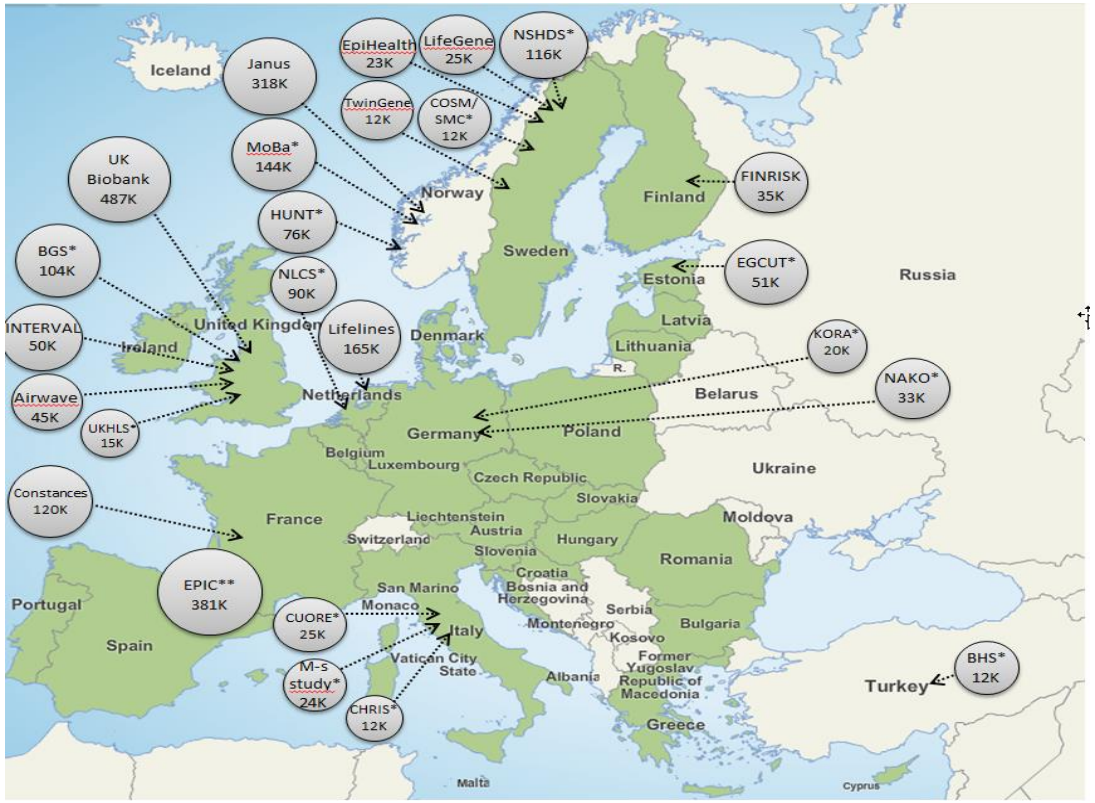


Valérie Siroux et al. Eur Respir Rev 2016;25:124-129

Exposome: potential to benefit from prior investment

ECC
EUROPEAN COHORT CONSORTIUM

- 25 prospective cohorts each with blood on >10,000 participants
- 2.4M participants with blood samples in biobanks
- Over 100 European collaborators supporting the project
- Potentially important infrastructure for cancer prevention research
- Currently inactive



Eur J Epidemiol (2017) 32:741–749
DOI 10.1007/s10654-017-0315-2

CrossMark

ESSAY

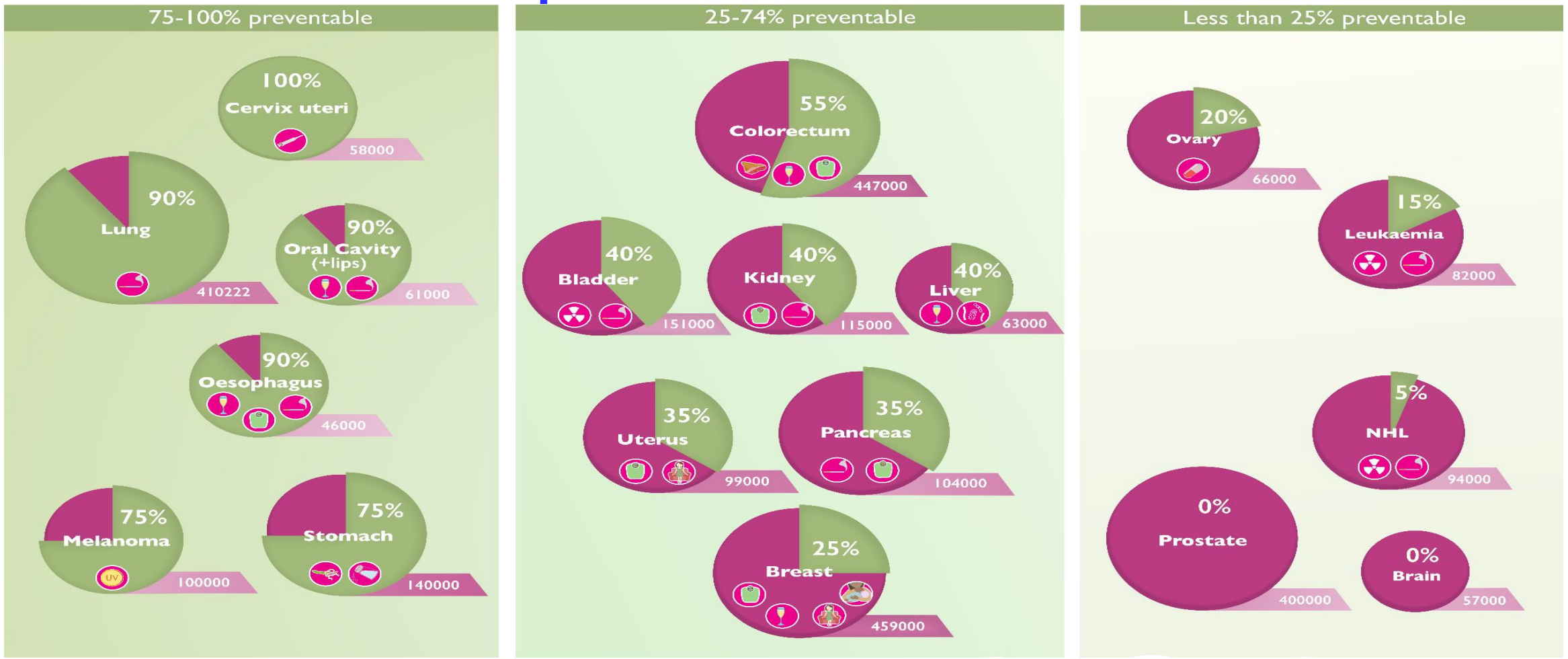
Chronic disease research in Europe and the need for integrated population cohorts

Paul Brennan[1] · Markus Perola[2] · Gert-Jan van Ommen[3,4] · Elio Riboli[5] ·
On behalf of the European Cohort Consortium

An opportunity for scientific innovation: in moving from science to regulation and policy

- Establishing causes (hazard and risk)
  - Exposure assessment in epidemiological studies, including ability to capture co-exposures, assess confounders etc
  - Provision of dose-response data for subsequent risk assessment
  - Biological plausibility of exposure-disease associations ("meet-in-the-middle" studies); bridging experimental and human data
  - Alternative/intermediate disease endpoints; risk of tumour sub-types
- Stratifying risk: susceptible sub-groups; critical windows in time
- Surveillance of exposure: (bio)monitoring of prevalence and level of exposure
- Evaluating interventions: provision of short-term endpoints, mechanism-based markers

Cancer prevention: the potential for primary prevention in Europe



…the perspective

Exposome research: some methodological challenges

- Validating exposure measurements – *ultimately need to link measures back to a modifiable exposure*
- Data integration and analysis – *big data is implicit in exposome research*
- Defining what is exposure and what is effect – *for example in interpreting omics data*

Exposome research: priorities

- Focus on the question - characterizing exposure:disease relationship in priority areas
  - *The exposome is a means to an end*
- Sustained funding - for method development (lab, informatics, statistics, databases); support to large-scale population studies (c.f. GWAS); encouragement of inter-disciplinary collaboration
- "Taste and see" – lessons from exposome studies should drive further methodological development

Exposome research: researchers need to engage in the regulatory and policy arenas

More scientists must be willing to cross the bridge, carrying something that can be used by those on the other side

Evidence-informed, rather than evidence-based, health policy *acknowledges that policy-making is an inherently political process in which research evidence is only one, albeit the most important, factor that influences decision-making.*

European Health Report 2018

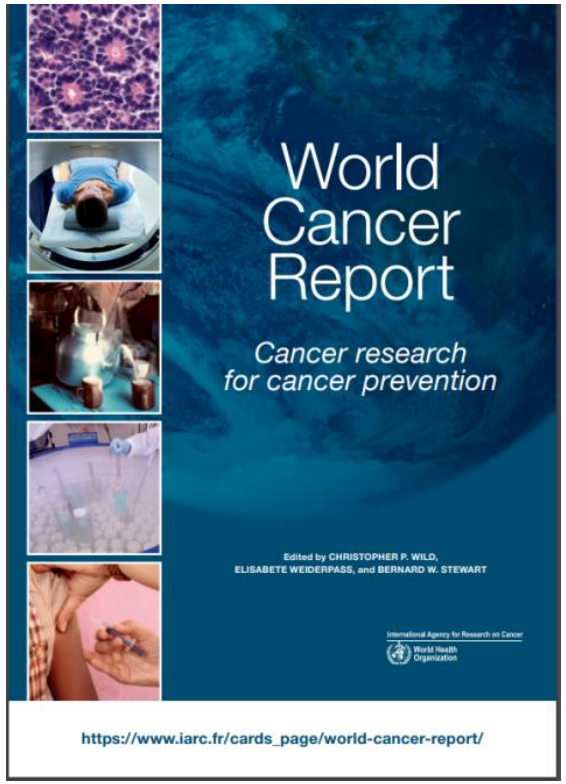
Exposome research: researchers need greater awareness in relation to vested interests – education goal

Common tactics used by vested interests to undermine independent scientific evaluation
• Accuse scientists or evaluation processes of cherry-picking data
• Sponsor/commission and publish scientific articles contradicting expert evaluations
• Engage scientists to ghost-write industry authored papers
• Establish scientific workshops, working groups or public-private foundations populated by industry-funded scientists
• Ensure editorial boards of scientific journals have industry-employed scientists to facilitate publications
• Develop and finance media outlets to cast doubt upon and counter scientific evidence and evaluations
• Lobby for political support to oppose regulatory action
• Conduct legal challenges, lawsuits, FOIA requests to slow implementation of regulations, intimidate independent scientists etc.

Conclusions

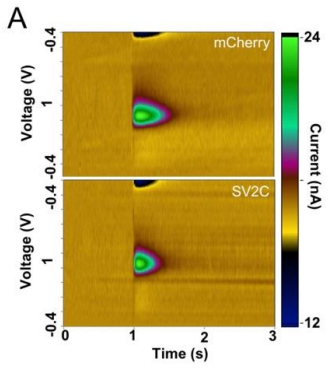
- The recognized need to prioritize research on NCD prevention provides an opportunity for exposome research
- The exposome concept has generated greater emphasis, innovative science and significant investment in the area of environment, behaviour and health
- Priority exposure-disease areas should be identified to which the exposome approach can be applied
- Sustained funding to support further development of exposome methodology must be prioritised – a young science

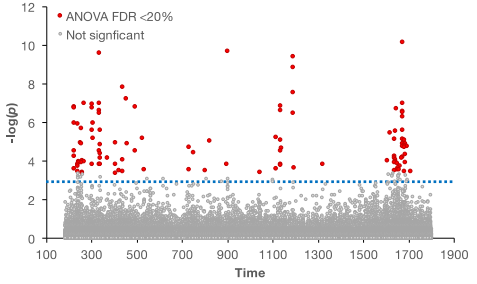
Thank you –
I wish I was starting out now!

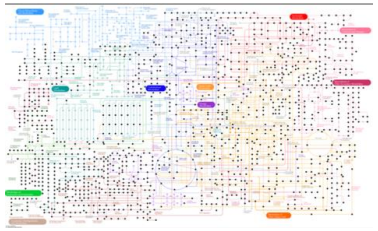


Gary W. Miller

The exposome: 21st century challenges







Gary W. Miller, Ph.D.
Vice Dean for Research Strategy and Innovation
Professor of Environmental Health Sciences
Mailman School of Public Health
Columbia University, New York, NY
gary.miller@columbia.edu

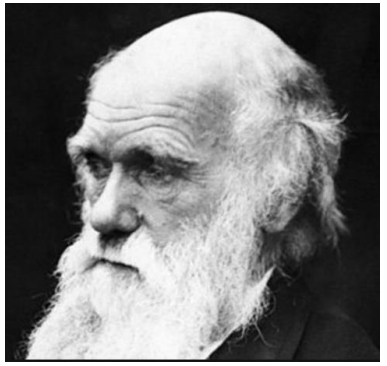
@exposome
@garywmiller3

Disease causation/ exacerbation = $\sum$ Genetic factors + $\sum$ External factors

Health/disease phenotype = Genome + Exposome

Exposome – a systematic, unbiased, and omic-scale examination of external factors contributing to disease or health status

An imbalanced equation



$$G \times E = P$$

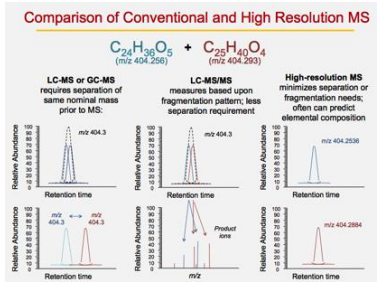
If our phenotype is a result of our genetics and environment, why then do we spend a disproportionate amount of time, money, and energy on genetics?

Exposome: the cumulative measure of the environmental influences and corresponding biological responses throughout the lifespan.

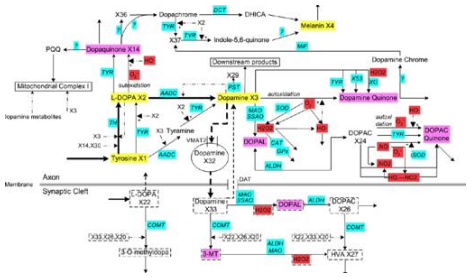
Miller GW, Jones DP. The Nature of Nurture: Refining the Definition of the Exposome. Toxicological Sciences, 137:1-2, January, 2014.

“Derived from the term exposure, the exposome is an omic-scale characterization of the nongenetic drivers of health and disease.”

MM Niedzwiecki, DI Walker, R Vermeulen, M Chadeau-Hyam, DP Jones, and GW Miller. The Exposome: Molecules to Populations. Annual Reviews of Pharmacology and Toxicology. 59:107-127, 2019



HERCULES
Exposome Research Center



Awarded in 2013 (NIH P30-ES019776), Funded through 2022

administration (Miller 2013-2018; now Marsit)

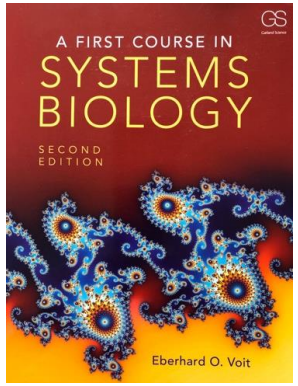
analytical chemistry-targeted (Barr, Ryan)

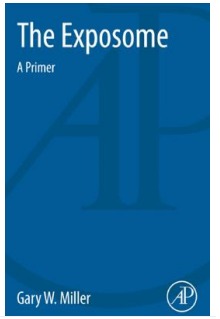
metabolomics/exposomics-untargeted (Jones, Li)

pilot awards (Morgan) and patient studies (Ziegler, Marsit)

community engagement (Kegler/Pearson)

data science/systems biology (Waller, Voit, Clifford, Li, Qiang, Kemp)



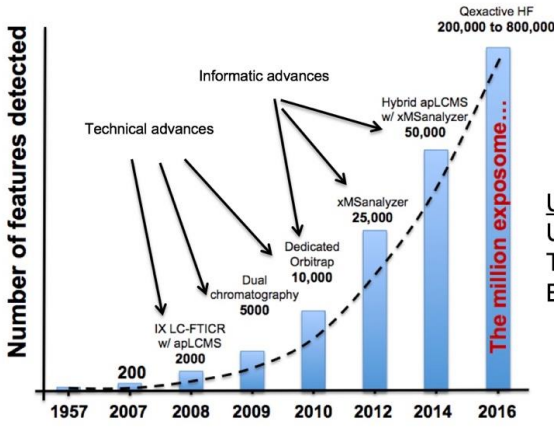


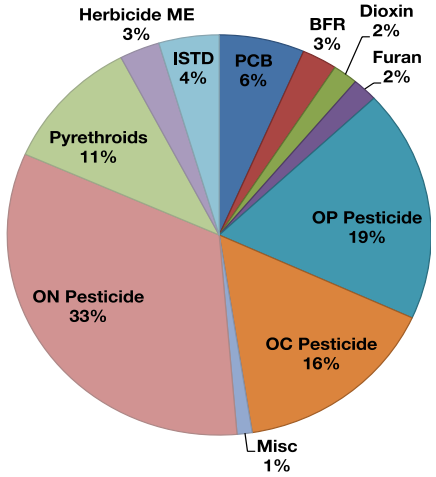
The Exposome: A Primer

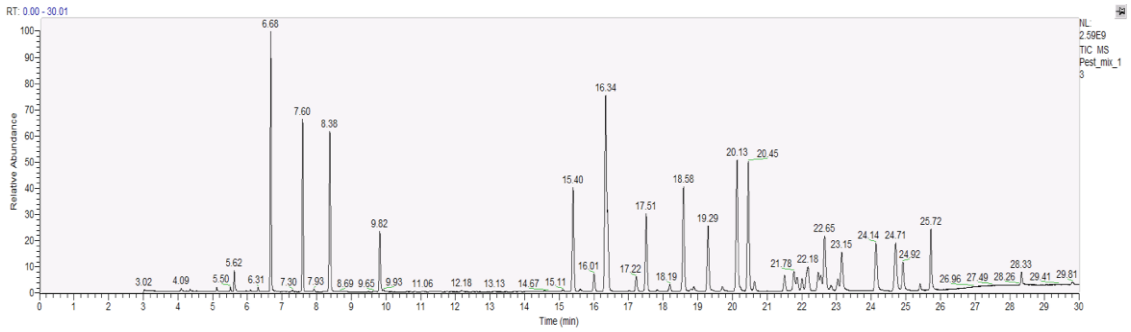
the ex-POZE-ohm: a pr ī m'-er

the environmental equivalent of the genome

Gary W. Miller, Ph.D.
Department of Environmental Health
Rollins School of Public Health
Emory University







Replicating the high-resolution metabolomics LC or GC HRMS at Columbia as part of the Irving Institute CTSA

Capturing exogenous chemicals and endogenous metabolites

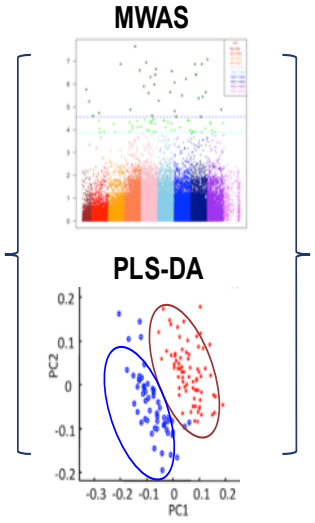
ESI LC-MS

Ultra-high resolution MS
LTQ-FT
LTQ-Velos Orbitrap
Q-Exactive HF
Thermo Fusion

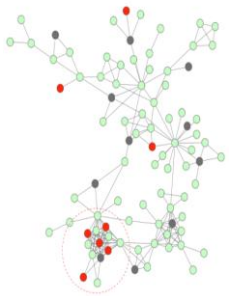
Data extraction

Data Table
***m/z*, RT, Intensity**
Quality metrics

Biostatistics Bioinformatics



Metabolites of interest



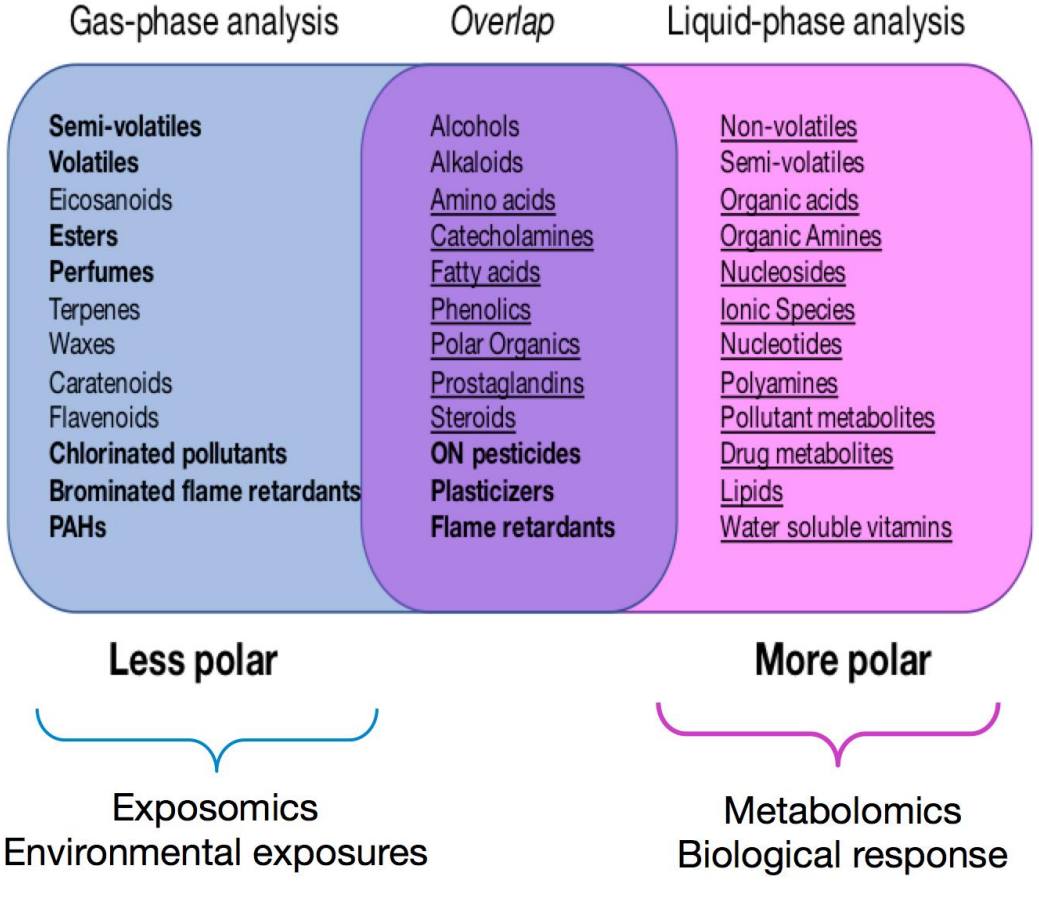
Network and pathway analysis: *Mummichog*, MetabNet, others

Metabolite forensics

Unequivocal Identification
MS^n; UHRAM MS; 1-D, 2-D NMR; ion Mobility; Chemical Reactivity, etc

T Yu et al 2009 Bioinformatics 25:1930-6
JM Johnson et al 2010 Analyst 135: 2864-2870
Q Soltow et al 2013 Metabolomics 9:S132–S143
T Yu et al 2013 J Proteome Res 12:1419-27
S Li et al 2013 Plos Comp Biol 9:e1003123
K Uppal et al 2013 BMC Bioinformatics 14:15
K Uppal et al 2015 Frontiers Bioeng Biotech 3:87

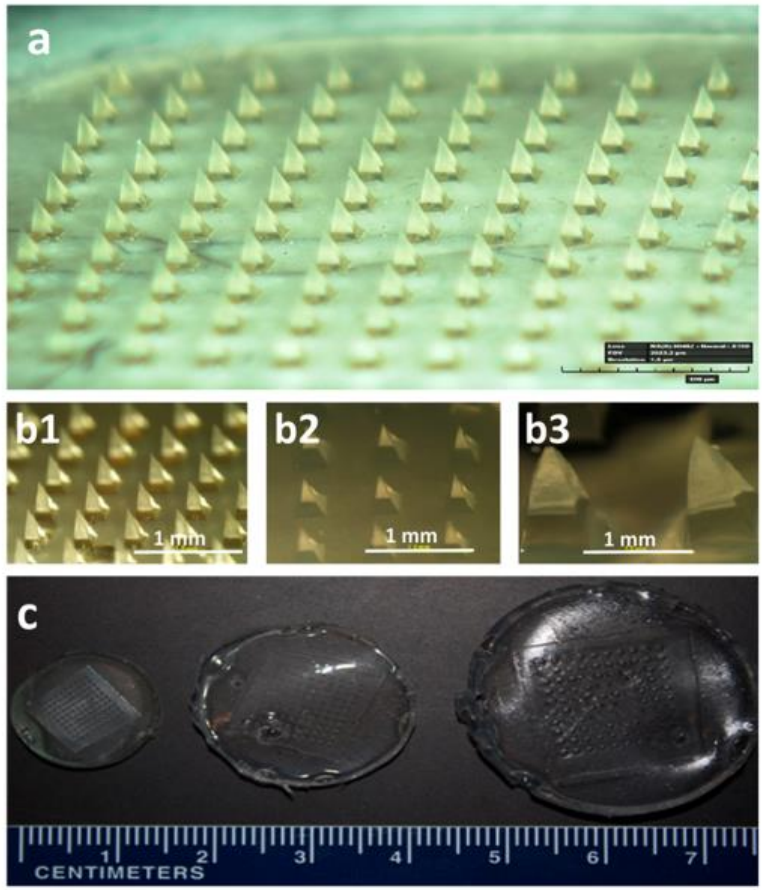
DP Jones 2016 *Tox Reports* **3**: 29-45



analytical chemistry
Letter
pubs.acs.org/ac

Collection of Analytes from Microneedle Patches

Andrey V. Romanyuk,[†] Vasiliy N. Zvezdin,[‡] Pradnya Samant,[†] Mark I. Grenader,[†] Marina Zemlyanova,[§] and Mark R. Prausnitz*[,†]

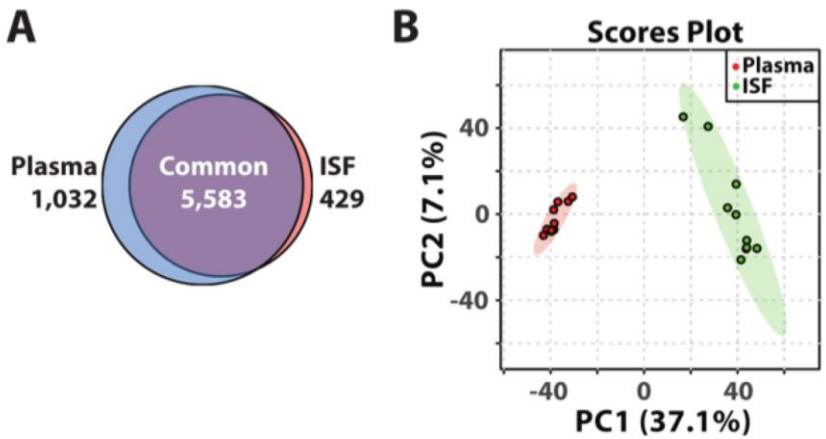


analytical chemistry
ACS AuthorChoice
Article
Cite This: Anal. Chem. 2018, 90, 3786–3792
pubs.acs.org/ac

Human Suction Blister Fluid Composition Determined Using High-Resolution Metabolomics

Megan M. Niedzwiecki,[†,∥] Pradnya Samant,[‡,∥] Douglas I. Walker,[§] ViLinh Tran,[§] Dean P. Jones,[§] Mark R. Prausnitz,*[,‡] and Gary W. Miller*[,†]

Figure 1. High-resolution untargeted metabolomic profiles of ISF and plasma.



Samant, Niedzwiecki, Raviele, Tran, Mena-Lapaix, Walker, Felner, Jones, Miller, Prausnitz. Science Translational Medicine-Under revision

Mega-scale identification of xenobiotic metabolites. Compound ID Core.

Jones, Morgan, Li, Miller (MPI)

A **Xenobiotic chemical with known structure**

B Predicted products from array of known xenobiotic metabolism systems

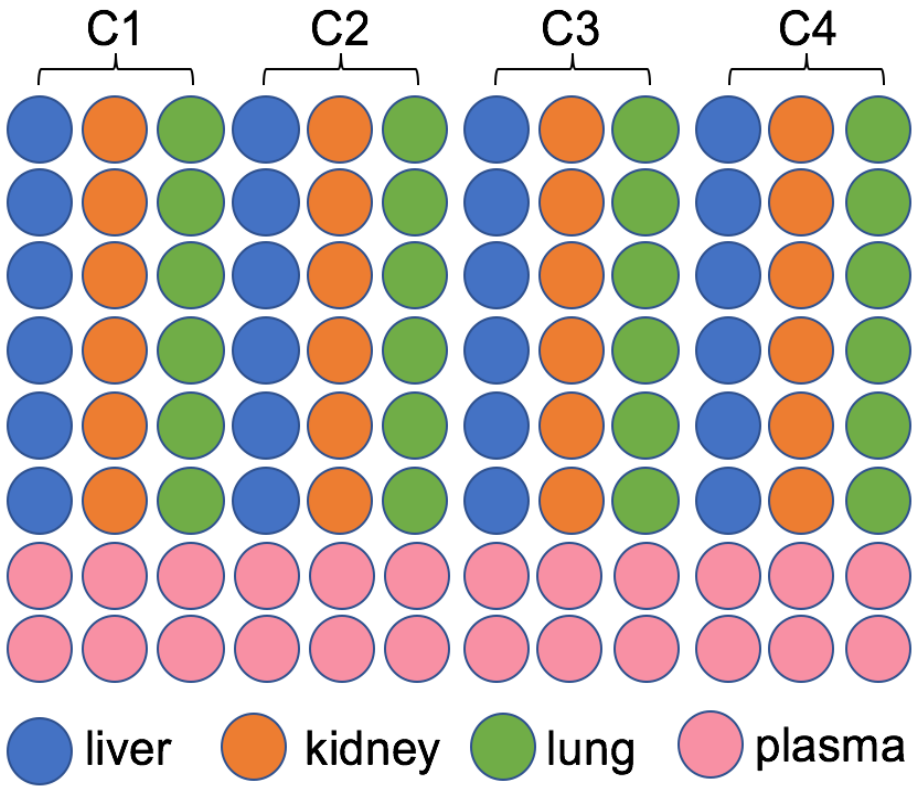
C Predicted MS/MS ions for each xenobiotic metabolite

D Transformation of xenobiotic by array of xenobiotic metabolizing systems

E MS programmed to fragment ions corresponding to predicted xenobiotic products

F **Algorithm to score quality of match of detected MS/MS ions with predicted MS/MS ions**

First generation 96-well plate assay, 4 tissues:
4 chemicals, 6 concentrations or
8 chemicals, 3 concentrations



96-well plate with human plasma, liver, kidney and lung S9 fractions to study metabolites of four chemicals, C1-C4.

Commercial S9 fractions (microsomes + cytosol) pooled from 50 human liver, kidney, and lung, are supplemented with necessary cofactors for oxidation, reduction, glucuronidation, sulfation, methylation and acetylation

A recent example from a collaboration with the Mayo Clinic

- ***Primary sclerosing cholangitis (PSC)***
- US prevalence: 13.6/100,000 (0.014%)
- Average age of diagnosis: 41 years
- Transplant free survival: 12 years
- Only treatment: Liver transplant
- Outcomes: malignancy, liver failure
- Mayo sees 5% of all U.S. patients with disease
- ~70% of cases have inflammatory bowel disease

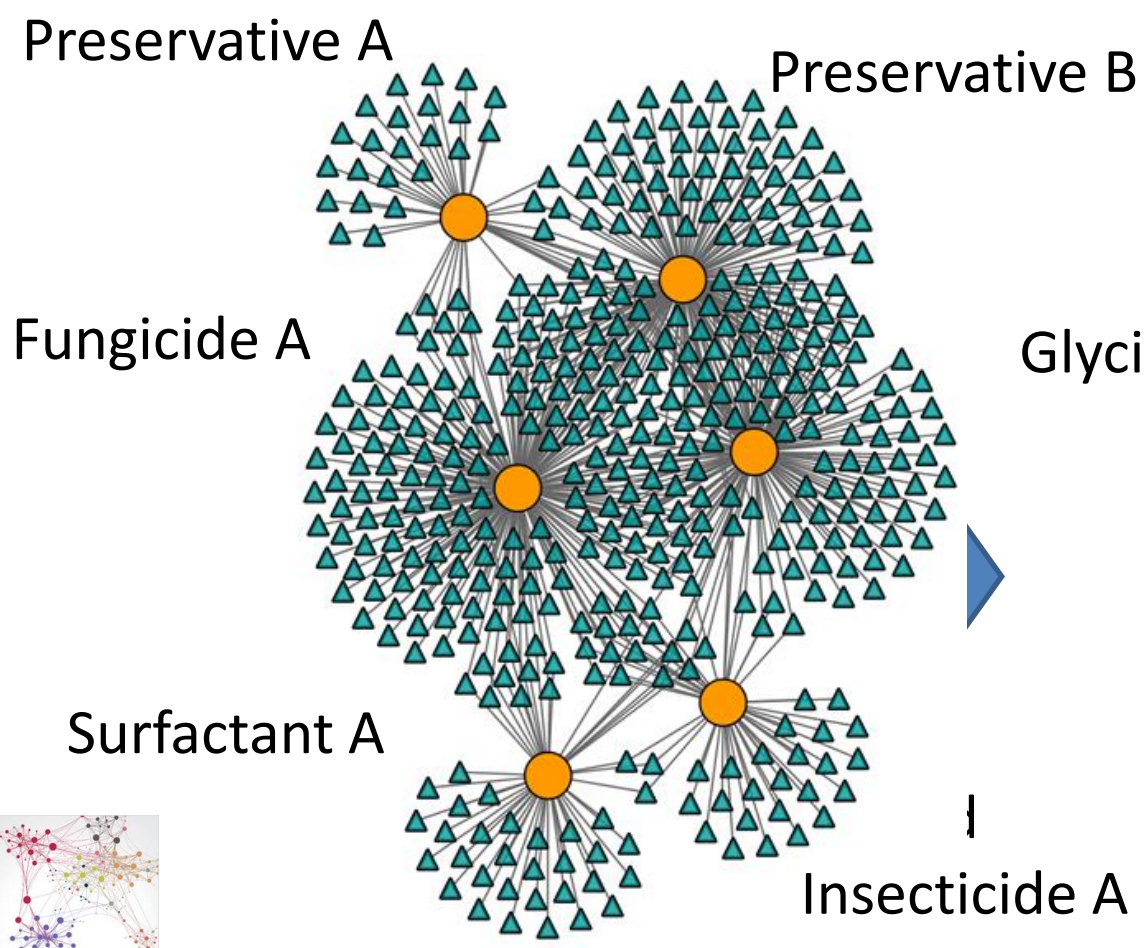
EWAS reveals altered levels of environmental pollutants
MWAS identified bile acid alterations

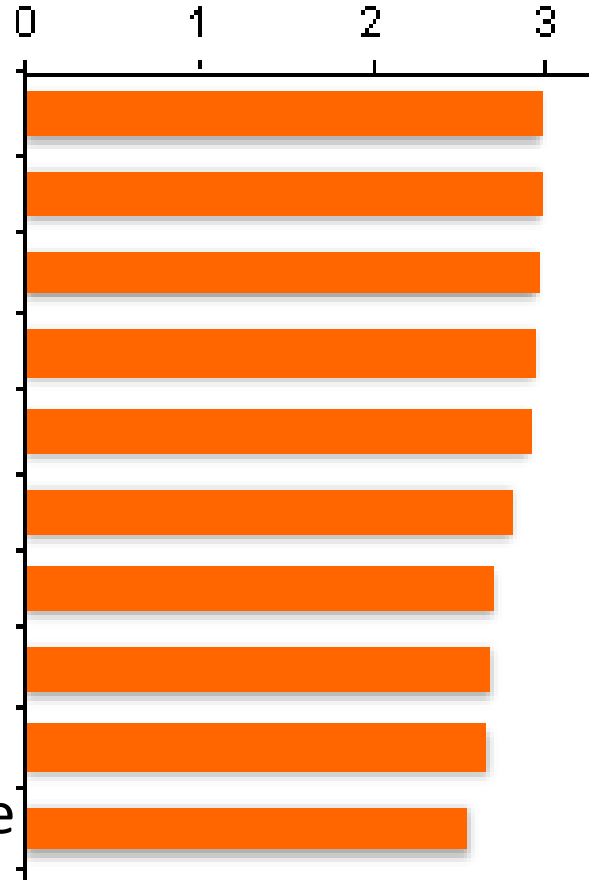
Chemical	*p-value*	Regression Coefficient	Odds ratio , IQR (95% Confidence interval)
Fenpropimorph	0.012	2.05	7.78 (2.47, 82.22)
Nonylphenol	0.002	1.04	2.84 (1.55, 5.89)
Protocatechuic acid	0.003	1.01	2.75 (1.53, 5.75)
Aldicarb sulfone/Acetamiprid	0.012	0.75	2.13 (1.28, 4.19)
Ethyl paraben	0.014	0.63	1.87 (1.22, 3.33)
Chlorthiophos	0.078	0.49	1.63 (0.97, 2.89)
Terbutylazine	0.056	0.48	1.62 (1.01, 2.75)
Fenvalerate	0.063	0.44	1.56 (1.00, 2.58)
Triclocarban	0.076	-0.24	0.79 (0.59, 1.02)
Anthraquinone	0.093	-0.37	0.69 (0.44, 1.05)
Perfluorooctanoic acid	0.084	-0.38	0.68 (0.44, 1.05)
Diphenamid	0.012	-0.40	0.67 (0.47, 0.9)
Diphenamid	0.052	-0.41	0.66 (0.43, 0.99)
Dimethachlor	0.049	-0.45	0.64 (0.40, 0.98)
Monocrotophos	0.030	-0.46	0.63 (0.41, 0.94)
Thiabendazole	0.062	-0.59	0.55 (0.29, 1.02)
Perfluorooctanesulfonic acid	0.007	-0.65	0.52 (0.31, 0.79)
Fenobucarb/Promecarb	0.019	-0.76	0.47 (0.24, 0.87)
Carbaryl	2.6E-05	-0.97	0.38 (0.23, 0.57)

>205 environmental chemical biomarkers identified in PSC, PBC and control population. Each was tested for association with disease status using logistic regression.

	Metabolite	OR
PSC	Glycochenodeoxycholic acid	>10
	Taurochenodeoxycholic acid	>10
	Taurine	2.8
PBC	Glycocholic acid	6
	Cholic acid	3
	Taurine	3.7

Exposomics-Metabolomics Networks Reveal Top Pathways Associated with PSC



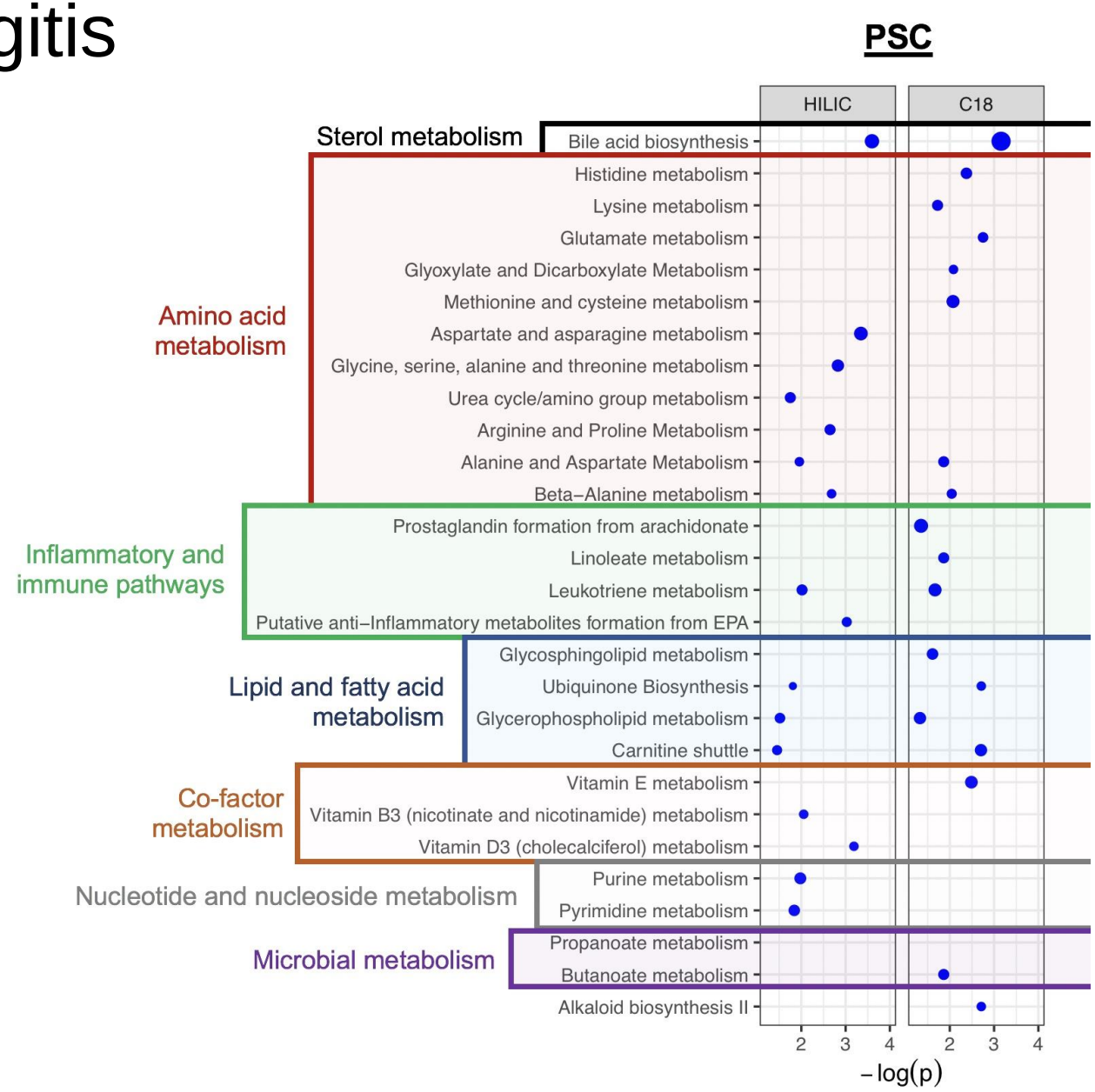


*** Only top 10 pathways shown**

Primary sclerosing cholangitis

Dissecting the pathogenesis an outcomes of PSC using multi-omics by studying the exposome and genome.
NIDDK RC2 $8M

>800 patients per group



Alzheimer's disease (93), Mild cognitive impairment (50), controls (59) APOEgentoype, CSF (AB42, pTau)

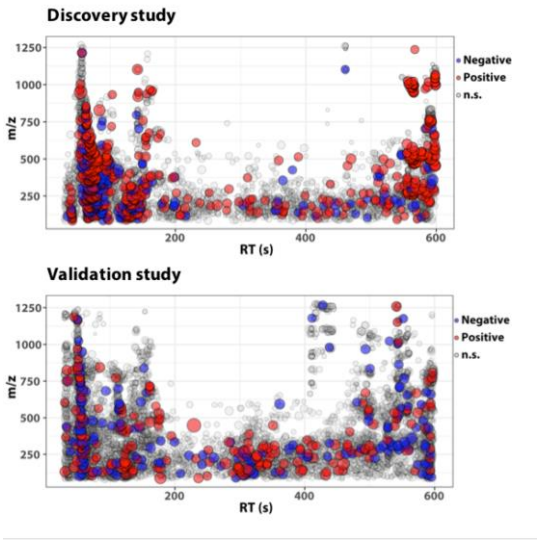


Table 4. Putative compound identification of plasma features from MWAS.

m/z	RT	Change in AD	Putative compound(s)	Predicted adduct	ID level[a]	Notes
129.0661	89	Higher	Glutamine (2 ppm)	$-H_2O+H$	1	--
231.1205	211	Higher	5S,6S-epoxy-15R-hydroxy-ETE (+Na, 0 ppm)	--	3	--
246.9550	127	Higher	Numerous database matches	$-H_2O+H$	--	Contains halogen (Cl and/or Br)
334.1410	86	Lower	Piperettine (1		4	--
349.1515	80	Lower	Piperine (1 ppm)	+ACN+Na	4	--
386.8946	61	Higher	1,1-Dichloro-2-(dihydroxy-4'-chlorophenyl)-2-(4'-chlorophenyl)ethylene (9 ppm)	+K	2	Contains halogen (Cl and/or Br)
662.0933	158	Higher	GDP-D-mannuronate (+ACN+H [M+1], 0 ppm); Chaetocin ($-2H_2O+H$ [M+1], 8 ppm); Blighinone (+H [M+1], 9 ppm)	[M+1] isotope	4	--
663.4524	36	Higher	Lipid A-disaccharide-1-P (+2H, 2 ppm); Aluminium dodecanoate (+K, 2 ppm)	--	4	--

Hydroxyated metabolite of DDE

[a]ID level indicates annotation confidence: 1, *m/z* and retention time confirmed with MS^2, 2: Multiple/isotopes present; 3: *m/z* matched single adduct mass within 10 ppm mass error, 4: *m/z* matched adduct mass of multiple isobaric species, probable identifications listed.

Niedzwiecki, Walker, Howell, Watts, Jones, Miller, Hu preliminary data

Metabolic, halogenated environmental chemical, dietary constituent, Alzheimer's medication

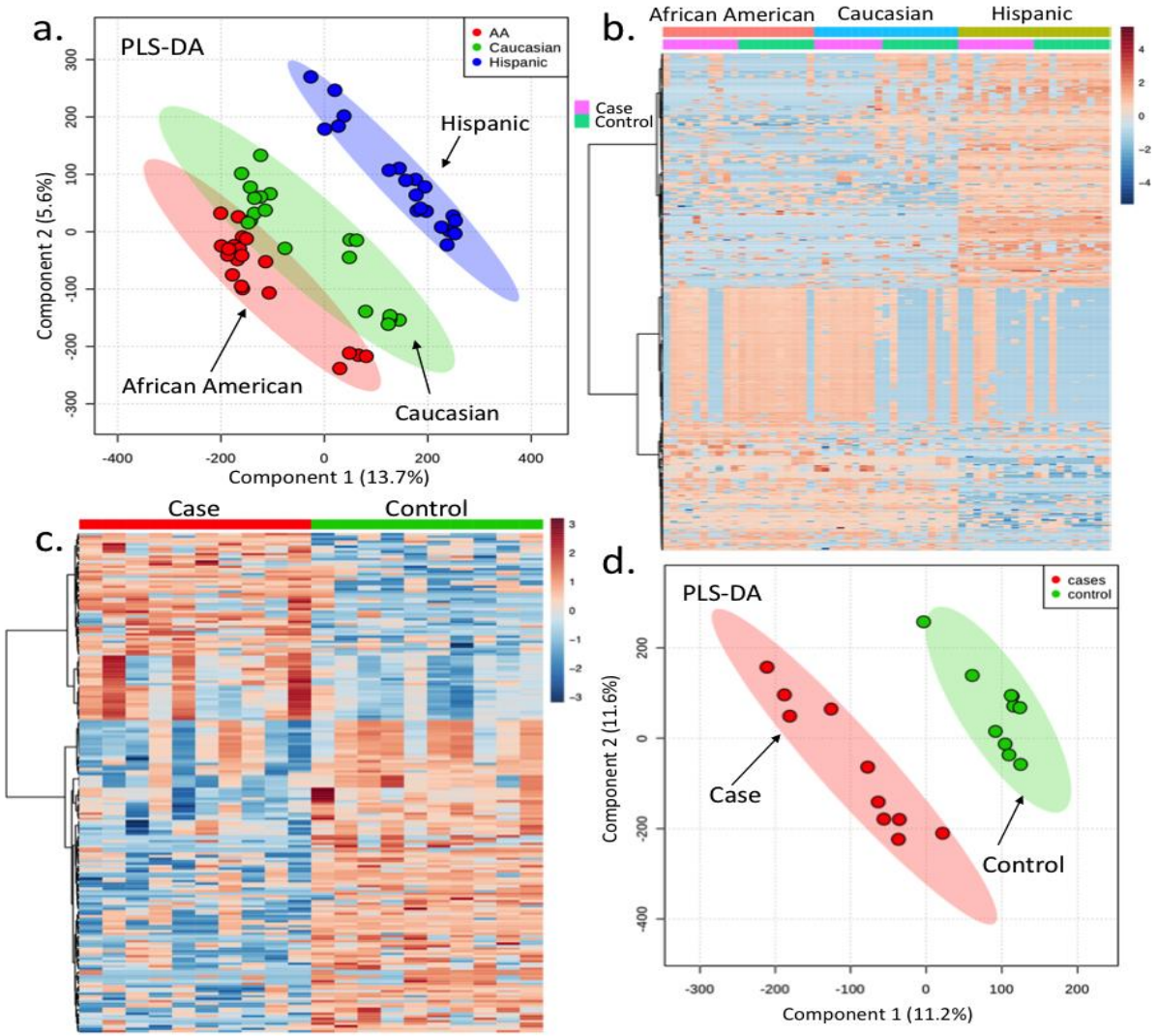
Table 2. Non-medication plasma metabolite features reproducibly associated with AD from MWAS

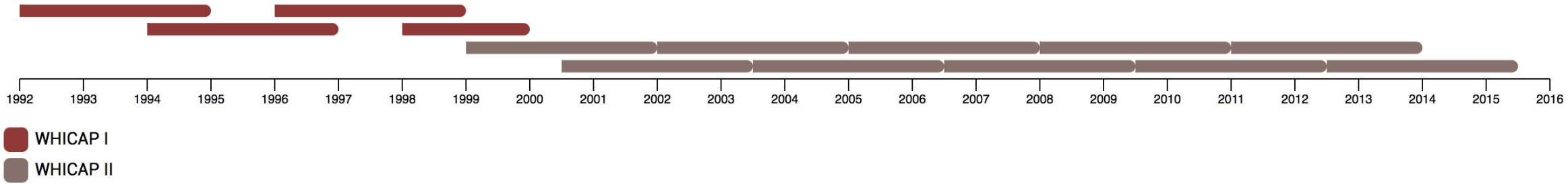
Feature			Study 1		Study 2		Meta-analysis		
m/z[a]	RT[a]	Metabolite	Est (SE)	*p*	Est (SE)	*p*	Est (SE)	*p*	FDR
129.0661	89	Glutamine	0.22 (0.11)	0.04	0.31 (0.13)	0.02	0.25 (0.08)	0.002	0.07
246.9550	127	Unknown	0.41 (0.17)	0.02	0.38 (0.21)	0.07	0.40 (0.14)	0.003	0.08
349.1515	80	Piperine	-0.59 (0.31)	0.06	-0.89 (0.49)	0.07	-0.68 (0.27)	0.01	0.18

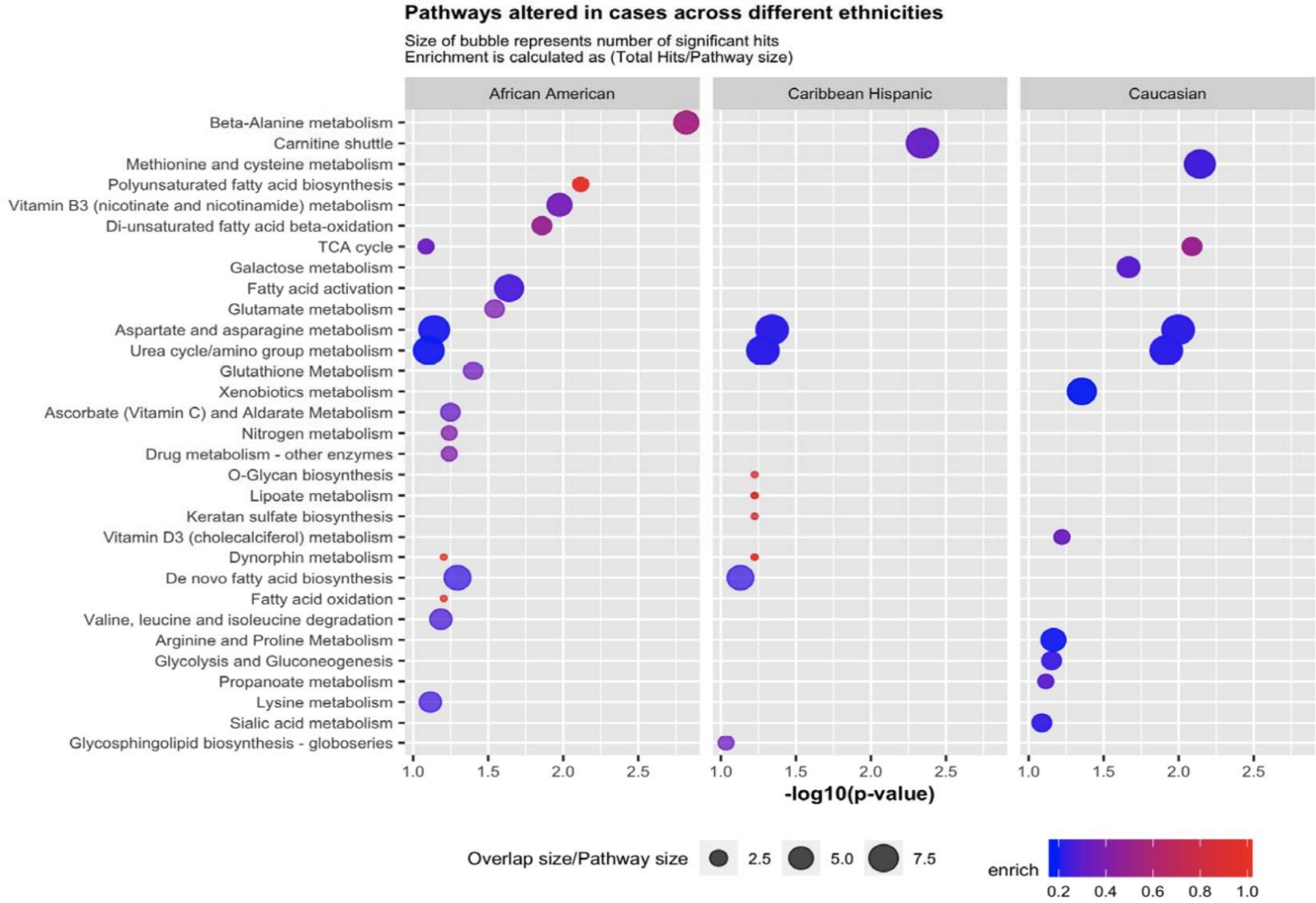
*Adduct of rivastigmine strongest feature associated with AD

Niedzwiecki et al., 2019 Annals of Clinical and Translational Neurology

WHICAP study of Alzheimer's disease, Richard Mayeux, PI Columbia University







Vardarajan et al. Differences in plasma metabolites related to Alzheimer's disease, APOE-ε4 status and ethnicity. medRxiv (PrePrint) posted January 20, 2020

Study	Diagnostic groups	Replication cohort
Orešič et al. 2011[48]	MCI (n=143), AD (n=47), Control (n=46)	None
Ibáñez et al. 2012[10]	AD (n=25), MCI-AD (n=13), MCI-SNAP (n=24), Control (n=23)	None
Trushina et al. 2013[73]	MCI (n=15), AD (n=15), Control (n=15)	None
Motsinger-Reif et al. 2013[55]	AD (n=40), Control (n=38)	None
Cui et al. 2014[49]	AD (n=46), Control (n=37)	AD (n=63), Control (n=67)
Graham et al. 2015[74]	MCI (n=16), MCI-AD (n=19), Control (n=37)	None
Morris et al. 2018[75]	AD (n=64), Control (n=62)	None
Pena-Bautista et al. 2019[76]	MCI-AD (n=29), Control (n=29)	None
Habartová et al. 2019[77]	AD (n=20), Control (n=13)	None

Study	Diagnostic groups	Replication cohort
Orešič et al. 2011[48]	MCI (n=143), AD (n=47), Control (n=46)	None
Ibáñez et al. 2012[10]	AD (n=25), MCI-AD (n=13), MCI-SNAP (n=24), Control (n=23)	None
Trushina et al. 2013[73]	MCI (n=15), AD (n=15), Control (n=15)	None
Motsinger-Reif et al. 2013[55]	AD (n=40), Control (n=38)	None
Cui et al. 2014[49]	AD (n=46), Control (n=37)	AD (n=63), Control (n=67)
Graham et al. 2015[74]	MCI (n=16), MCI-AD (n=19), Control (n=37)	None
Morris et al. 2018[75]	AD (n=64), Control (n=62)	None
Pena-Bautista et al. 2019[76]	MCI-AD (n=29), Control (n=29)	None
Habartová et al. 2019[77]	AD (n=20), Control (n=13)	None

Table 2. Number of blood samples	SA1		SA 2a	All Aims
	Controls	Incident AD	Prevalent AD	Metabolomes
2 +	724	247	375	3,692
3 (or more) ++	760	529	260	4,647
Totals	1484	776	635	8,339

R. Mayeux, B. Vardarajan, G. Miller, Y. Gu., I. Ionita-Laza

The Irving Institute for Clinical and Translational Science

The Irving Institute for Clinical and Translational Research, funded by a National Institutes of Health Clinical and Translational Science Award (CTSA), serves as the cornerstone of translational science for the Columbia Precision Medicine Initiative.

All of Us RESEARCH PROGRAM | The Precision Medicine Initiative

ESI LC-MS

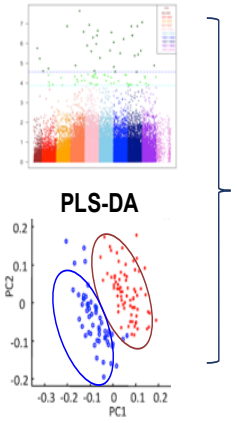
Ultra-high resolution MS
LTQ-FT
LTQ-Velos Orbitrap
Q-Exactive HF
Thermo Fusion

Unequivocal Identification
MS^n; UHRAM MS; 1-D, 2-D NMR; ion Mobility; Chemical Reactivity, etc

Data extraction

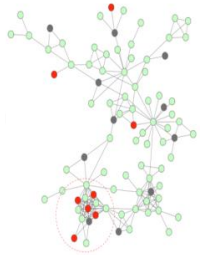
Data Table
m/z, RT, Intensity
Quality metrics

Biostatistics
Bioinformatics



Metabolites of interest

Metabolite forensics

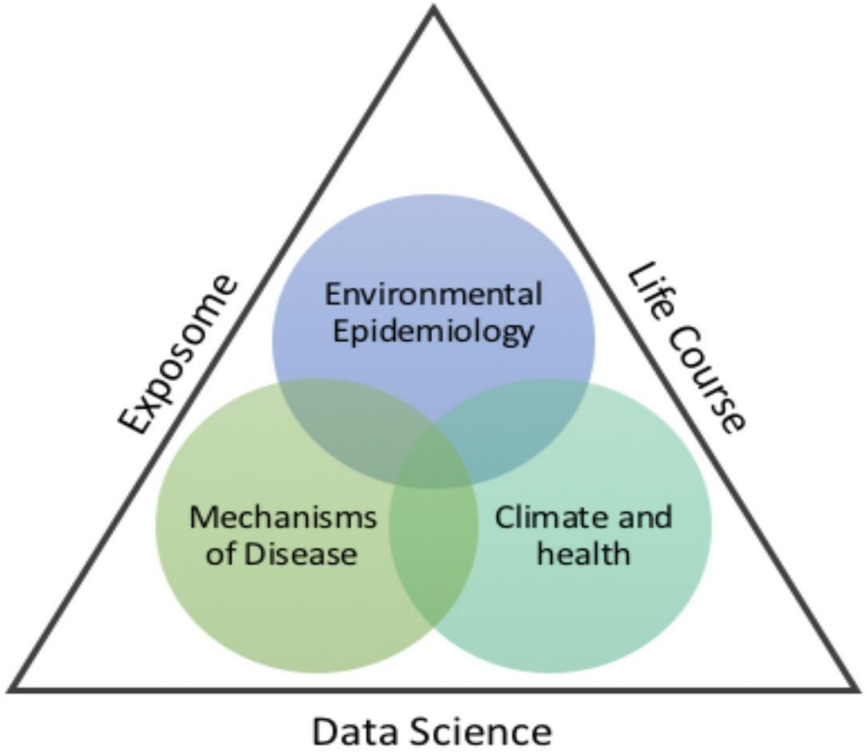


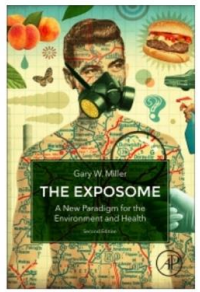
Network and pathway analysis: *Mummichog*, MetabNet, others

T Yu et al 2009 Bioinformatics 25:1930-6
JM Johnson et al 2010 Analyst 135: 2864-2870
Q Soltow et al 2013 Metabolomics 9:S132–S143
T Yu et al 2013 J Proteome Res 12:1419-27
S Li et al 2013 Plos Comp Biol 9:e1003123
K Uppal et al 2013 BMC Bioinformatics 14:15
K Uppal et al 2015 Frontiers Bioeng Biotech 3:87

DP Jones 2016 *Tox Reports* **3**: 29-45

Exposome Training Efforts





The Exposome

2nd Edition

A New Paradigm for the Environment and Health

☆☆☆☆☆ Write a review

Authors: Gary W. Miller

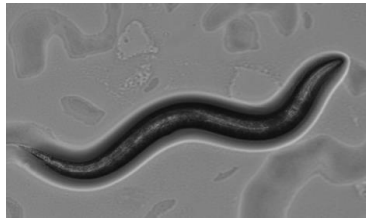
Paperback ISBN: 9780128140796

Imprint: Academic Press

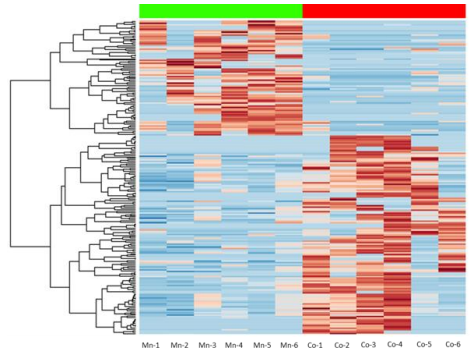
Published Date: 1st July 2020

Page Count: 320

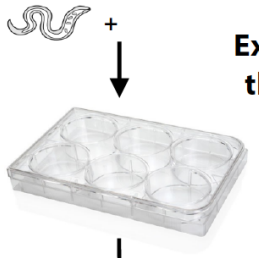
These fellows will enhance their leadership skills by facilitating our workshops, bootcamps, and mini-courses **(machine learning, data visualization, network science)** for the predoctoral trainees



The metabolomic/exposomic analysis works in as few as 500 worms



Metabolomics sample preparation



Exposure to chemical mixtures that represent the exposome

Aliquots of 500 worms stored at -80℃
Metabolites extracted in organic solvent using a bead-beater

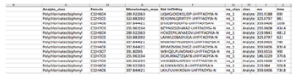
Samples run on a high-resolution metabolomics platform

Metabolomics data processing

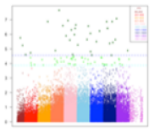
Data Table, *m/z*, RT, Intensity Quality metrics, Peak grouping/deconvolution

Biostatistics and bioinformatics

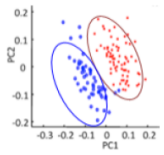
Database of m/z, time, and intensity



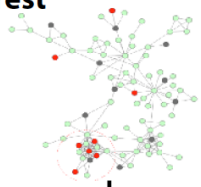
MWAS



PLS-DA

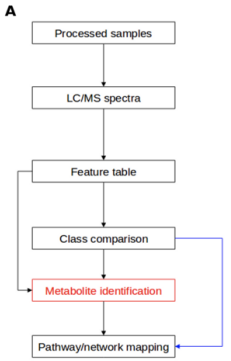


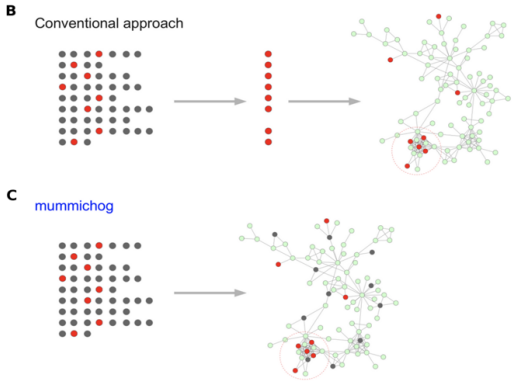
Metabolites of interest

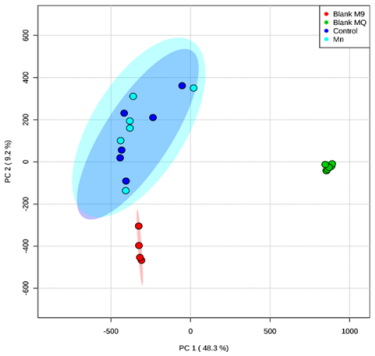


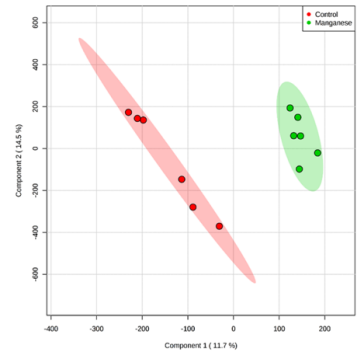
Network and pathway analysis

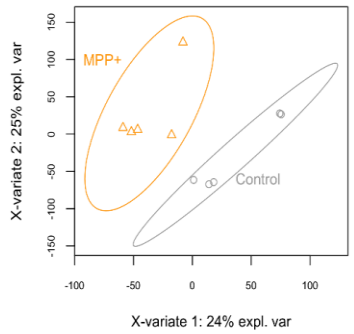
Metabolite forensics:
Spectral databases, Isotope matching, Mass defect searching, Fragments/sub-structures

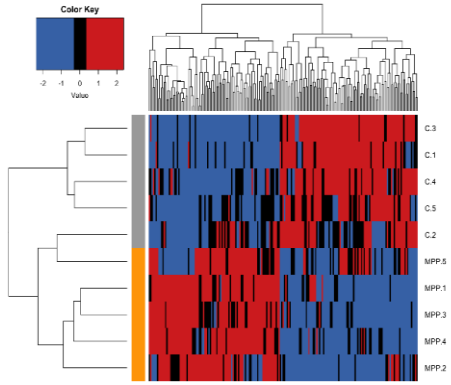


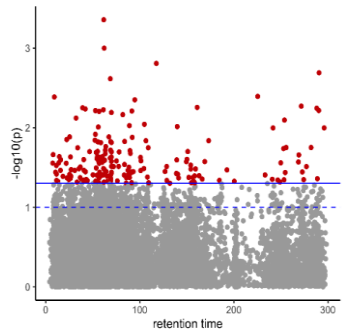


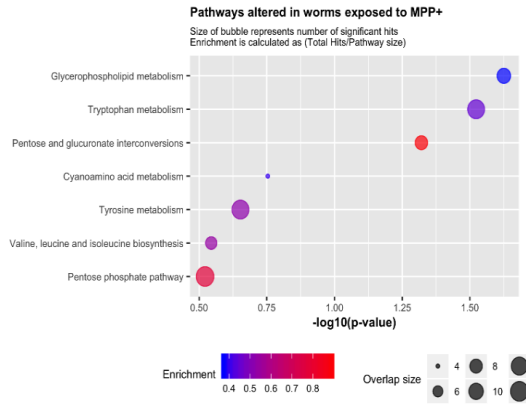




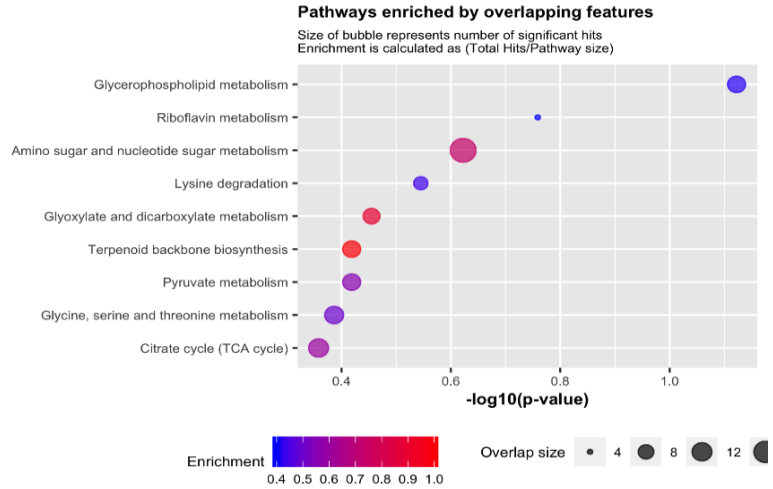


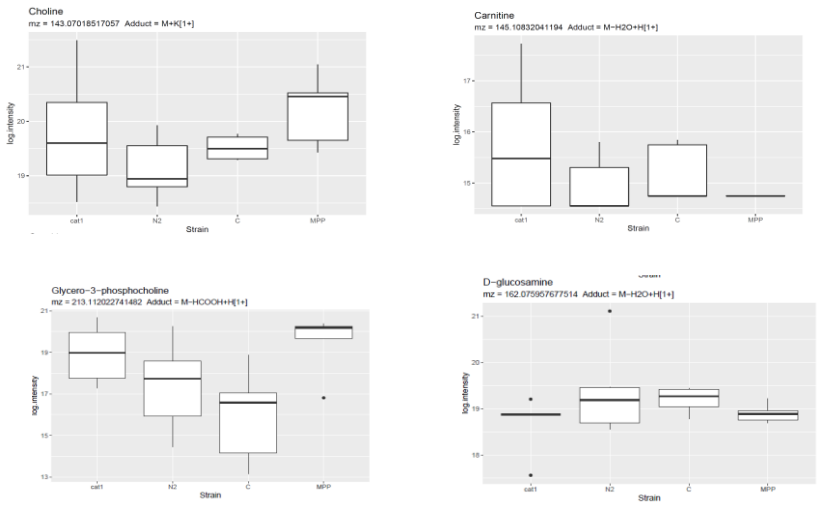






A) PLS-DA analysis comparing N2 worms with N2 worms treated with 1mM MPP+ **B)** Manhattan plot shows features higher (red) and lower (gray) in 1mM MPP+ treated N2's compared to untreated N2 worms **C)** Hierarchical clustering of features detected **D)** Top pathways altered in 1mM MPP+ treated N2 worms, using Mummichog





A) Mummichog analysis of overlapping patterns of pathway enrichment between *cat-1* (*ok411*) worms and N2 worms treated with MPP+

Global Exposome Harmonization Project

Validation inter/intra laboratory
Harmonization of exposome measures
Standardization of operating procedures
Radical transparency
Shared pooled standards
Shared bioinformatic platforms

Columbia, Mt. Sinai, Emory, Mayo Clinic, Yale, Brown (open to other participants)

Inserm (France), Masaryk Univ (Czech Repub), Utrecht (Netherlands), Antwerp (Belgium), Helmholtz (Germany), Univ of Vienna (Austria), Imperial Univ (UK)
Human Biomonitoring for the European Union (HBM4EU)

European Commission Human Exposome Network

EXPANSE: Exposome powered tools for healthy living in urban settings - Prof Roel Vermeulen, Institute for Risk Assessment Sciences, Utrecht University, The Netherlands

EQUAL LIFE: Early Environmental quality and life-course mental health effects – Dr Irene van Kamp, Senior Researcher, National Institute for Public Health and the Environment (RIVM), The Netherlands

LONGITOOLS: Dynamic longitudinal exposome trajectories in cardiovascular and metabolic non-communicable diseases – Dr Sylvain Sebert, University of Oulu, Finland

ATHLETE: Advancing tools for human early lifecourse exposome research and translation - Prof Martine Vrijheid, Barcelona Institute for Global Health, Spain

EXIMIOUS: Mapping exposure-induced immune effects: connecting the exposome and the immunome – Prof Peter Hoet, Catholic University of Leuven Belgium

HEDIMED: Human exposomic determinants of immune mediated diseases – Prof Heikki Hyöty, University of Tampere, Finland

HEAP: Human Exposome Assessment Platform - Prof Joakim Dillner, Karolinska Institute, Sweden

REMEDIA: Impact of exposome on the course of lung diseases – Dr Sophie Lanone, Research Director, French National Institute of Health and Medical Research (INSERM), France

EPHOR: Exposome project for health and occupational research – Dr Anjoeka Pronk, Senior Scientist, Netherlands Organisation for Applied Scientific Research (TNO), The Netherlands

$\sum$ Human Exposome Network and other European partners + $\sum$ Other global partners in the Americas, Japan, China, and India = Human Exposome Project…

….that rivals the Human Genome Project

$$\sum \text{Human Genome} + \sum \text{Human Exposome} = \text{True nature of health and disease}$$

Possible steps and principles

Commitment of collaboration to advance the field

Shared pooled reference material

Shared data and bioinformatic platforms

Standardized confidence levels for identification

Validation among laboratories (instrument-specific)

Investigator exchange program

Standardized operating procedures for harmonized projects

Establishment of a steering/leadership committee

Conclusions

High-resolution mass spectrometry has become the *de facto* machinery for the **exposome (in biological and environmental matrices: plasma, urine, water, dust, air, passive samplers)**

Current technologies, computational workflows, throughput, and costs/sample are insufficient for the needs of the biomedical, clinical, and environmental research communities

As such, a concerted effort to create fit-for-purpose, instrumentation, automation (technical and informatic), and computational systems is essential to balance G x E = P

ASMS

Organizers

Jarod Grossman
Agilent Technologies

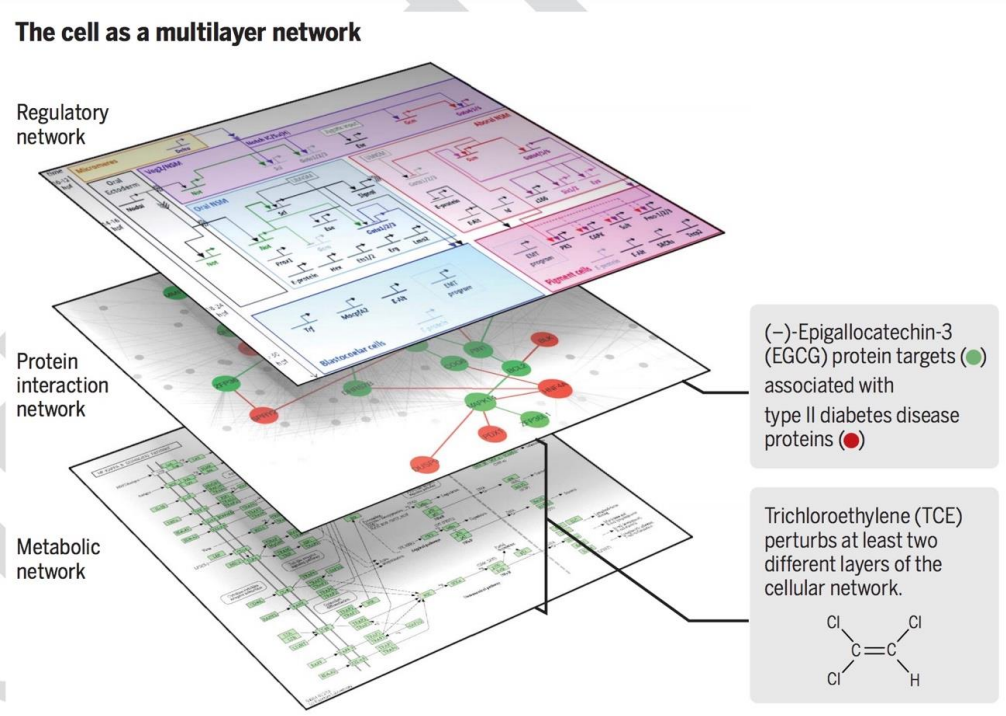
Anthony Macherone
Agilent Technologies &
Johns Hopkins University
School of Medicine

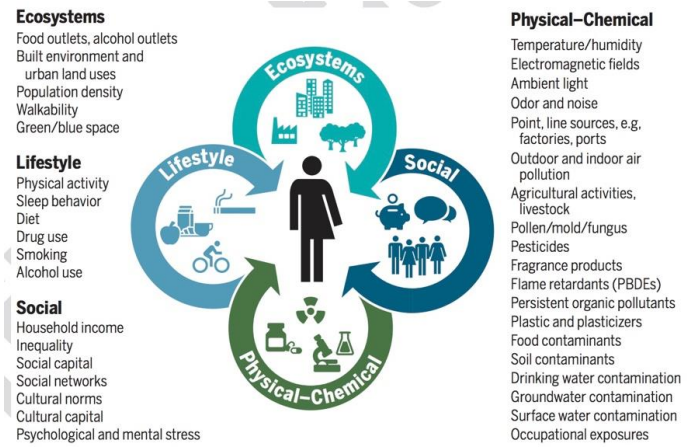
REVIEW

The exposome and health: Where chemistry meets biology

Roel Vermeulen[1,2]*, Emma L. Schymanski[3], Albert-Laszlo Barabási[4,5,6], Gary W. Miller[7]*

Despite extensive evidence showing that exposure to specific chemicals can lead to disease, current research approaches and regulatory policies fail to address the chemical complexity of our world. To safeguard current and future generations from the increasing number of chemicals polluting our environment, a systematic and agnostic approach is needed. The "exposome" concept strives to capture the diversity and range of exposures to synthetic chemicals, dietary constituents, psychosocial stressors, and physical factors, as well as their corresponding biological responses. Technological advances such as high-resolution mass spectrometry and network science have allowed us to take the first steps toward a comprehensive assessment of the exposome. Given the increased recognition of the dominant role that nongenetic factors play in disease, an effort to characterize the exposome at a scale comparable to that of the human genome is warranted.





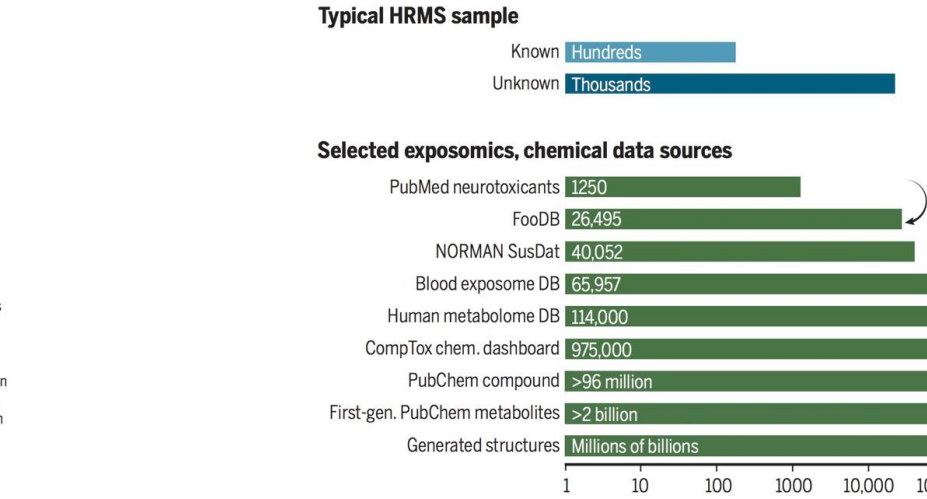


Fig. 2. Chemical complexity of HRMS and the exposome. Top: Known versus unknown features in a typical HRMS measurement [data from (*7*)]. Bottom: Selected data sources relevant to the chemical exposome (*10–14*, *19*). Arrows show the overlap of potential neurotoxicants in FooDB (http://foodb.ca/) and FooDB components in NORMAN SusDat (www.norman-network.com/nds/susdat/) (prioritized chemicals of environmental interest).

Science. 367: 392-396, January 24, 2020

Roel Vermeulen

&

Joakim Dillner

The European Human Exposome Network

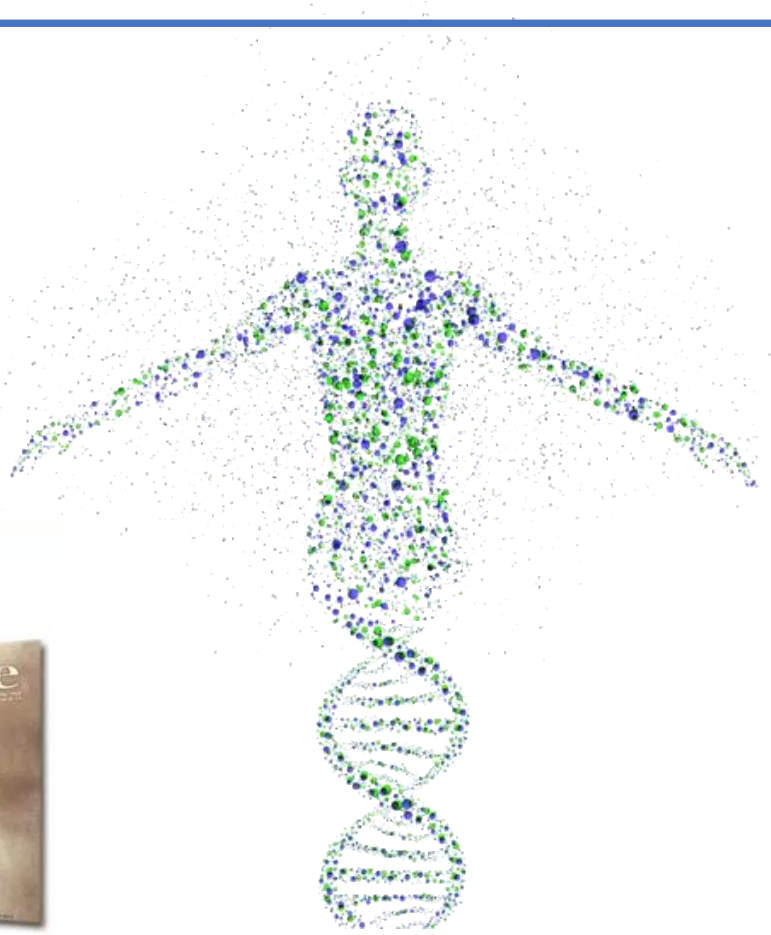
Roel C.H. Vermeulen and
Joakim Dillner
Coordinators of EXPANSE & HEAP

Currently chairing the
European Human Exposome Network

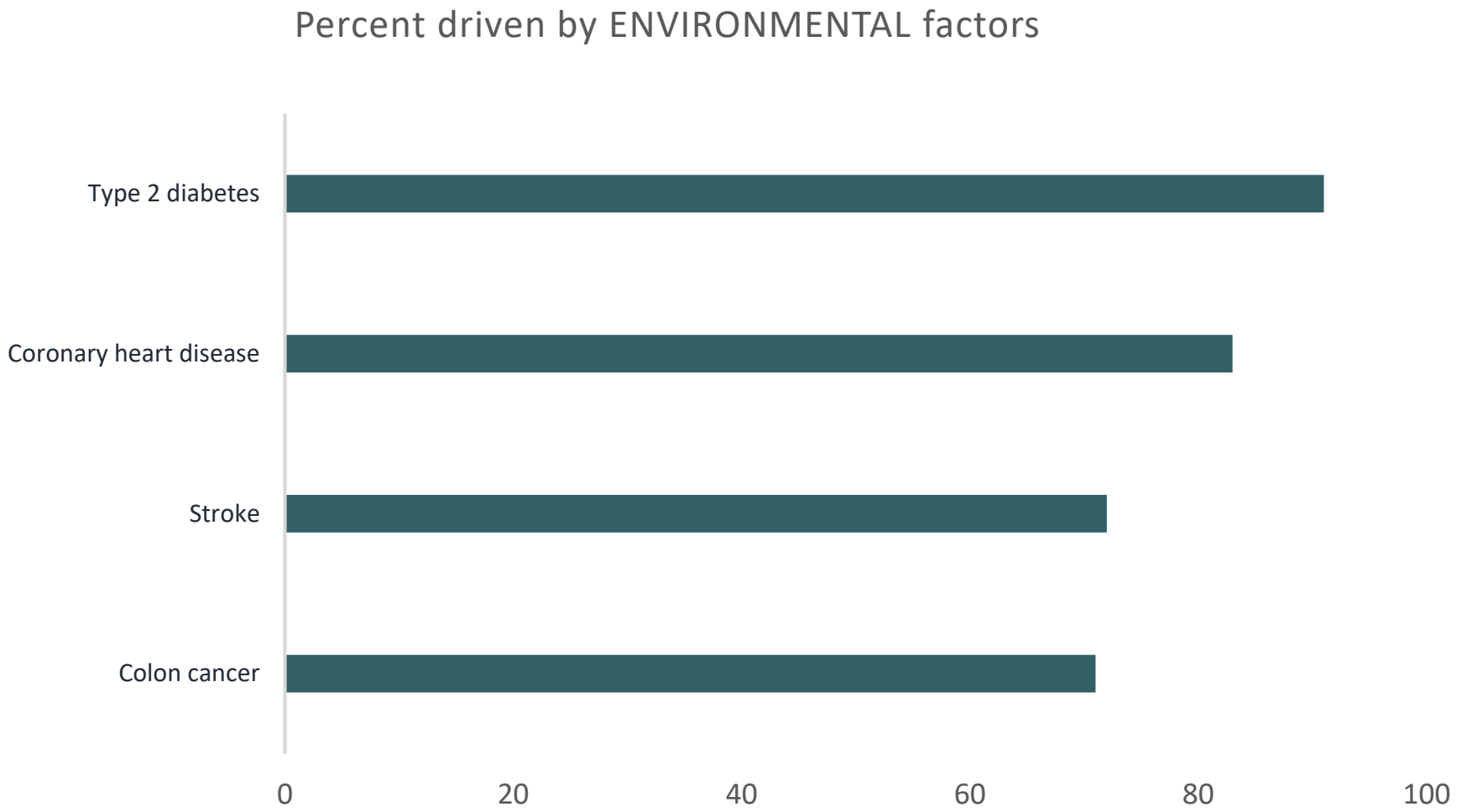
www.humanexposome.eu

Human genome project:
new level of understanding in the cause of diseases

1990 2001

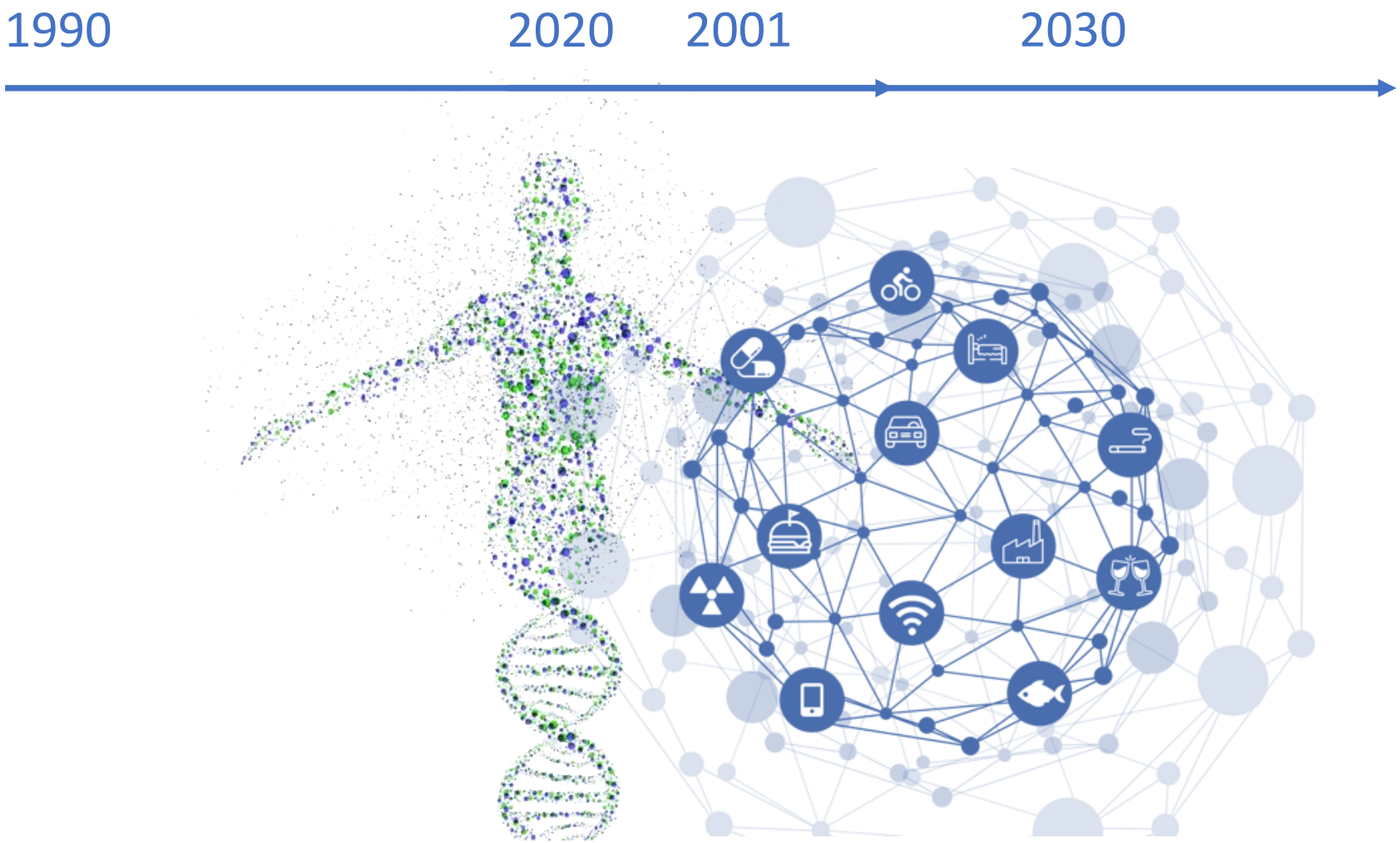


But genes do not kill (on their own)



Walter Willet, 2002

Human EXPOSOME project: A paradigm shift to a new systematic understanding of the cause of diseases



For the health of our citizens, our children and grandchildren, Europe needs to move towards a zero-pollution ambition. I will put forward a cross-cutting strategy to protect citizens' health from environmental degradation and pollution, addressing air and water quality, hazardous chemicals, industrial emissions, pesticides and endocrine disruptors

EXPOSOME

The human exposome encompasses exposures to environmental factors **throughout life**, starting from conception and pregnancy.

Environmental factor exposures are diverse

POLLUTION

DIET

URBAN

And have an impact on our health

The European Human Exposome Network

126
Research groups

24
Countries

9
Large-scale projects

106
Million euros from the European Commission

One Common Goal

Understanding the health impacts of a lifetime of environmental exposures

Nine large consortia in a formalized collaboration

ATHLETE - Advancing tools for human early lifecourse exposome research and translation

EPHOR - Exposome project for health and occupational research

EQUAL-LIFE -Early environmental quality and life-course mental health effects

EXIMIOUS - Mapping exposure-induced immune effects: connecting the exposome and the immunome

EXPANSE - Exposome powered tools for healthy living in urban settings

HEAP - Human exposome assessment platform

HEDIMED - Human exposomic determinants of immune mediated diseases

LONGITOOLS - Dynamic longitudinal exposome trajectories in cardiovascular and metabolic non-communicable diseases

REMEDIA - Impact of exposome on the course of lung diseases

Goals of today

Actually measuring the environmental exposures……..

- How could this affect the health and welfare of all of us in EU?
- What are the biological effects of the different exposures?
- How could the data on exposures help us to promote a healthy environment?
- What could be done to promote *data-driven* interventions towards a healthier environment?

COFFEE BREAK 11:00-11:30

Research and Innovation

Audience participation in the panel discussions

Go to www.menti.com
and use the code
86 98 50

Social media

Relevant hashtags:
#**Exposome**
#EUHealthResearch
#H2020
#HumanExposome

EC Twitter tags:
@EUScienceInnov
@EU_H2020

EXPANSE

European Human Exposome Project

EXPANSE

Roel Vermeulen - Utrecht University

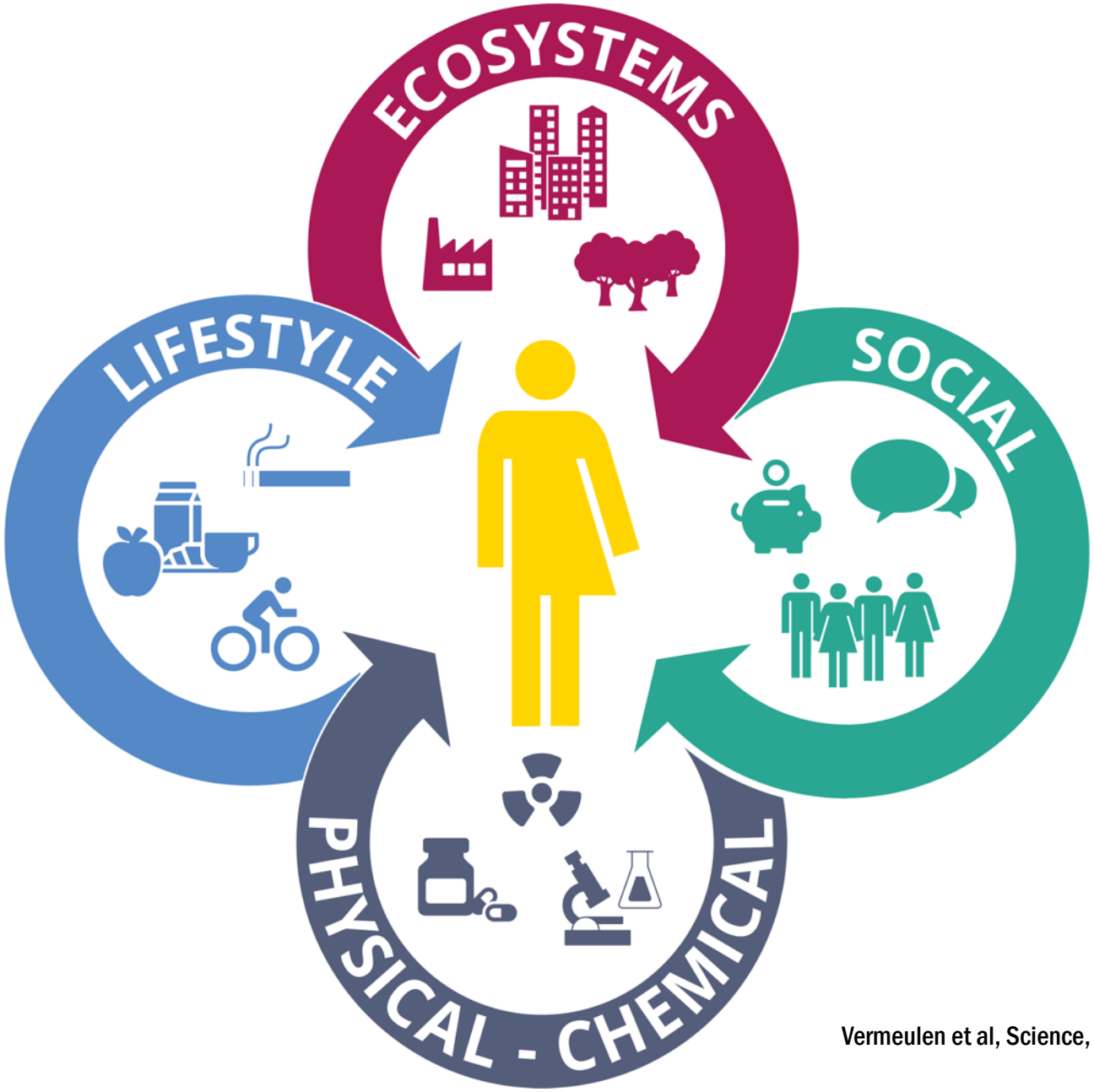
Utrecht University

Why focus on urban?

EXPANSE will address one of the most pertinent questions for urban planners, policy makers, and inhabitants in Europe:

“How to maximize one’s health in a modern urban environment?”

EXPANSE defines the Urban Exposome as the complex mixture of social and environmental factors in the urban environment that collectively have an impact on health

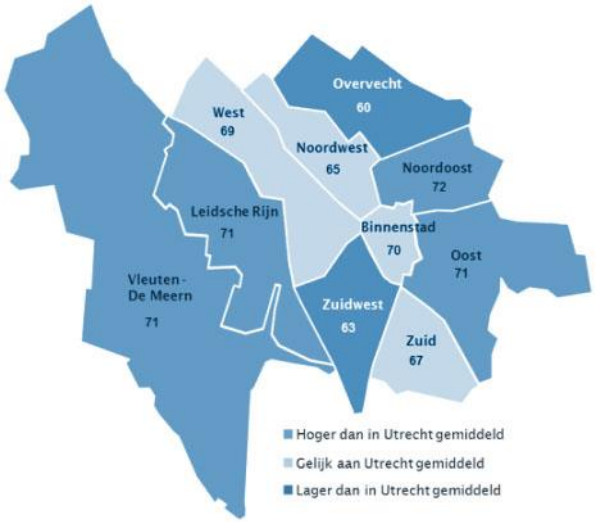


Vermeulen et al, Science, 2020

Why is this important?

Reduced burden of NCDs

Utrecht, The Netherlands



How will EXPANSE reach that goal?

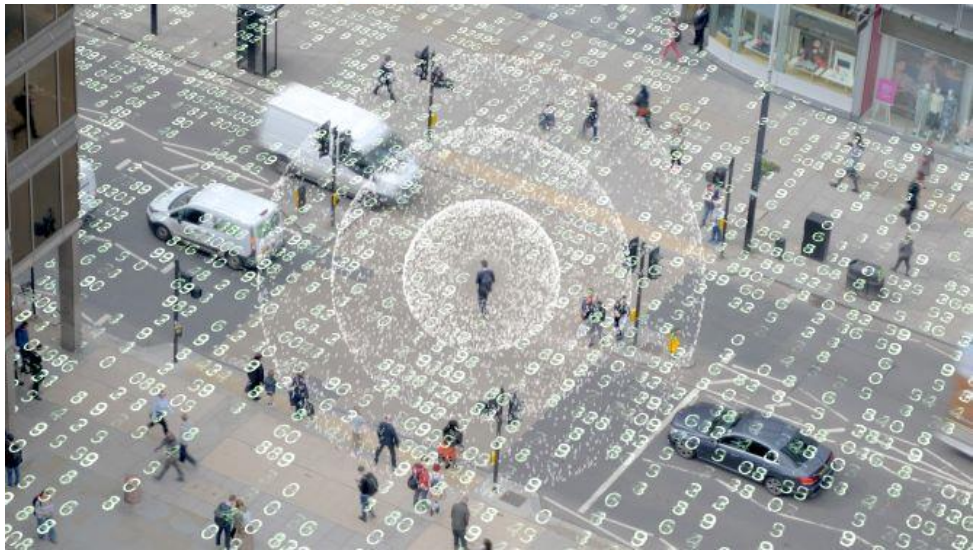
Personalised urban exposome and health assessment over the life course for 55 million European inhabitants across 12 countries

>25,000 DNA methylation, transcriptomic, proteomic and microbiomics profiles

10,000 de novo ultra high resolution mass spectrometry profiles using a novel approach detecting thousands of exogenous and ten-thousands of endogenous compounds

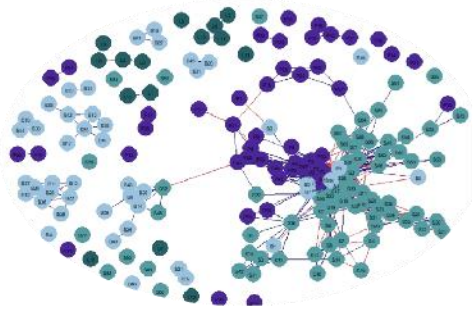
Novel big data approaches to identify the life course impact of the urban exposome on population clustering, their biological consequences, and cardio-metabolomic-pulmonary health

Large scale tracking and natural experiments in the urban labs

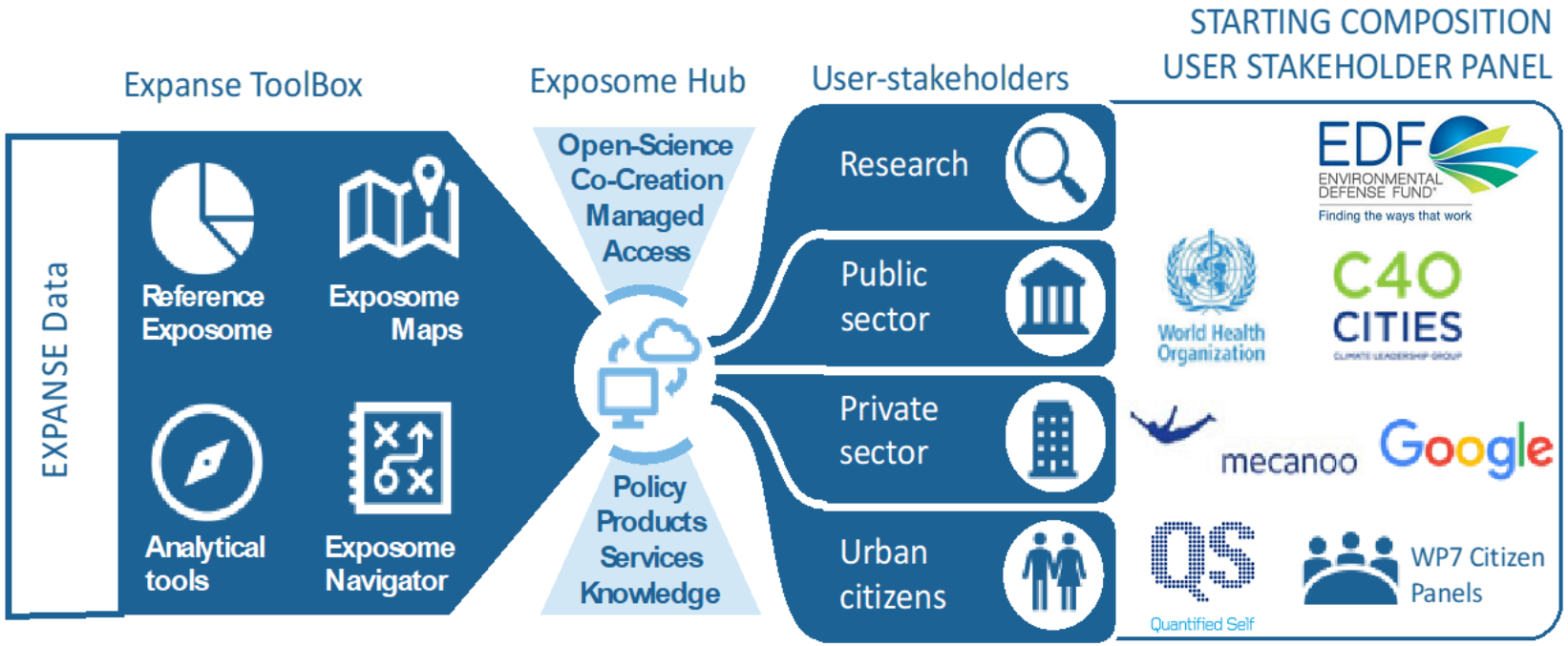


What will EXPANSE deliver in 5 years.....

Reference
Exposome



What are the critical needs for success?



Large data-pooling
Infrastructure (EIRENE)
GDPR

Open Science
DORA
OSCU

Active involvement of stakeholders
Stakeholder panel

Acknowledgements

our partners

Karolinska Institute

Sweden

Helmholtz Zentrum

Germany

Imperial college

United Kingdom

UMC Utrecht

The Netherlands

VU Medical Centre

The Netherlands

Game Solutions Lab

The Netherlands

M2M4ALL

The Netherlands

Columbia University

US

ICAHN School of Medicine

US

Tartu Ülikool

Estland

Instytut Medycyny Pracy

Poland

Institut de la Salut Global

Spain

Azienda Sanitaria Locale Roma

Italy

Masarykova Univerzita

Czech Republic

Jagiellonian University

Poland

Institute National de la Sante

France

IARC

France

Schweizerisches Tropen und Public Health Institut

Switzerland

Acknowledgements

user stakeholder panel

Environmental Defense Fund

World Health Organization

C40 Cities Network

MECANOO

GOOGLE

BERTHA Aarhus University

CANUE program

Quantified self

Utrecht University

EQUAL-LIFE

Research and
Innovation

EU-Humane Exposome Project

Early Environmental quality and

Life-course mental health effects (Equal-Life)

Irene van Kamp

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874724

What is Equal-Life about?

- **Objective #1**: Enhance cognitive development and mental health at early life stages by improving the physical and social environments;
- **Objective #2:** Define and map the (environmental) health enhancing mental health and cognitive development;
- **Objective #3**: Compose and explore a set of interventions for different life-stages with the purpose to enhance the quality of locations and spaces relevant for children's activities;
- **Objective #4**: Develop a "living" Equal-Life digital Toolkit and Guidance document anticipating scenarios of changes in environments relevant for different developmental phases.

Why is this important?

Specific challenge in the call

- Improve Health
- Provide new and improved knowledge of health risks
- Building blocks for a set of future interventions
- More complete and accurate exposure data
- Toolkit and guidance document

And how we will achieve them

- Mental health enhancing environments will be defined for different life stages in of children and adolescents, developing the exposome in a sensible manner.
- Link exposure and micro data are linked to longitudinal data on child development and early indicators of mental health.
- Analysis of the complex pathways for different age groups in different settings.
- Combine data at different levels with social data and data gathered with new devices such as sensors, devices and heads.
- Describing a set of interventions co deigned with different stakeholders in several cities

Design, Steps Activities and Data Sources,

Time Line

STEPS	ACTIVITIES	Sources & data
1 DEFINE	**WP1 &4** describe Mechanism, fomulate questions and hypothesse	**Literature** **Theory** **New exposure data (experiment, sensors)** **New Outcome data**
2 CONSULT & SELECT	**WP8** discuss with stakeholders And cities >> SELECT	
3 COLLECT *Model* *Measure* *Datamining* *Enrich*	**WP1, 2, 3, 4, 5** Primary and Secondary Data collection	**GIS-based historical data** **Measures** **Internet**
	WP6 & 7 Collect multimodal exposure data with health data and relevant factors Case control>>> biomarkers	
4 MATCH		
5 ANALYSE	**WP 6 , 2, 7** Apply mixed methods for analysis (targeted and untargeted)	**Birth cohort data** **School data** **Longitudinal data**
6 TRANSLATE RESULTS *Interventions* *Tools*	**WP8, WP9** Translate results in Interventions, "live" tool : methods, data algorithms	
7 COMMUNICATION	**WP9 , WP10** Training, communication to a broader audience **WP 11** CLUSTER ACTIVITIES	

What will Equal-Life deliver in 5 years?

- ✓ Equal-Life will provide instructions for risk assessment of physical and social exposures associated with (mental) health and cognitive development of children;
- ✓Deliver publicly available toolkits for policymakers, health practitioners and others;
- ✓ Provide access to information about implementation and good practice examples for interventions.
- ✓The contribution to the Exposome Toolbox will be a set of algorithms that can be applied in different settings and guidance to stakeholder involvement and a living handbook

How will Equal-Life improve urban life ?

By the end product of our project:

- a living tool and guidance document including cues for indicators, interventions, approaches, integrated exposure data, and pooled mental health data, methods and sources, algorithms and good practices.
- new insight into the relationship between the social and physical environments and cognitive and mental health.

Together this will enhance the living conditions of children especially, but not exclusively in urbanized areas.

What are the critical needs for success?

- ✓Our Slogan is: Know each other, work together and create synergy on the impact.
- ✓Equal-Life will include representatives from most relevant stakeholders at an early stage. They will participate in Working Groups and their views will be solicited at the workshops and the project web site;
- ✓Equal- Life will organize joint meetings with other initiatives and projects to reduce costs according to the EU wishes for projects under the same call.

Partners and Advisors

LONGITOOLS

Research and
Innovation

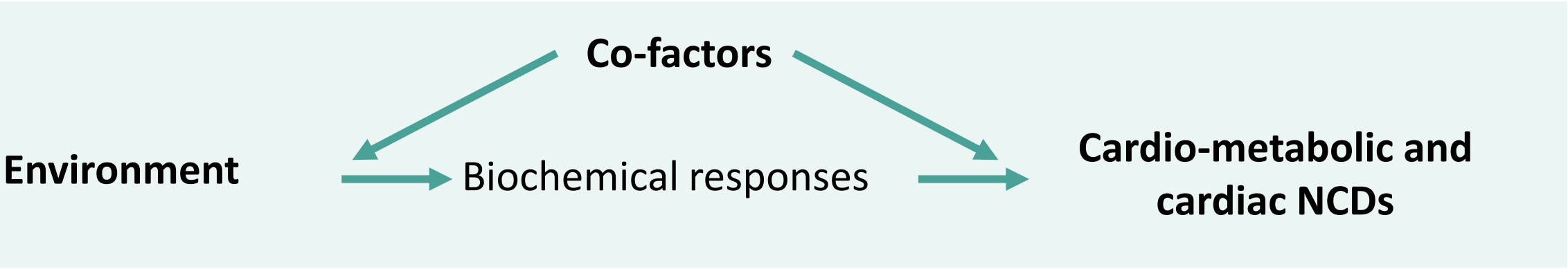
European Human Exposome Project

longITools

Sylvain Sebert

University of Oulu - FI

What is longITools HEALTH & ENVIRONMENT DYNAMICS about?



[long].[IT].[Tools]

Longitudinal
Understanding changes
Borrowing power from repeated measures

IT
Data servers
FAIR data
Computation and statistics

Tools
Apps
Policies
Innovation platform

Why is this important?

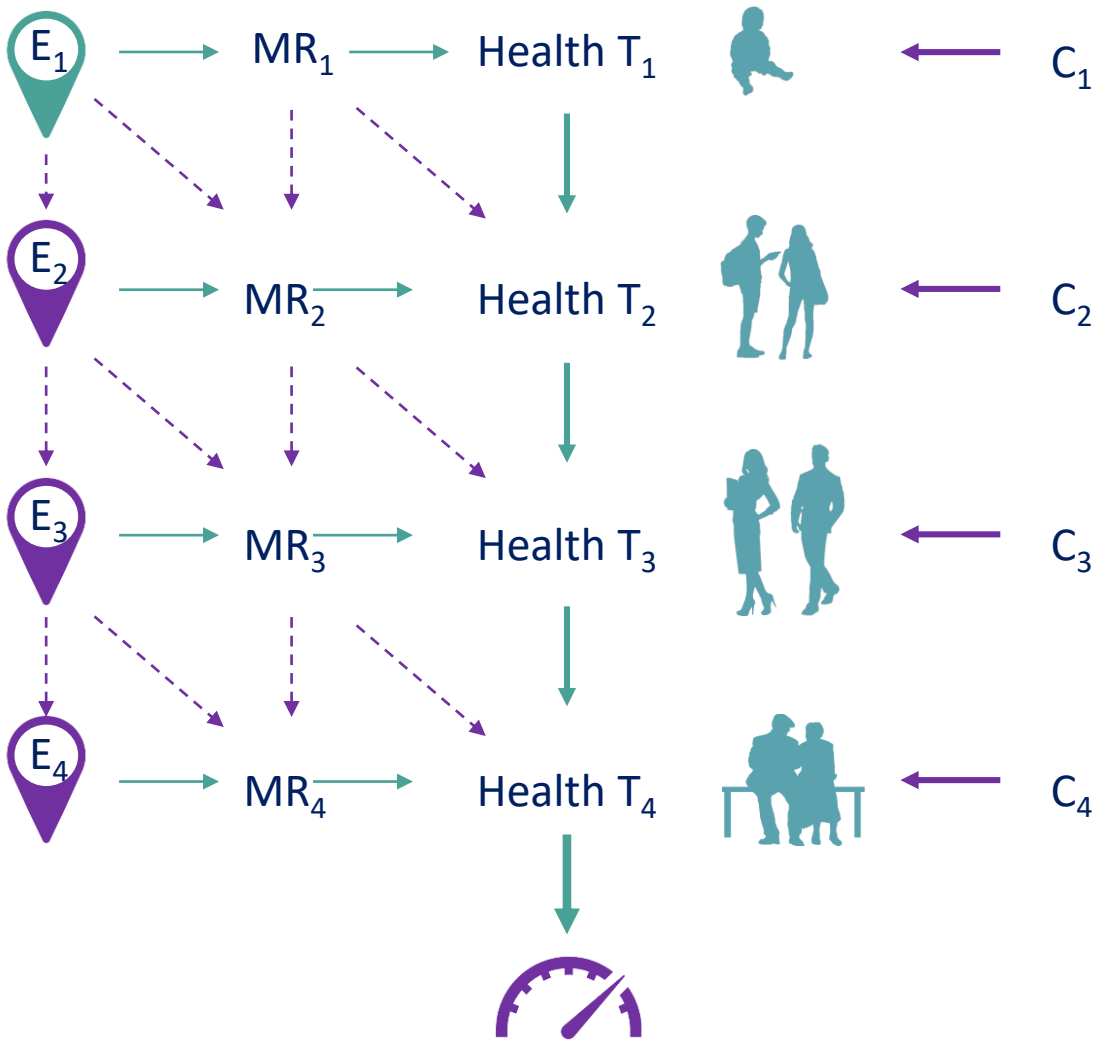
- Society is **ageing**
  - Cardio-metabolic and cardio-vascular diseases leading cause of morbidity and mortality
    - Large proportion of the attributed **risks** are **man-made**
      - Entrenched in the **social and geographical context**
        - Sustainable intervention acts via causal pathways

THU 23 JAN

Research to build on data from 11 million European citizens

Consortium's research will build on life-course data to study cardio-metabolic health trajectories from birth to old age.

Life-course **exposome** of cardio-metabolic health



Capacities and **opportunity** for changes

Models and simulation

CVD **health** and **economic** burden

What will longITools deliver in 5 years?

HEALTH & ENVIRONMENT DYNAMICS

FAIR METADATA

THU 23 JAN

Research to build on data from 11 million European citizens

longITools HEALTH & ENVIRONMENT DYNAMICS

ABOUT | PARTNERS | NEWS & EVENTS | IMPACT | PUBLICATIONS | CONTACT | INNOVATION PLATFORM

INNOVATION PLATFORM

Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua.

Leverage agile frameworks to provide a robust synopsis for high level overviews. Iterative approaches to corporate strategy foster collaborative thinking to further the overall value proposition. Organically grow the holistic world view of disruptive innovation via workplace diversity and empowerment.

Author

Title

Date of publication

Topic area

Link (URL)

Summary

SUBMIT TO THE INNOVATION PLATFORM

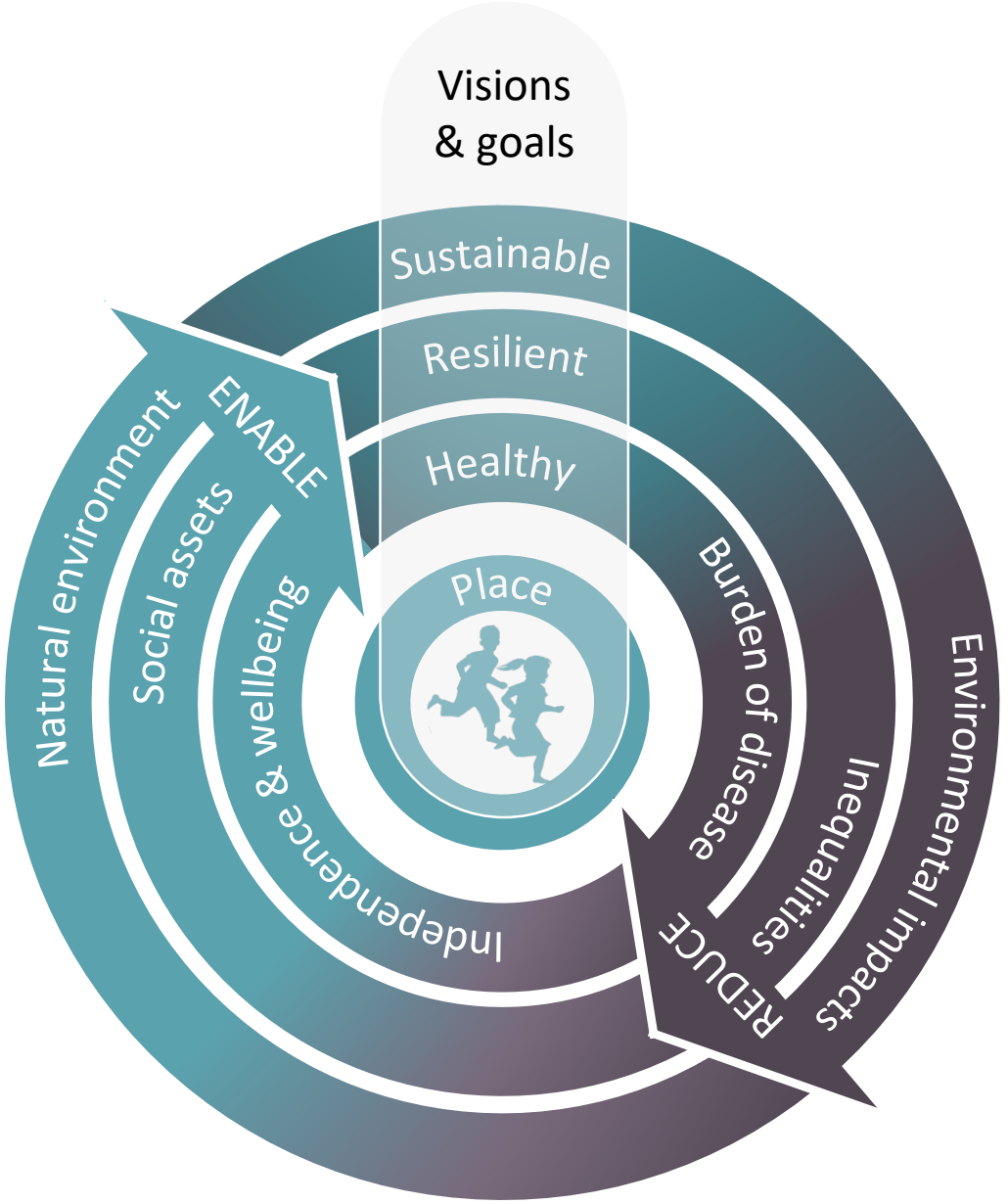
Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua.

Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua.

Lorem ipsum dolor sit amet, consectetur adipisicing elit, sed do eiusmod tempor incididunt ut labore et dolore magna aliqua.

longITools
HEALTH & ENVIRONMENT DYNAMICS

Co-create a one health approach to improve urban life



What are the critical needs for success?

(i) Stakeholder **interaction**

Co-creative workshops

Proof-of-concept applications

Synthetic data for simulation

Expertise

(ii) EU – Human Exposome network – **Interaction**

Reusable and interoperable data

Publicly available methods with online training

Identification of gaps and overlaps

Environmentally-friendly and stress-free meetings

University of Oulu

Finland

Erasmus MC

The Netherlands

Imperial college

United Kingdom

Betatechnology

United Kingdom

University of Eastern Finland

Finland

Chalmers University of technology

Sweden

University MC Groningen

The Netherlands

National Institute of medical research

France

University college London

United Kingdom

University of Utrecht

The Netherlands

University of Surrey

United Kingdom

Amsterdam MC

The Netherlands

University of Oslo

Norway

University of Bristol

United Kingdom

University of Barcelona

Spain

Abacus

Italy

Cynexo

Italy

University of Rome Tor Vergata

Italy

Audience participation in the panel discussions

Go to www.menti.com
and use the code
86 98 50

Social media

Relevant hashtags:
#**Exposome**
#EUHealthResearch
#H2020
#HumanExposome

EC Twitter tags:
@EUScienceInnov
@EU_H2020

Panel: Exposome and urban life

Moderator: Anya Sitaram, Rockhopper Media, IE

- **Annette Peters**, Director, Institute of Epidemiology, Helmholtz Centre for Environmental Health, DE
- **Laura Hetel**, Policy Officer, Future Urban and Mobility Systems, DG Research and Innovation
- **Peter van den Hazel**, President, Health and Environment Alliance, BE

- **Roel Vermeulen**, Professor of Environmental Epidemiology and Exposome, Institute for Risk Assessment Sciences, Utrecht University,NL
- **Irene van Kamp**, Senior Researcher, National Institute for Public Health and the Environment (RIVM), NL
- **Sylvain Sebert**, Associate Professor in Developmental and Lifecourse Biology and Epidemiology, University of Oulu, FI

European Commission

LUNCH BREAK 12:45-13:45

Please fill-in our survey:

https://ec.europa.eu/info/events/launch-event-european-human-exposome-network-2020_en

Research and Innovation

ATHLETE

Research and Innovation

European Human Exposome Network

ATHLETE

The Exposome from Evidence to Translation

Advancing **T**ools for **H**uman Early **L**ifecourse **E**xposome Research and **T**ranslation

Prof Martine Vrijheid

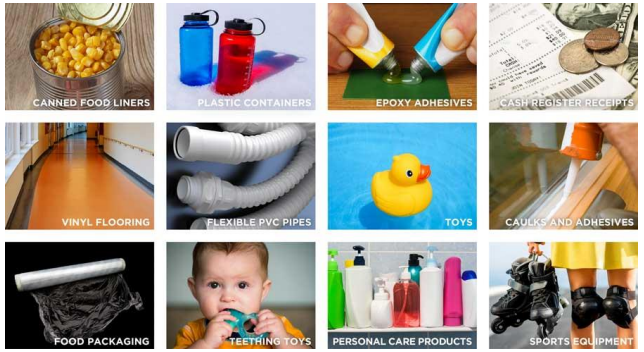
ISGlobal Barcelona Institute for Global Health

What is ATHLETE about?

ATHLETE
The Exposome from Evidence to Translation

"Better understanding and preventing health damage from **multiple** environmental agents and their mixtures, from the **earliest parts of the life course** onward"

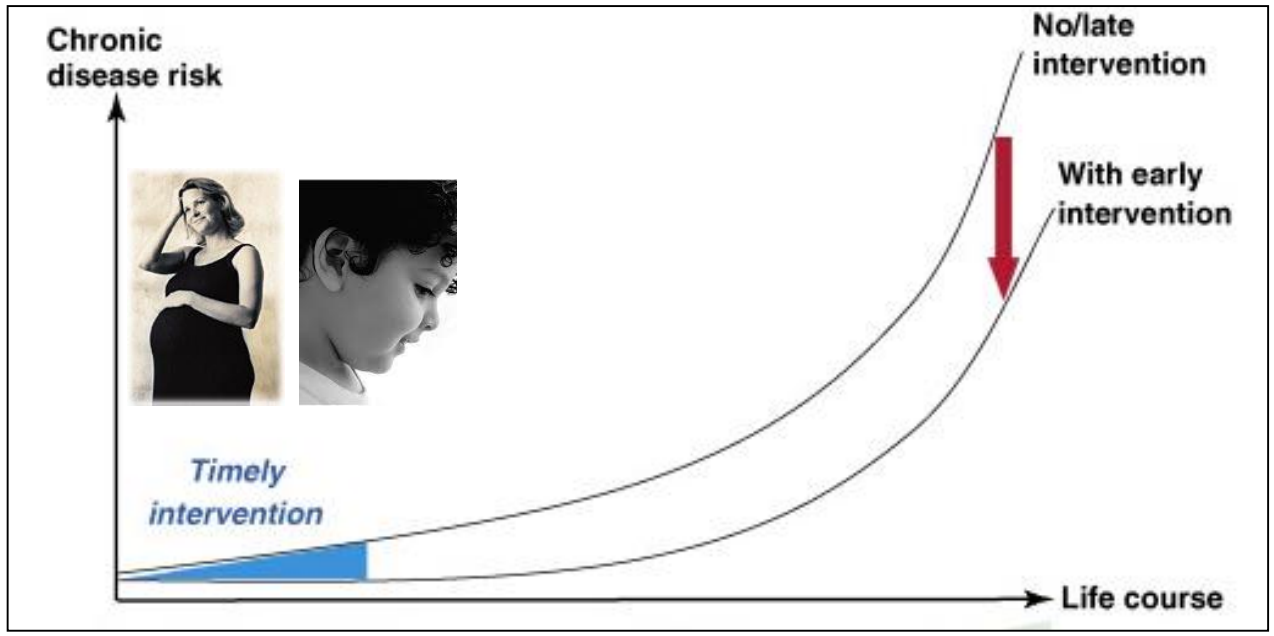
- ✓ Developing exposome **tools, data** and a **prospective exposome cohort**
- ✓ Providing new longitudinal **evidence** linking the exposome to health and biological pathways during the first 2 decades of life
- ✓ Implementing **interventions**
- ✓ **Translating** knowledge

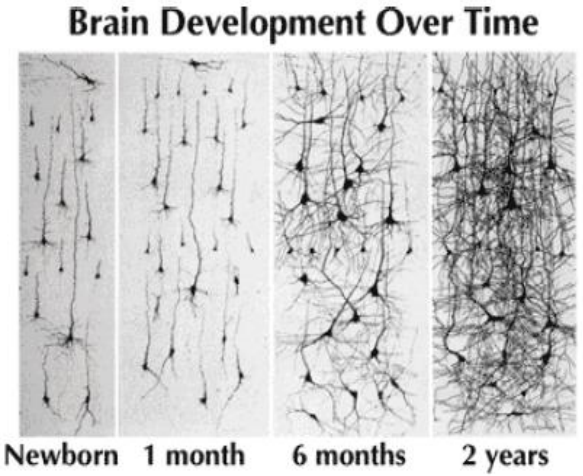


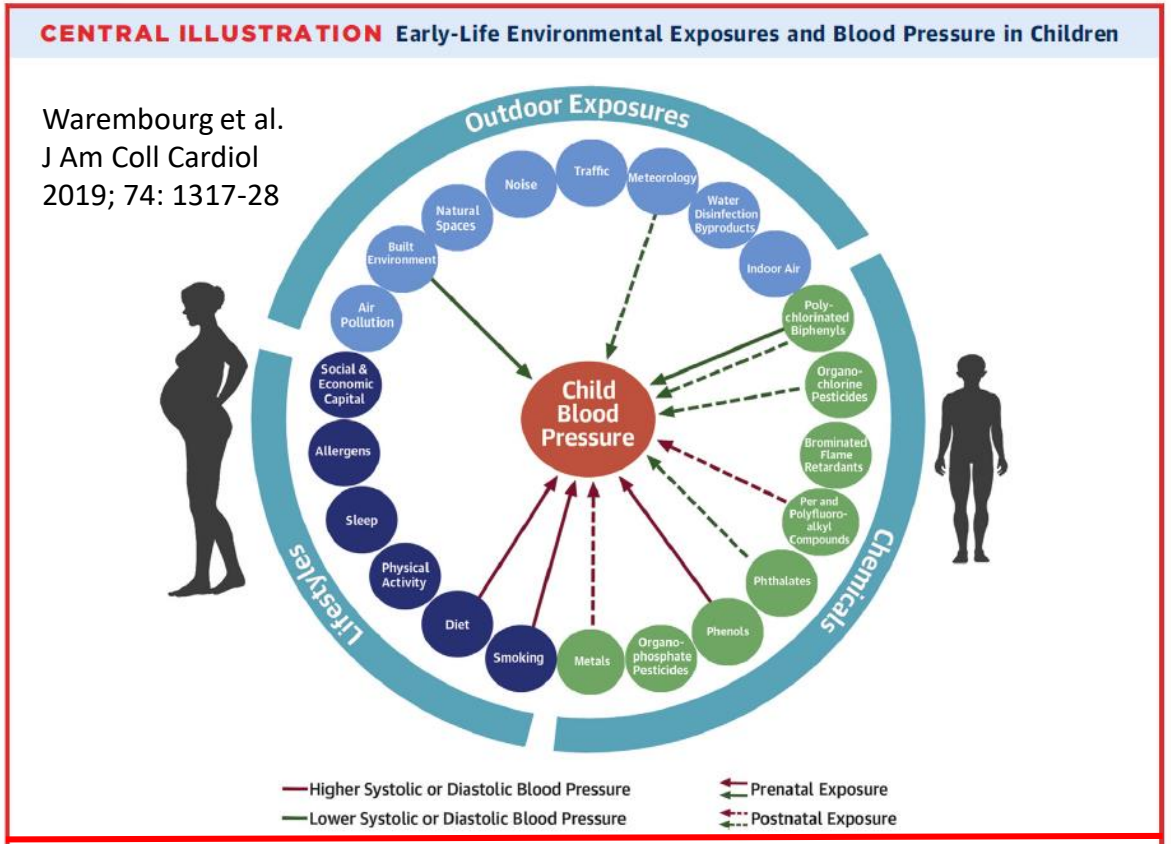
Why is this important?

EARLY LIFE *as a key target period for solid, cost-effective preventive actions and policies related to multiple adverse environmental exposures*

- ✓ Vulnerable periods of rapid organ development
- ✓ Chronic diseases have part of their origin in early life
- ✓ Lifetime influence
- ✓ Effective prevention







How will ATHLETE reach that goal?

Exposome Data and Analysis Tools

Data infrastructure
ATHLETE EXPOSOME COHORT
- FAIR
- Harmonisation
- New cohort follow-up data

Exposure science tools
- High throughput targeted biomonitoring
- Untargeted HR-MS screening
- App and wearables
- GIS, remote sensing
- Source-exposure tools

Exposome data analysis toolbox
- Agnostic data mining, longitudinal effects
- Combined exposure effects
- Causal structures
- Cross-omics
- Software, tutorials, courses, E-learning

Longitudinal Exposome Evidence

External Exposome
DRIVERS AND SOURCES
- Urban, built, traffic
- Natural spaces
- Food, consumer products
- Social deprivation
- Climate

Personal Exposome
- Chemical
- Physical
- Behavioural / lifestyle
- Social / psychosocial

Biological pathways
- Metabolomics
- Metagenomics
- Epigenetics
- Ageing / stress
- Adverse outcome pathways

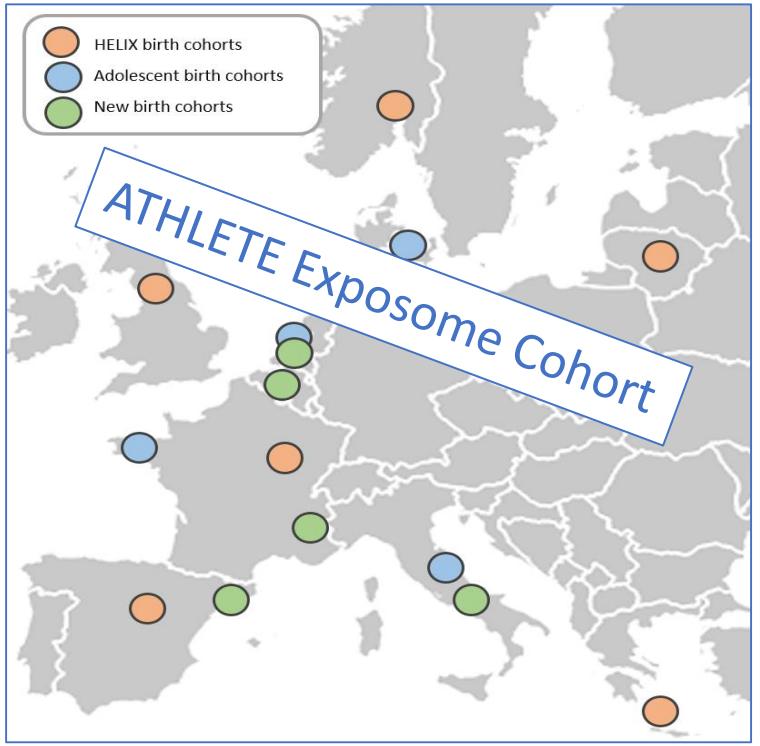
(Pre) Clinical end-points
0-18 YEARS
- Brain
- Cardiometabolic
- Respiratory

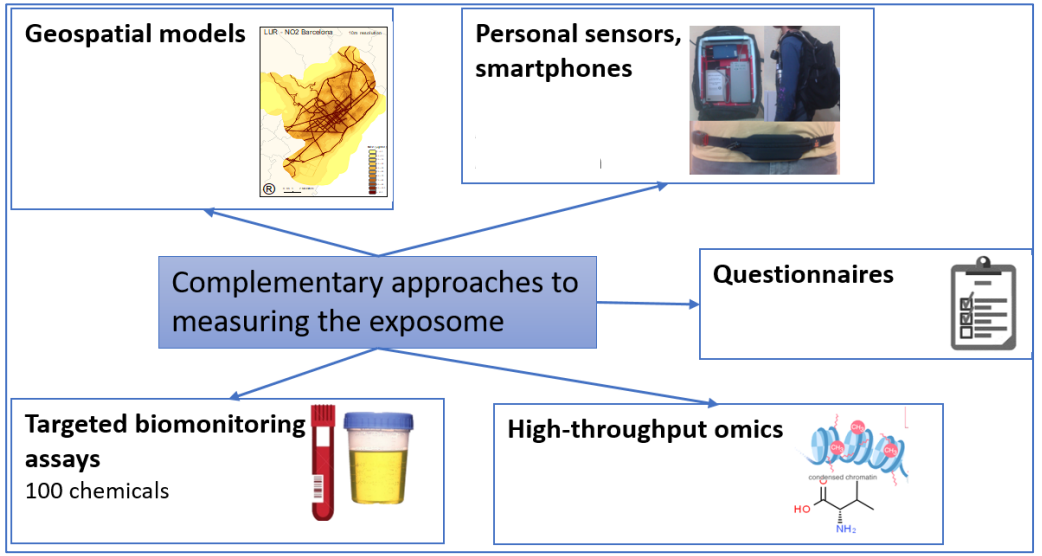
Exposome Knowledge Translation Tools

Interventions
- Urban exposome
- Chemical exposome
- Intervention priorities
- Guide for decision makers

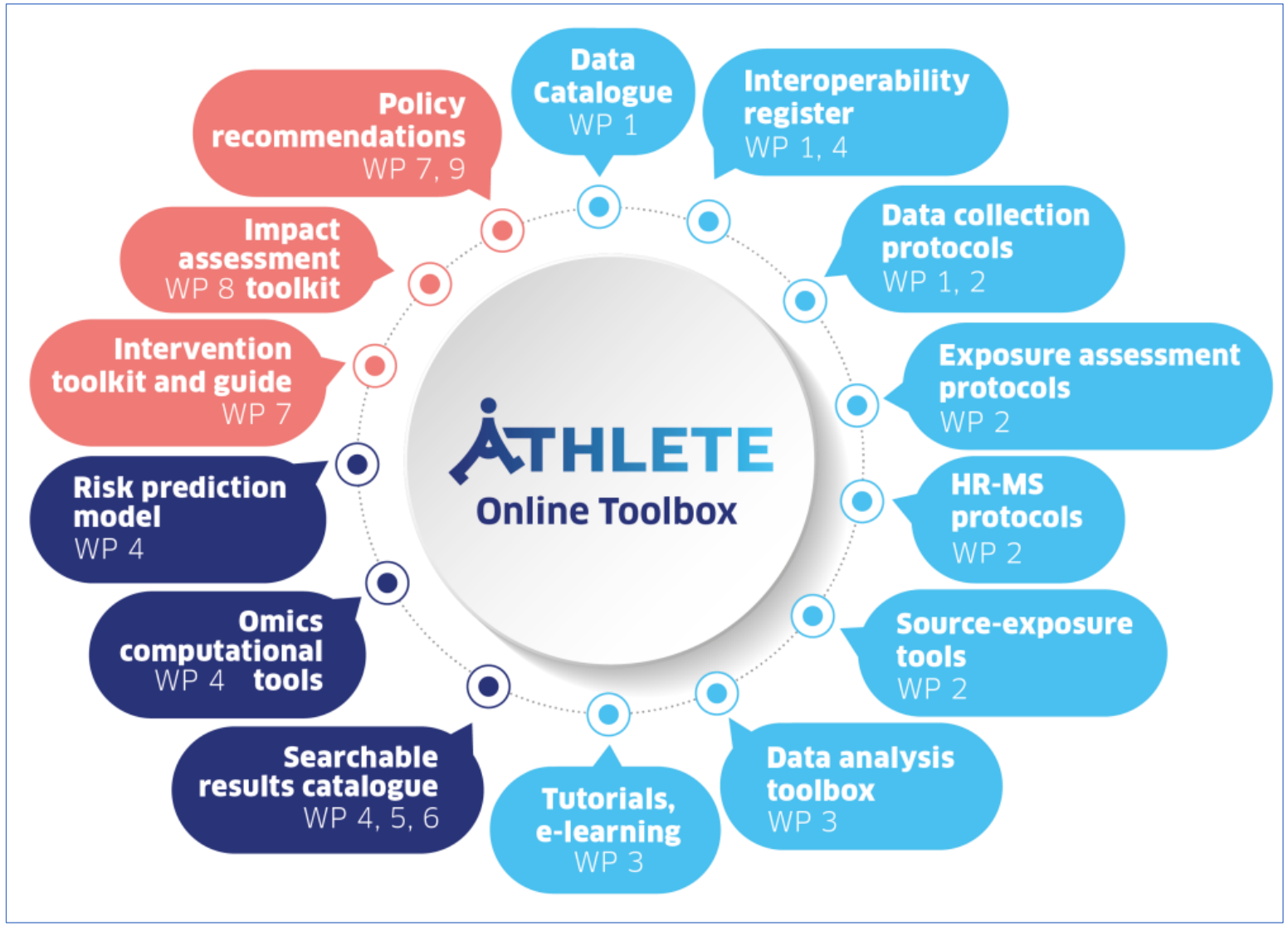
Impact assessment
- Health impact
- Economic cost
- Cost-benefit of interventions
- Uncertainty analysis
- Toolkit

Dissemination, Exploitation, Visibility
- Mapping policy framework
- Engagement of stakeholders
- Communication materials
- Policy recommendations
- ATHLETE online toolbox





What will ATHLETE deliver in 5 years?

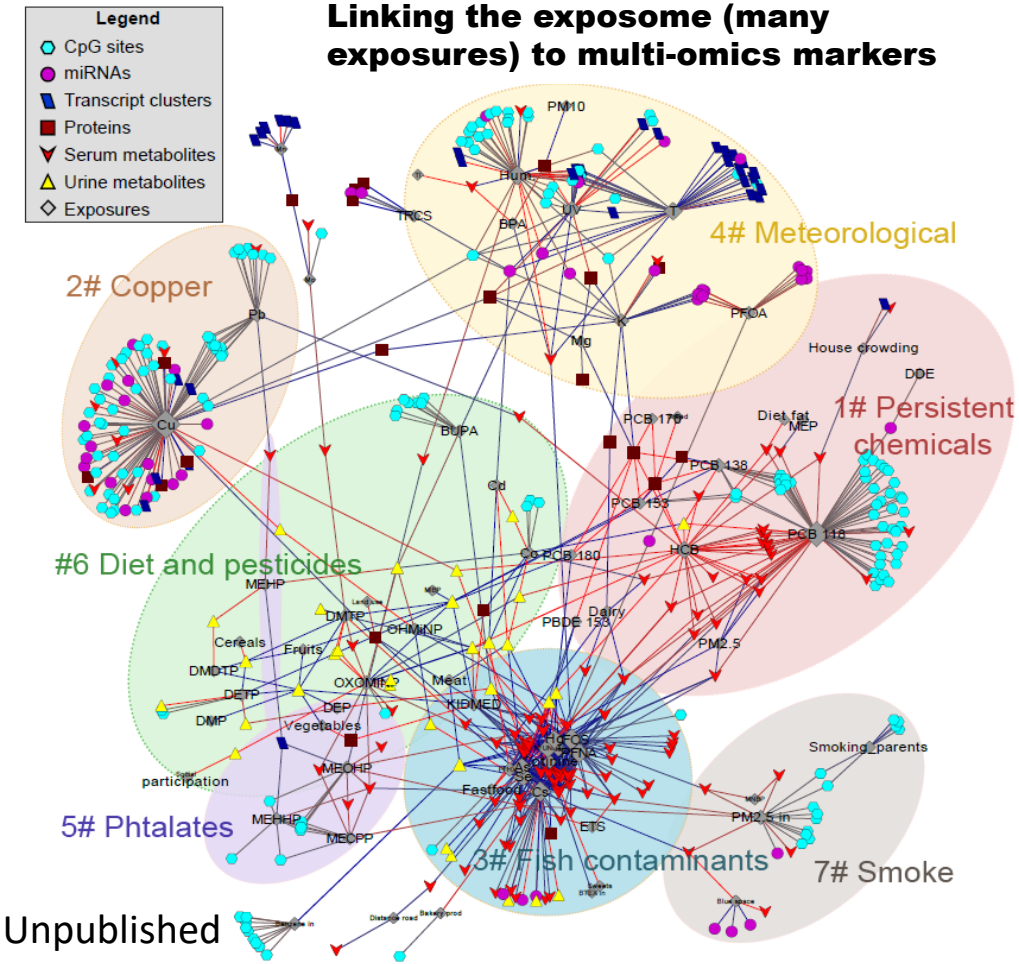


How will ATHLETE elucidate the biological effects of the exposome?

"Integrating knowledge on biological responses and pathways related to the exposome will help to better understand the **early molecular events leading to later adverse health**, and the early part of the life course is crucial to this."

Building on first results:

- ✓ Replication, tissue specificity, dynamics
- ✓ Microbiome-metabolome
- ✓ Composite scores/pathways (e.g. stress axis)
- ✓ Poly-environmental/omics prediction scores
- ✓ Adverse outcome pathways

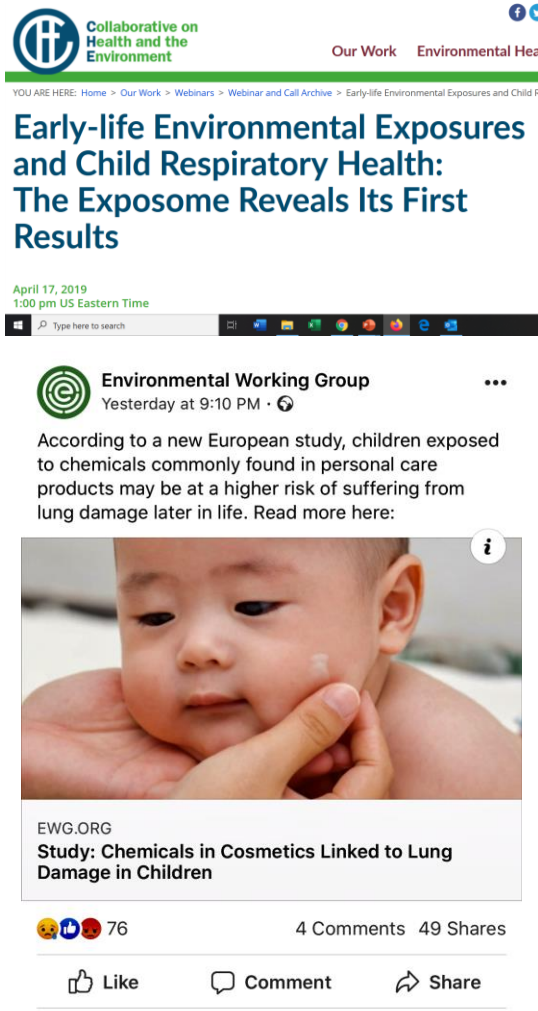


Maitre, Bustamante et al. Unpublished

What are the critical needs for success?

➢ What interaction with stakeholders do you need to make your project a success?

Who?	Example
Study participants and communities/citizens	Co-production of interventions Engaging cohort participants (adolescents)
Local policy and decision makers	Identifying barriers and enablers to intervention adoption → practical guides to modifying personal exposomes
European policy and decision-makers, international forums	Targeted events
Industry	Metabolomic profiling and smartphone APP development
Wider society	Engagement activities, social media, etc



What interaction with other projects is needed to make the network a succes?

- **Share expertise** → working groups
- **Make tools easily accessible** → one common toolbox
- **Common strategy for dissemination & stakeholder engagement**

ATHLETE

The Exposome from Evidence to Translation

22 partners
from 11 countries

❖ “This project has received funding from the European Union’s Horizon 2020 research and innovation programme under grant agreement No 874583”.

EXIMIOUS

Research and
Innovation

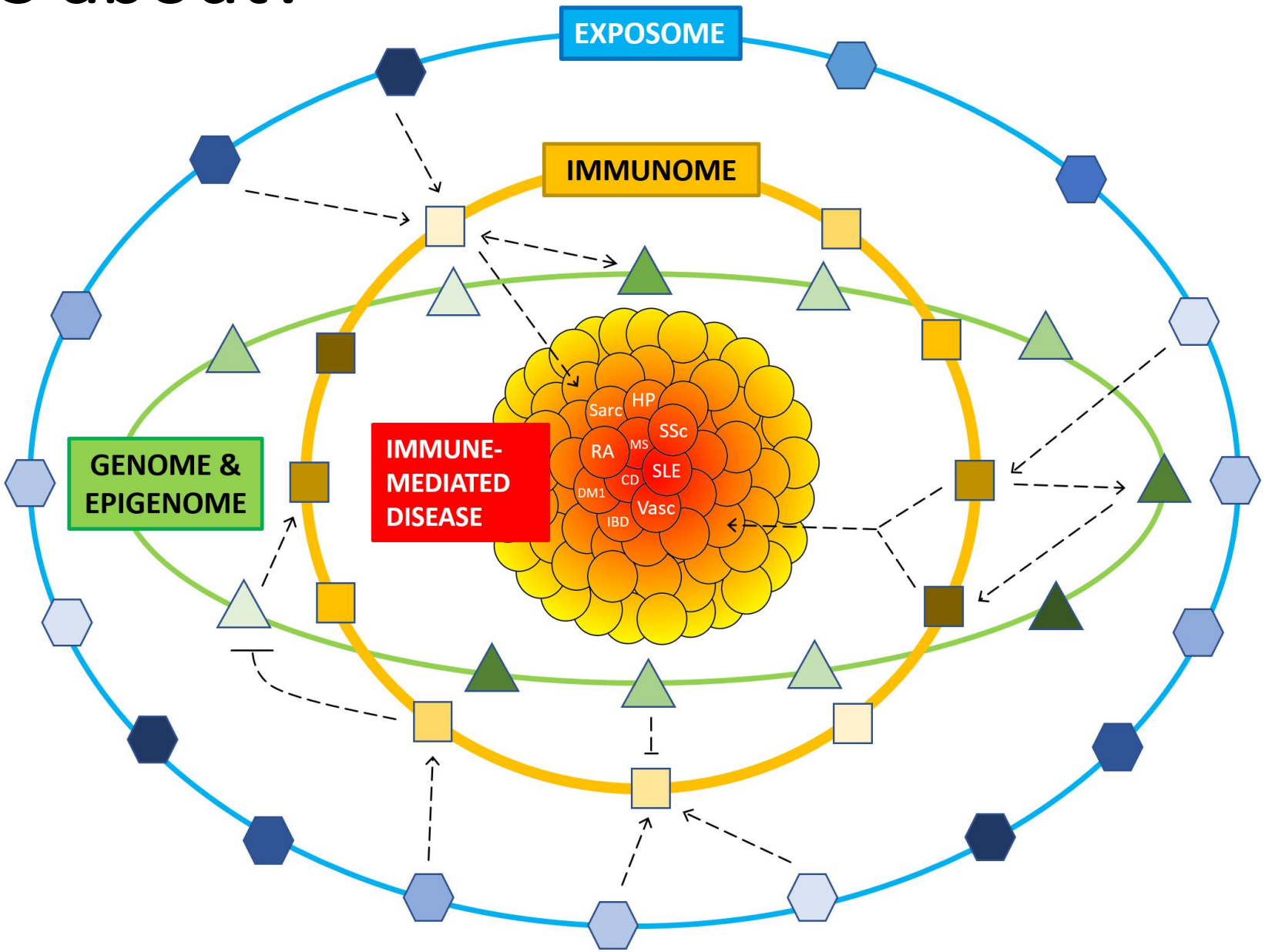
EU-Humane Exposome Project

EXIMIOUS

Mapping Exposure-Induced Immune Effects

Peter Hoet

What is EXIMIOUS about?



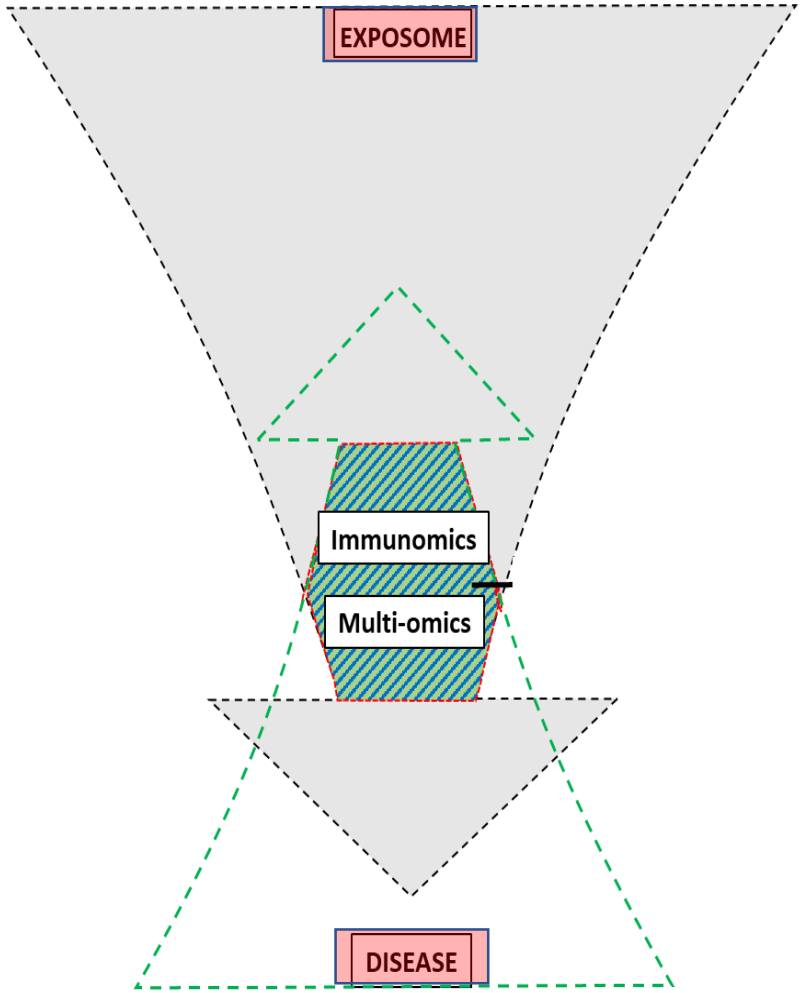
Why is this important?

- Immune-mediated disorders such as autoimmune diseases (AD) are **non-communicable chronic** diseases → pivotal role of **immune system**.
  - Affecting 7.6–9.4% of the EU population .
  - Autoimmune diseases are a leading causes of death in **women** under the age of 65.
  - Socio-economic factor → poorer people being at much greater risk.
  - Financial costs (USA) annual expenditure associated with AD ~ $100 billion

- World Health Organisation (WHO) recognised the **involvement of environmental exposure** BUT underlying causes, mechanisms and prevention remains **underexplored**

- Immune-mediated disorders represent in the hundreds of diseases or syndromes
  → generic vs disease per disease approach

How will EXIMIOUS reach these goals?



FIRST APPROACH: STARTING FROM THE EXPOSOME

Cohorts that cover the entire lifespan: general and birth cohorts (LifeLines, DOC*X and DOC*X Generation, ENVIRONAGE) and

Occupational cohorts (park workers, paint factory workers, miners, metallurgy workers, waste handlers and administrative workers).

SECOND APPROACH: STARTING FROM THE DISEASE

Cohorts with potentially exposure-related, immune-mediated diseases

e.g. systemic sclerosis (SSc), systemic lupus erythematosus (SLE), rheumatoid arthritis (RA), sarcoidosis and hypersensitivity pneumonitis (HP).

What will EXIMIOUS deliver in 5 years

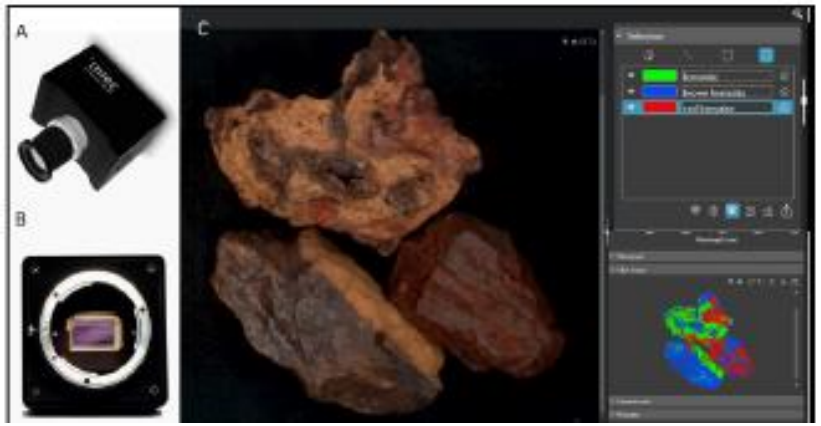
Overlapping markers ➔ ‘Immune Fingerprint’

- Exposure
  - → Reflecting person’s lifetime exposome (~ biomarker)
- Disease
  - → Reflecting person’s health

Predictors of disease at the individual level

Hyperspectral imaging (HSI) sensors:

- Rapid determination of environmental samples



How will EXIMIOUS elucidate the biological effects of the exposome

- Specific exposures & genetic predisposition & immune interactions

- Better prediction of disease risk by acquiring new knowledge on the influence of external exposures on biological pathways at different life-stages and identification of early signs of health damage caused by environmental factors.

- Common elements in genesis of immune-mediated disorders.

What are the critical needs for success

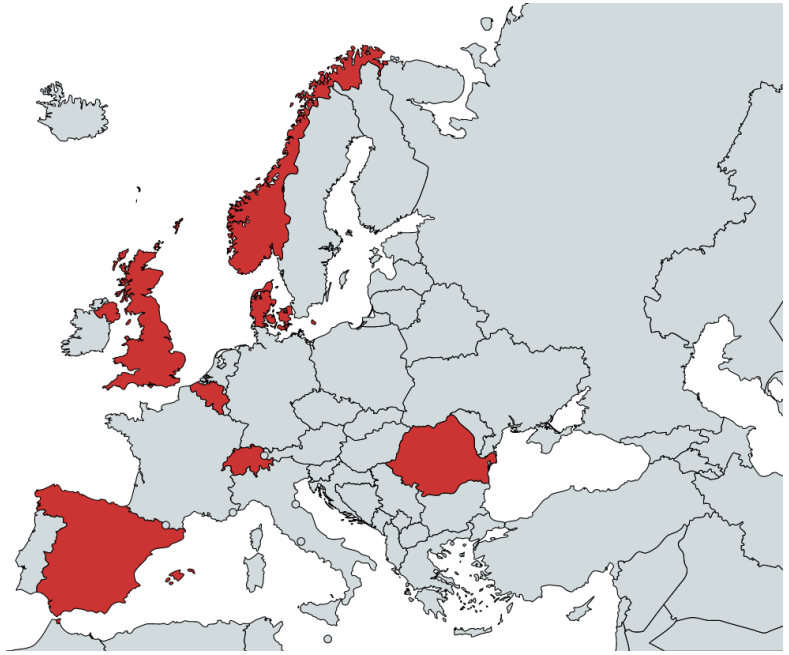
Stakeholder involvement

- Diseased cohorts & past exposure
- Database based analysis – capturing existing data

Exposome network

- Exposure at work → JEM's
- Environmental exposure close to polluting sides → models

Acknowledgements



Participant No. *	Participant organisation name	Short name	Country
1 (Coordinator)	Katholieke Universiteit Leuven	KUL	Belgium
2	University of Hasselt, Centre for Environmental Sciences	UH	Belgium
3	Norwegian Institute of Public Health, Toxicology and Risk Assessment	NIPH	Norway
4	National Research Centre for the Working Environment	NRCWE	Denmark
5	Belgian Center for Occupational Hygiene	BECOH	Belgium
6	imec, Leuven	IMEC	Belgium
7	Université Catholique de Louvain, Louvain Centre for Toxicology and Applied Pharmacology (LTAP), Brussels	UCL	Belgium
8	Babraham Institute, Cambridge	BI	UK
9	Queen's University Belfast, School of Pharmacy, Belfast	QUB	UK
10	Region Hovedstaden	REGIONH	Denmark
11	Biogenity	BioG	Denmark
12	Vall D'Hebron Research Institute, Barcelona	VHIR	Spain
13	Aarhus University, Section of Atmospheric Modelling, Department of Environmental Science	AAU	Denmark
14	University of Medicine, Pharmacy, Science and Technology of Targu Mures, Department of Occupational Medicine	UMFST	Romania
15	Accelopment	ACCEL	Switzerland

Thank You

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874707.

EXIMIOUS
Mapping Exposure-Induced Immune Effects

HEDIMED

Research and
Innovation

European Human Exposome Network

HEDIMED

Human Exposomic Determinants of Immune Mediated Diseases

Prof. Heikki Hyöty

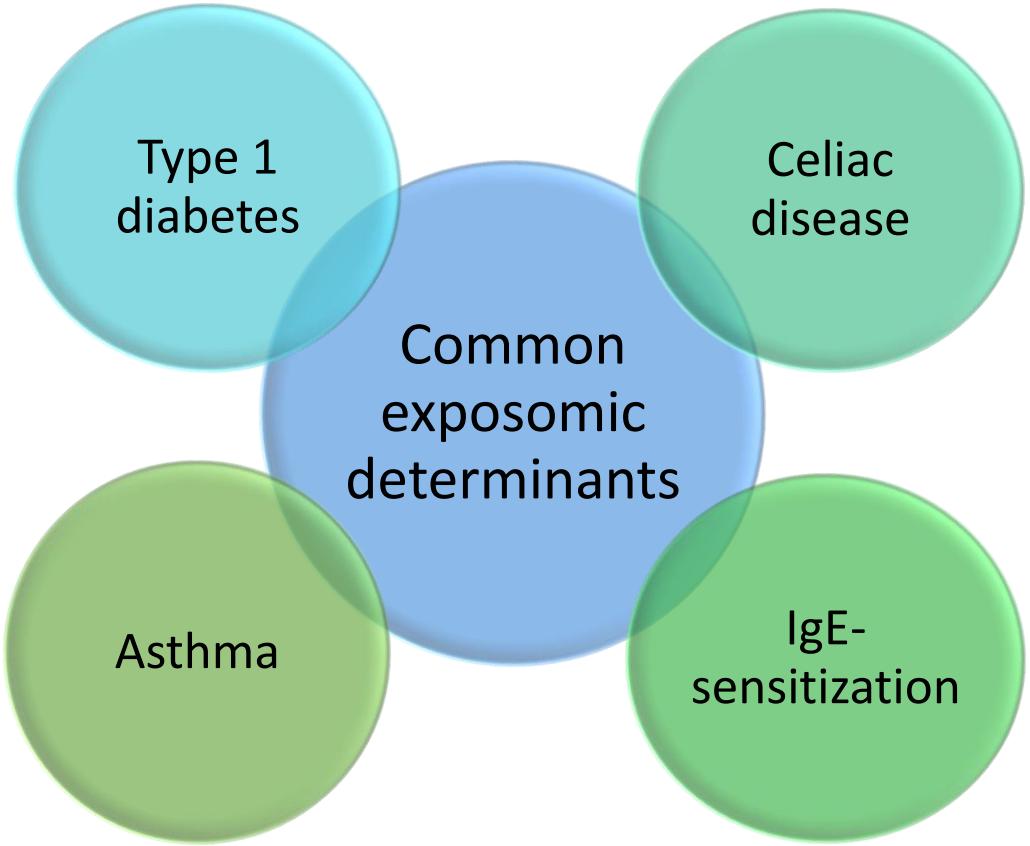
Tampere University

Finland

HEDIMED
Human Exposomic Determinants of Immune Mediated Diseases

What is HEDIMED about?

- Identification and modelling of exposomic factors relevant for immune-mediated diseases (IMDs)
- Key exposomic factors under study
  - Microbes
  - Environmental biodiversity
  - Toxins
  - Diet
  - Physiological factors
  - Physical activity
  - Host response to exposomic factors



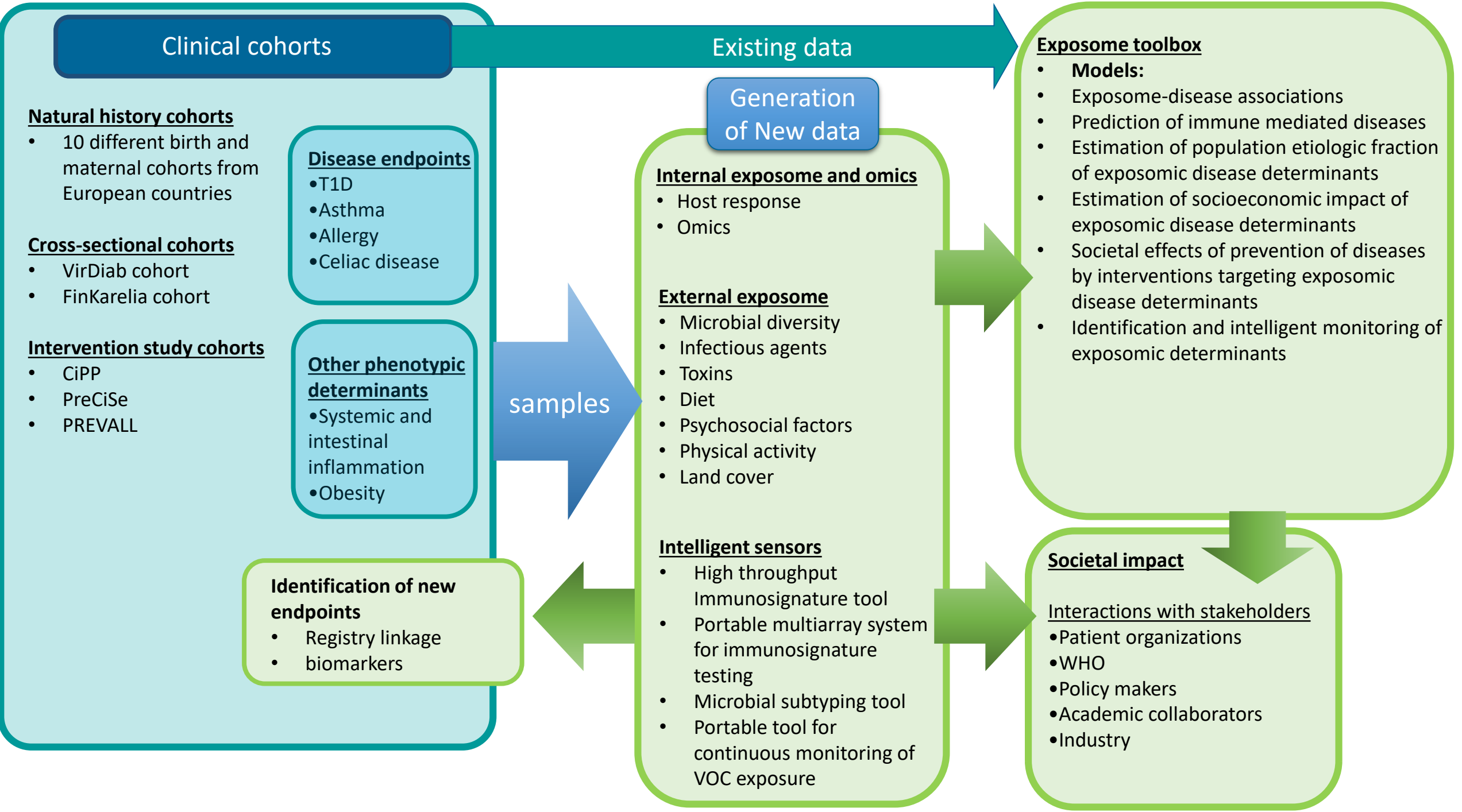
Why is this important?

HEDIMED
Human Exposomic Determinants of Immune Mediated Diseases

HEDIMED

- explores the role of exposome in **several IMDs** to identify disease-specific and common exposomic determinants.
- utilizes samples and data from **unique clinical cohorts and trials** providing huge number of study end-points (diseases) in different populations.
- is based on **multidisciplinary research** allowing identification of novel exposomic determinants, their interactions and mechanisms of actions.
- includes development of **new technologies** for the identification of exposomic determinants of diseases.
- will make data, research tools and latest discoveries **available for various stakeholders (toolbox)**

How will HEDIMED reach that goal?


Clinical cohorts
Existing data
Natural history cohorts
• 10 different birth and maternal cohorts from European countries
Cross-sectional cohorts
• VirDiab cohort
• FinKarelia cohort
Intervention study cohorts
• CiPP
• PreCiSe
• PREVALL
Disease endpoints
•T1D
•Asthma
•Allergy
•Celiac disease
Other phenotypic determinants
•Systemic and intestinal inflammation
•Obesity
samples
Generation of New data
Internal exposome and omics
• Host response
• Omics
External exposome
• Microbial diversity
• Infectious agents
• Toxins
• Diet
• Psychosocial factors
• Physical activity
• Land cover
Intelligent sensors
• High throughput Immunosignature tool
• Portable multiarray system for immunosignature testing
• Microbial subtyping tool
• Portable tool for continuous monitoring of VOC exposure
Identification of new endpoints
• Registry linkage
• biomarkers
Exposome toolbox
• Models:
• Exposome-disease associations
• Prediction of immune mediated diseases
• Estimation of population etiologic fraction of exposomic disease determinants
• Estimation of socioeconomic impact of exposomic disease determinants
• Societal effects of prevention of diseases by interventions targeting exposomic disease determinants
• Identification and intelligent monitoring of exposomic determinants
Societal impact
Interactions with stakeholders
•Patient organizations
•WHO
•Policy makers
•Academic collaborators
•Industry

HEDIMED
Human Exposomic Determinants of Immune Mediated Diseases

What will HEDIMED deliver in 5 years

- Concrete points of to be delivered
  - identification of exposomic determinants of IMDs

- What will HEDIMED contribute to the Exposome Toolbox
  - tools for identification of exposomic determinants of IMDs
  - tools for prediction of disease risk
  - novel exposure strategies to reduce the risk of IMDs
  - information of latest discoveries
  - tools for decision-makers, stakeholders and public to reduce the risk of IMDs

IMD = immune-mediated disease (such as type 1 diabetes, celiac disease, allergies and asthma)

Link to panel discussion

- How will HEDIMED elucidate the biological effects of the exposome

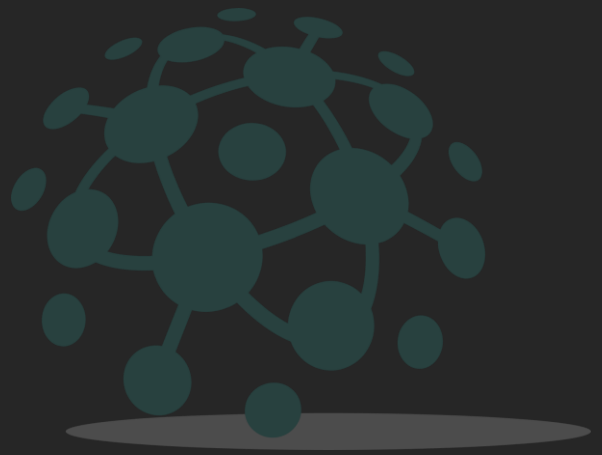
What are the critical needs for success

- What interaction with stakeholders do you need to make your project a success?
  - exploitation and dissemination of the findings
    - Identification of associations between exposomic factors and the risk of IMDs
    - development of novel exposure approaches to reduce the likelihood of IMDs
  - funding opportunities for new research initiatives
  - feedback from the end-users of toolbox
- What interaction with other projects is needed to make the network a success?
  - exchange of expertise, methods, samples and knowledge
  - common procedures for exploitation and interactions with stakeholders
  - creation of common metadatabase and website

Acknowledgements

- Involved partners:

- This project has received funding from the European Union's Horizon 2020 research and innovation programme under Grant Agreement No: 874864



No.	Beneficiary organisation name and abbreviation	Country
1	University of Tampere (TAU)	FI
2	University of Lund (ULUND)	SE
3	University of Helsinki (UH)	FI
4	Norwegian Institute of Public Health (NIPH)	NO
5	University of Turku (UTU)	FI
6	University of Oulu (UOULU)	FI
7	Tartu University Hospital (TUH)	EE
8	University of Siena (UNISI)	IT
9	Finnish National Institute for Health and Welfare (THL)	FI
10	Charles Univerity (CU)	CZ
11	Czech University of Life Sciences (CULS)	CZ
12	VTT Technical Research Centre of Finland Ltd (VTT)	FI
13	University of Tartu (UTARTU)	EE
14	Centre Suisse d'Electronique et de Microtechnique SA – Recherche et Developpement (CSEM)	CH
15	Graz University of Technology (TUG)	AT
16	Baylor College of Medicine (BCM)	US
17	Empirica GmBH (EMPIRICA)	DE
18	Satellio Oy (Satellio Oy)	FI
19	Gnomon Informatics SA (GNOMON)	EL
20	Copenhagen Prospective Studies on Asthma in Childhood (COPSAC)	DK
21	Pirkanmaa Hospital District (TAUH)	FI
22	Natural Resources Institute Finland (LUKE)	FI

Audience participation in the panel discussions

Go to www.menti.com
and use the code
86 98 50

Social media

Relevant hashtags:
#**Exposome**
#EUHealthResearch
#H2020
#HumanExposome

EC Twitter tags:
@EUScienceInnov
@EU_H2020

Panel: Exposome and biological effects

Moderator: Anya Sitaram, Rockhopper Media, IE

- **Christopher Wild**, Emeritus Director, International Agency for Research on Cancer, FR
- **Jacqueline Bowman-Busato**, EU Policy Lead, European Association for the Study of Obesity, BE
- **Robert Barouki**, Director Unit 1124, INSERM, Director Department of Clinical Metabolomics and Proteomic Biochemistry,Necker Hospital, FR
- **Panagiotis Chaslaridis**, Policy Advisor, European Federation of Allergy and Airways Diseases Patients' Associations, BE

- **Martine Vrijheid**, Research Professor, Barcelona Institute for Global Health, ES
- **Peter Hoet**, Head of Centre for Environment and Health, Catholic University of Leuven, BE
- **Heikki Hyöty**, Professor of Virology, University of Tampere, FI

European Commission

COFFEE BREAK 15:00 – 15:30

Please fill-in our survey:

https://ec.europa.eu/info/events/launch-event-european-human-exposome-network-2020_en

Research and Innovation

HEAP

Research and
Innovation

EU Human Exposome Project

The Human Exposome Assessment Platform (HEAP)

Joakim Dillner

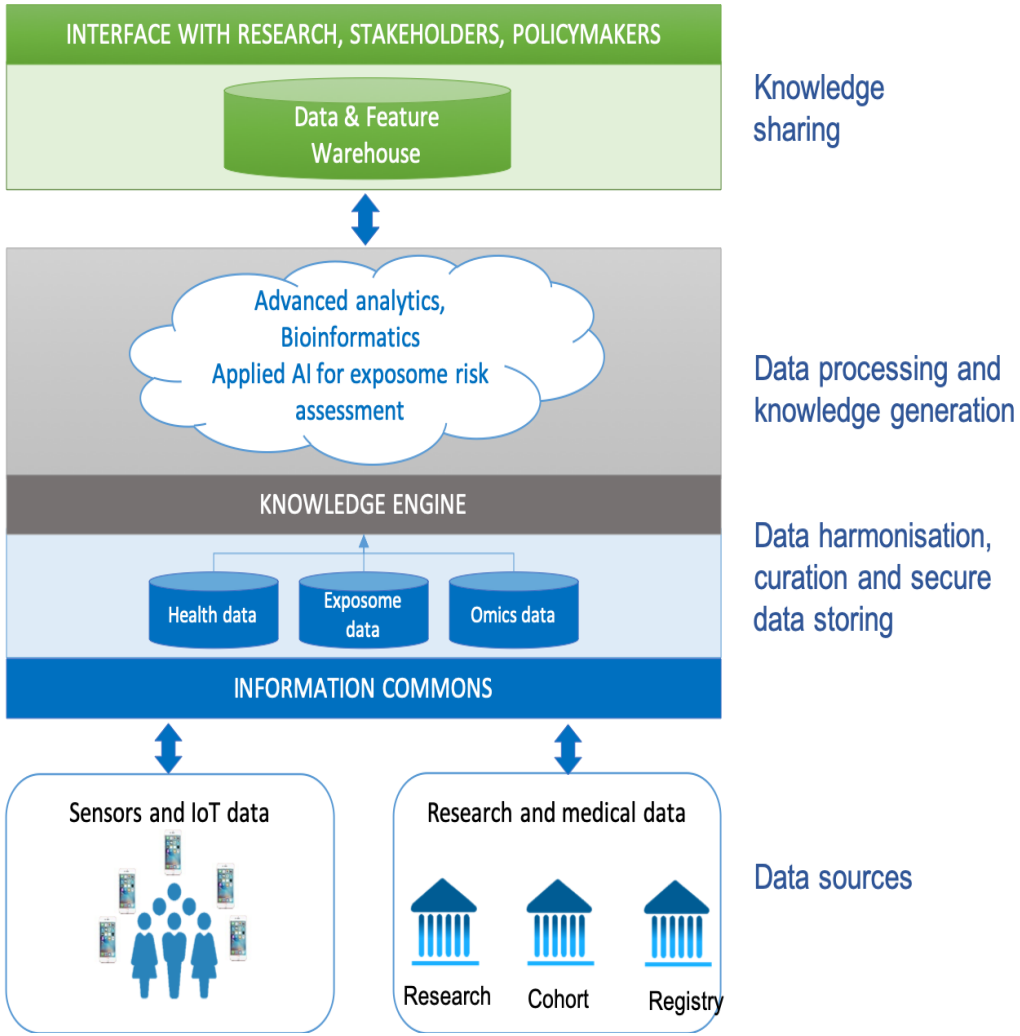
Karolinska Institutet
Stockholm
Sweden

www.humanexpsome.eu

The Human Exposome Assessment Platform

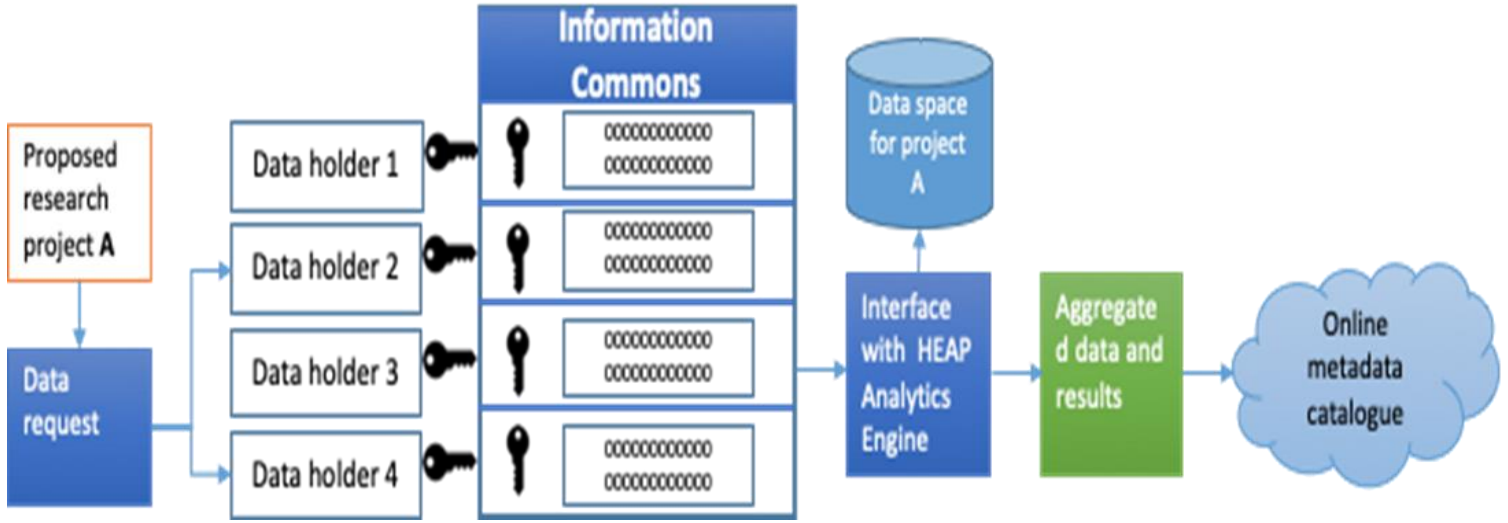
1) Launch an integrated and reproducible informatics platform that can be deployed in computer clusters and computing centres worldwide.

2) Populate the platform with data from exposome assessment



Launch an integrated and reproducible informatics platform that can be deployed in computer clusters and computing centres worldwide.

Innovative data management, Open Science and Integrity Protection: Clear ethico-legal governance system. Efficient and secure sharing of data access with others

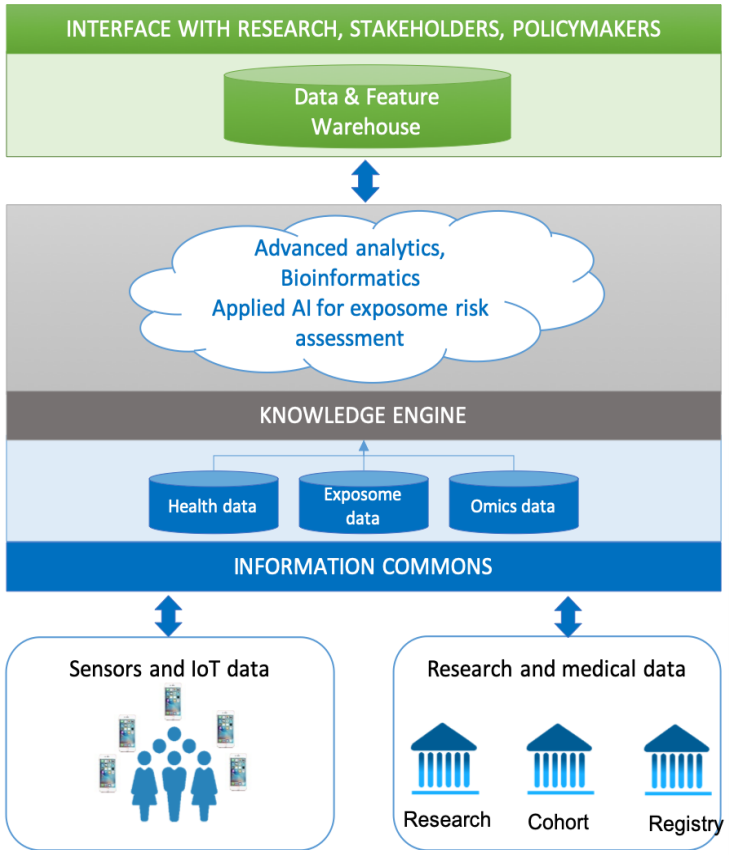


Populate the platform with data from exposome assessment

Exposome assessment using Sensors

Chemicals=
Mass spectrometry

Biologics=
Sequencing



-Population-based sample cohorts with advanced analyses (e.g. Metagenomics, epigenomics)

Exposome assesment using Consumer Receipts

Strategic importance of HEAP

1. Moving away from “One project on One exposure and One Disease”

Open Science: Multiple projects (also by others) on Multiple Exposures and Multiple Diseases.

Improved Integrity protection: Clear rules and securitity standards for data access

2. **Furthering Advances** being made in different countries using international collaboration. E.g. on:

-Improved **environmental safety:** Continuous exposure measurements using sensors

-Improved **consumer protection:** Continuous measuring if specific purchases affect health

-Improved **understanding of environmental determinants of disease**: Towards new strategies for healthy childbearing and cancer prevention

After 5 years we will have delivered

- **A flexible technical platform** (both software and hardware) proven to be efficient & safe for **data acquisition (**from e.g. **wearable sensors**, **purchases** and **"omics",** for **data management, AI and knowledge discovery, visualization** and **education**.
- **Exposome data** and **analysis results** from four large-scale population **cohorts** and from a pilot adding wearable **sensors** for personal exposome profiling.

At least 1 case where exposome knowledge has translated to action for improving health of EU citizens: either on

Improved **environmental safety;**

Improved **consumer protection** or

Improved **understanding of environmental determinants of disease**

The EU Green Deal and the Exposome

- **New technologies, sustainable solutions and disruptive innovation are critical to achieve the objectives of the European Green Deal.**
- **Accessible and interoperable data are at the heart of data-driven innovation**
  - Digital infrastructure and artificial intelligence solutions will facilitate evidence-based decisions and expand the capacity to understand and tackle environmental challenges.
- **European food: safe, nutritious and of high quality.**
  - Low quality diets contribute to obesity and diseases such as cancer.

- **HEAP will provide a sustainable infrastructure and an improved evidence base towards these goals**

Critical needs for success

- Widespread recognition of and support for
  - i) the specific work of the Human Exposome Assessment Platform
  - ii) the concept that high quality, interoperable exposome measurements will be necessary for health & welfare of the citizens of the European Union.

- Exploit overlaps with other European Human Exposome Network projects – increased critical mass & expertise will propagate progress

The Partners in the Human Exposome Assessment Platform (HEAP)

Karolinska Institutet

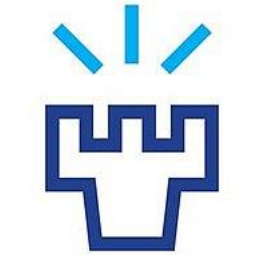
World Health Organization

UNIVERSITY OF WARSAW

LOGICAL CLOCKS

STATENS SERUM INSTITUT

STICHTING MLC FOUNDATION



REMEDIA

Research and
Innovation

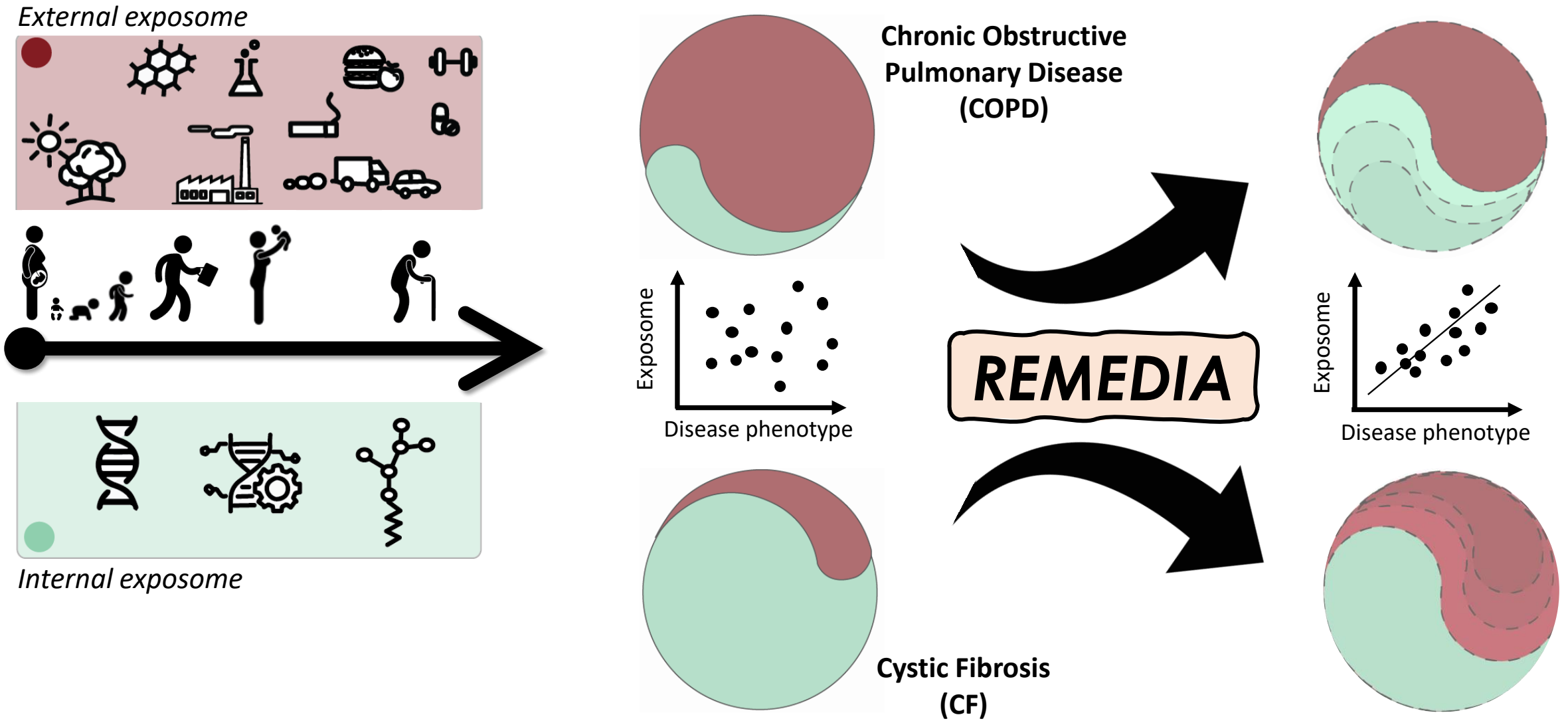
EU-Human Exposome Project

REMEDIA

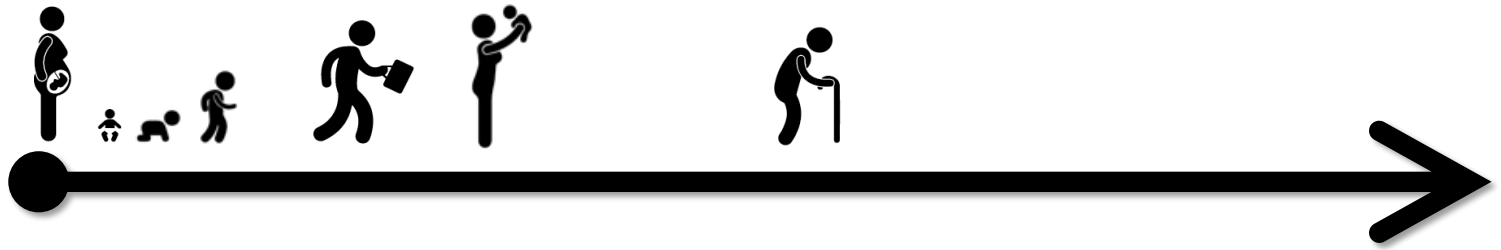
Sophie Lanone

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement #874753

What is REMEDIA about?

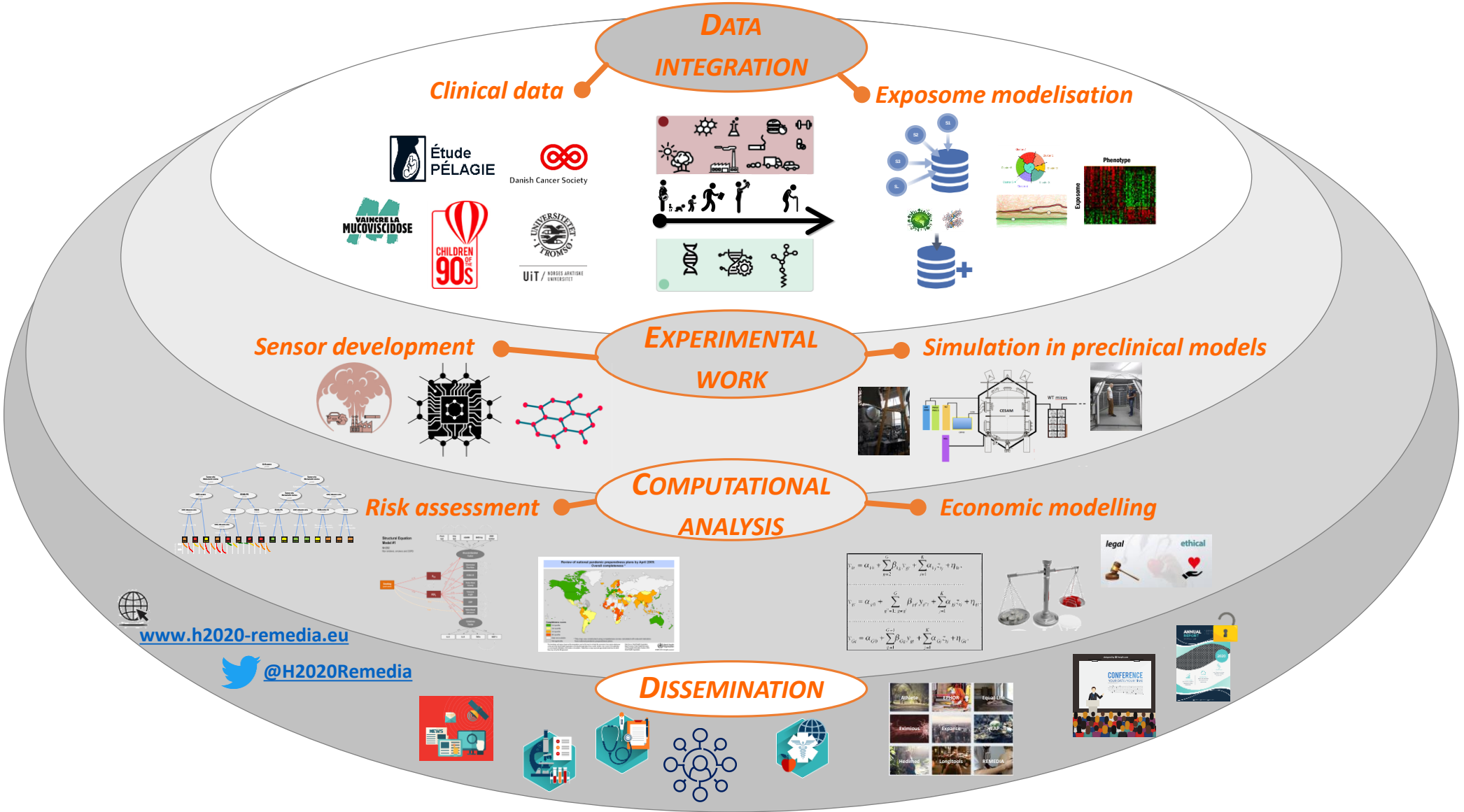


Why is this important?



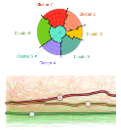
- **High burden**:
  - COPD: 3rd cause of death
  - CF: most common inherited genetic disorder
- **Invalidating diseases** - progressive decline of lung function
- **Fatal diseases** - no curative treatment
- **High phenotypic variability** of unknown origin - no good therapeutic efficacy

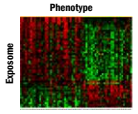
How will REMEDIA reach that goal?



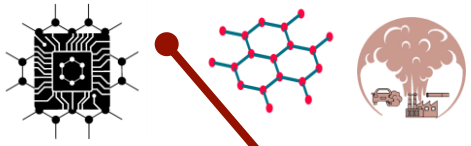
What will REMEDIA deliver in 5 years

Global unified database

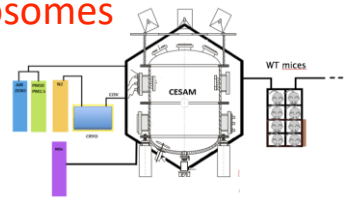




Combined sensor device



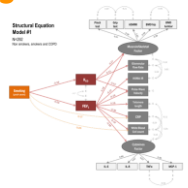
Versatile atmospheric simulation chamber
to target specific complex exposomes



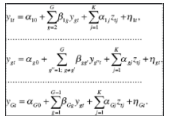
Machine learning supervised analyses
to predict health outcomes

New guidelines and recommendations
based on REMEDIA findings to better predict disease risks

Causal inference models
to identify relevant risk factors



Cost-effectiveness models to assess the costs, performance and cost-effectiveness of a selection of prevention strategies targeting exposome risk factors



Econometric models to test the interactions between economic, environmental and epidemiological variables

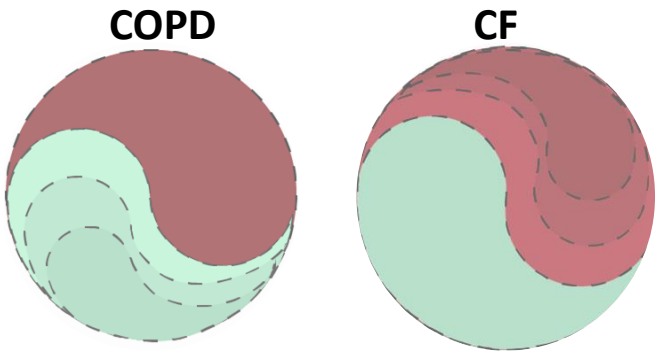
A **Pan-European multi-criteria risk assessment** tool to map the overall exposome risk-related pulmonary diseases in Europe

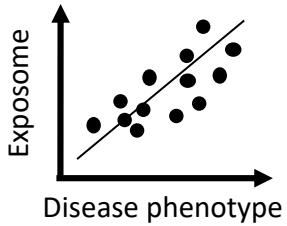
How will REMEDIA contribute to reaching the goals of the Green Deal

Green Deal

Protect the health and well-being of citizens from environmental-related risks

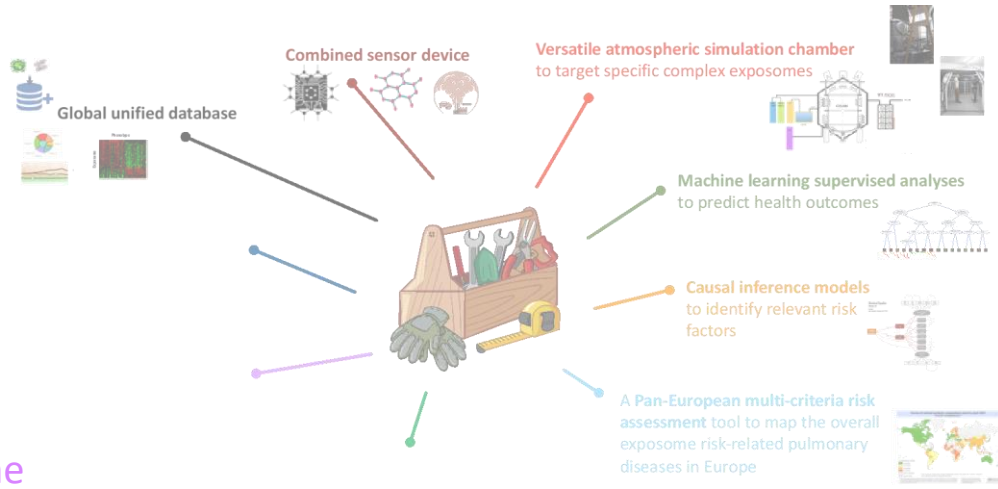
- REMEDIA outputs:



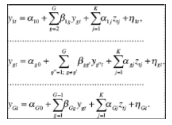


New guidelines and recommendations based on REMEDIA findings to better predict disease risks



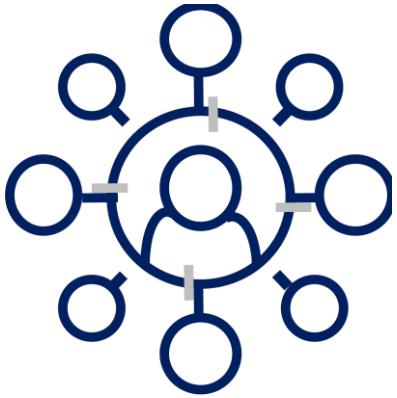


Cost-effectiveness models to assess the costs, performance and cost-effectiveness of a selection of prevention strategies targeting exposome risk factors



Econometric models to test the interactions between economic, environmental and epidemiological variables

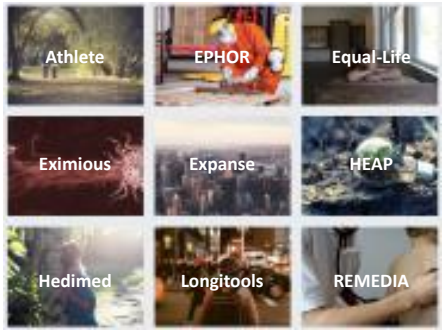
What are the critical needs for success



Identify decision makers, regulators, stakeholders from civil society to establish direct interaction with them throughout the project

Feed-back from policy making, NGOs, international organizations and patient associations to

- discuss their needs and adapt our guidelines / toolbox to their needs
- contribute to optimize / promote the dissemination of results



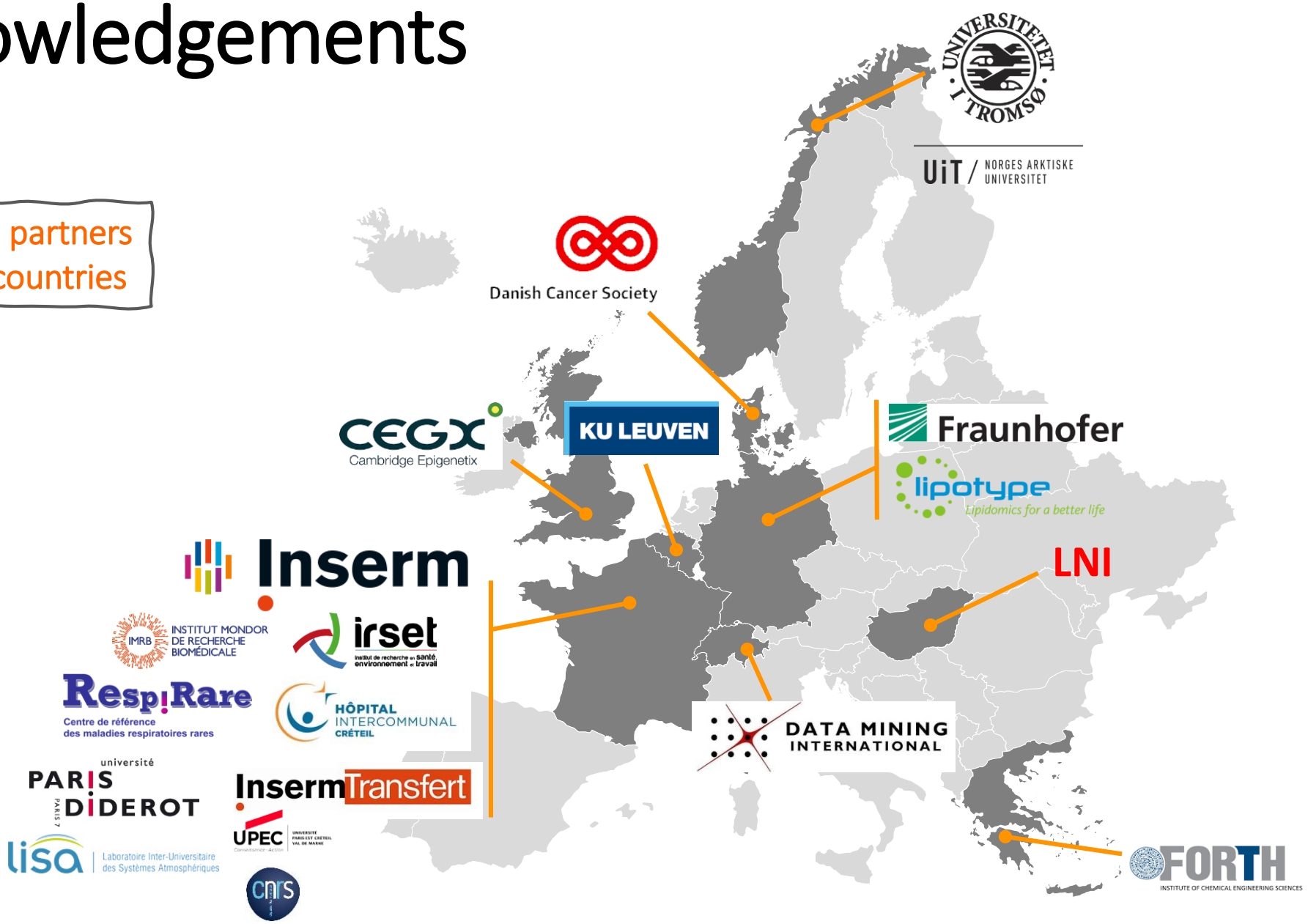
Sharing data on key component(s) to be considered in other Exposome Network projects with respiratory diseases as endpoints

Take advantage of the different approaches developed (exposome components, clinical endpoints, analytical methodologies, …) to achieve larger picture

Address the robustness of each project individual Toolbox (i.e. simulation chamber, multi-risk assessment map for REMEDIA) in all Exposome Network projects

Acknowledgements

13 partners
9 countries



EPHOR

Research and
Innovation

EU-Human Exposome Project

EXPOSOME PROJECT FOR HEALTH AND OCCUPATIONAL RESEARCH (EPHOR)

Anjoeka Pronk, Rob Stierum (TNO, The Netherlands)

TNO innovation for life

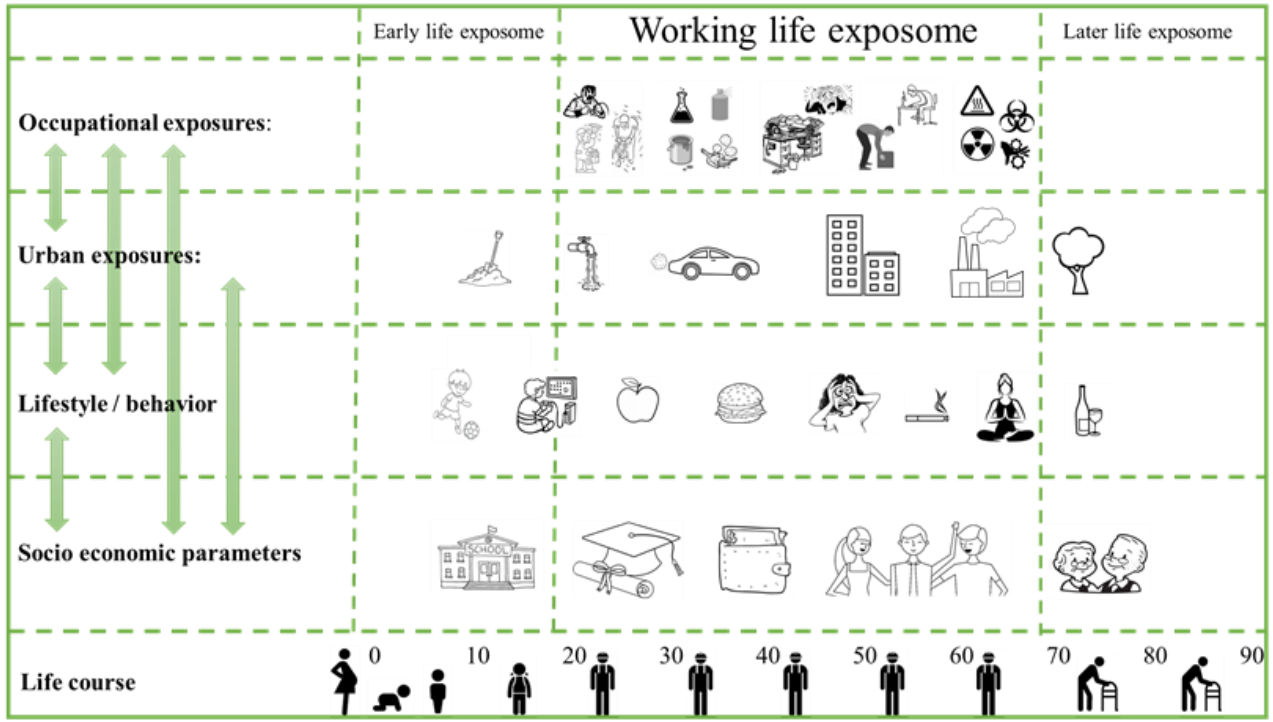
EPHOR Exposome tools for a healthy working life

EPHOR Exposome tools for a healthy working life

What is EPHOR about?

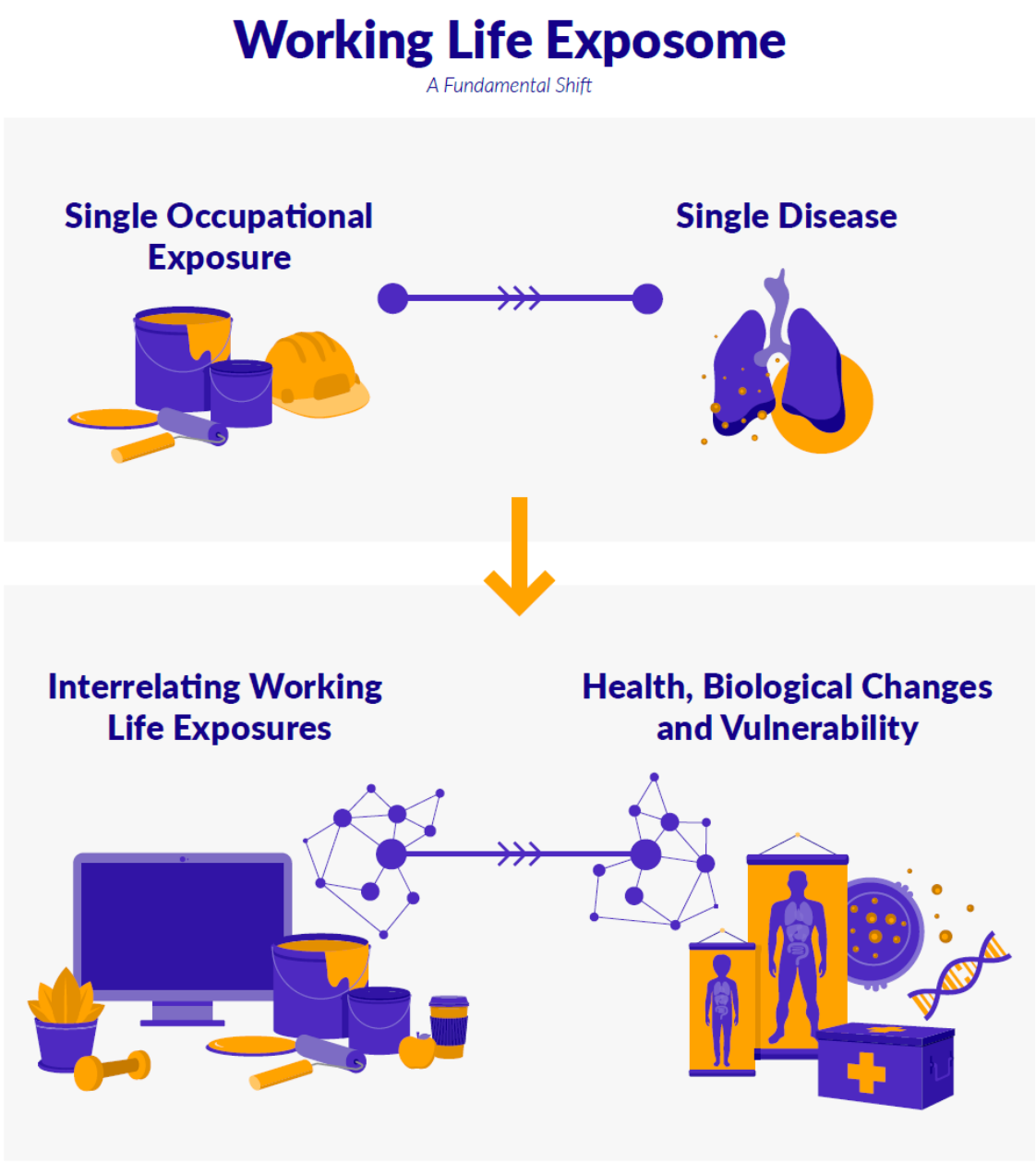
The working life exposome: 'All occupational and related non-occupational (i.e. general environment, lifestyle, behavioural and socio-economic) exposure factors'

- Applying the exposome concept to working life health
- Providing better insights into the relationships between exposures during the working life and health at different life stages
- Laying the groundwork for evidence based and cost effective preventive actions



Why is this important?

- Occupational disease in EU countries:
  - 5-7% mortality, 2-6% GDP
- Challenges:
  - Single occupational exposure-single disease
  - Vulnerability unknown
  - Biological mechanisms unknown
  - Upcoming challenges:
    - Demographic changes: Ageing workforce, female participation
    - Changing nature of work
- Working life largely neglected in exposome studies



How will EPHOR reach that goal?

Approach

Mega cohort
(>20M)

Case studies
(respiratory, shift work)

Data

Existing data
(cohorts, databases)

Also new data
(sensor, biomarkers)

Exposure-response

Interactions, vulnerability, life course

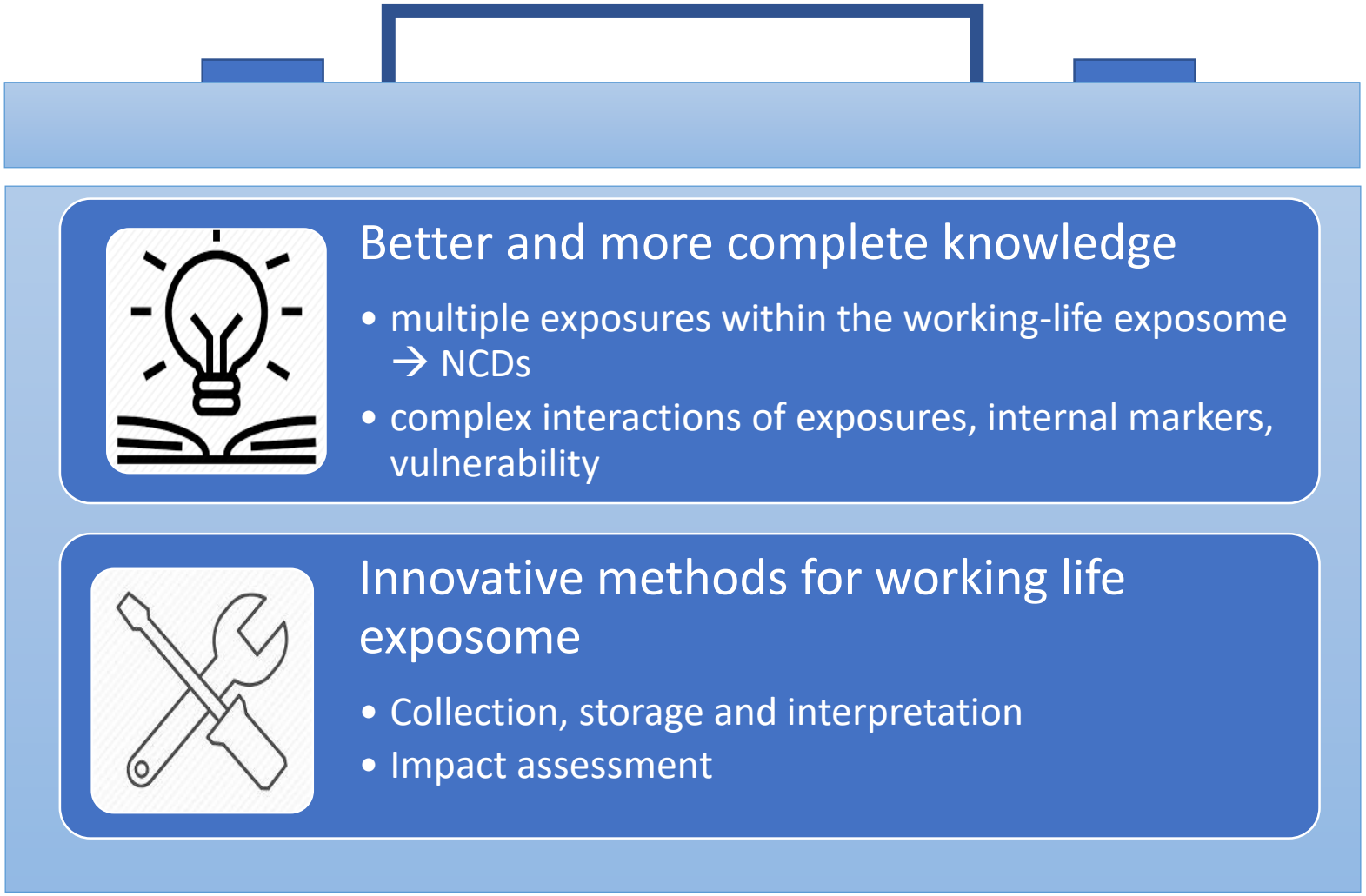
Biomarkers, higher resolution

Impact assessment

New concepts and methods

EPHOR Exposome tools for a healthy working life

What will EPHOR deliver in 5 years

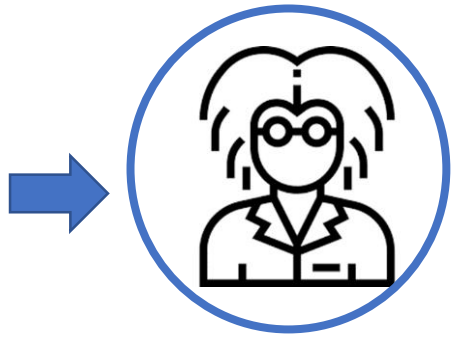


Better and more complete knowledge

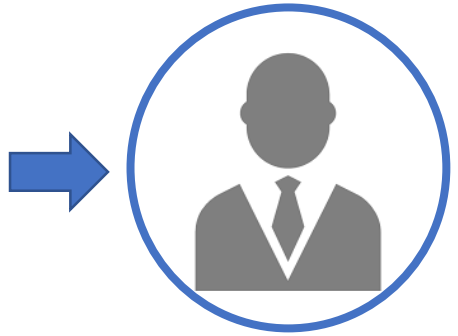
- multiple exposures within the working-life exposome → NCDs
- complex interactions of exposures, internal markers, vulnerability

Innovative methods for working life exposome

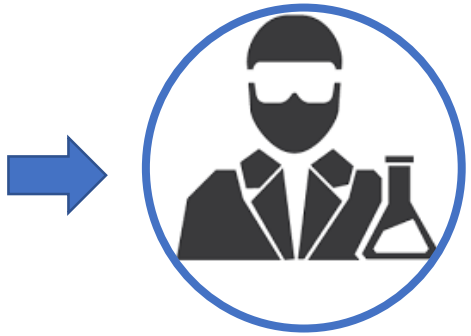
- Collection, storage and interpretation
- Impact assessment



Scientists



Policy makers

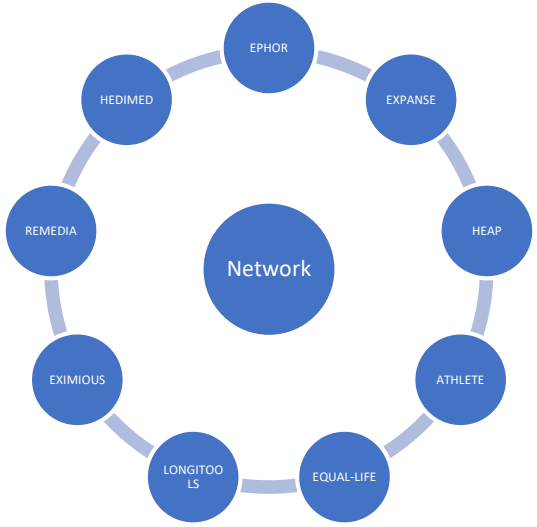


Occ. health practitioners

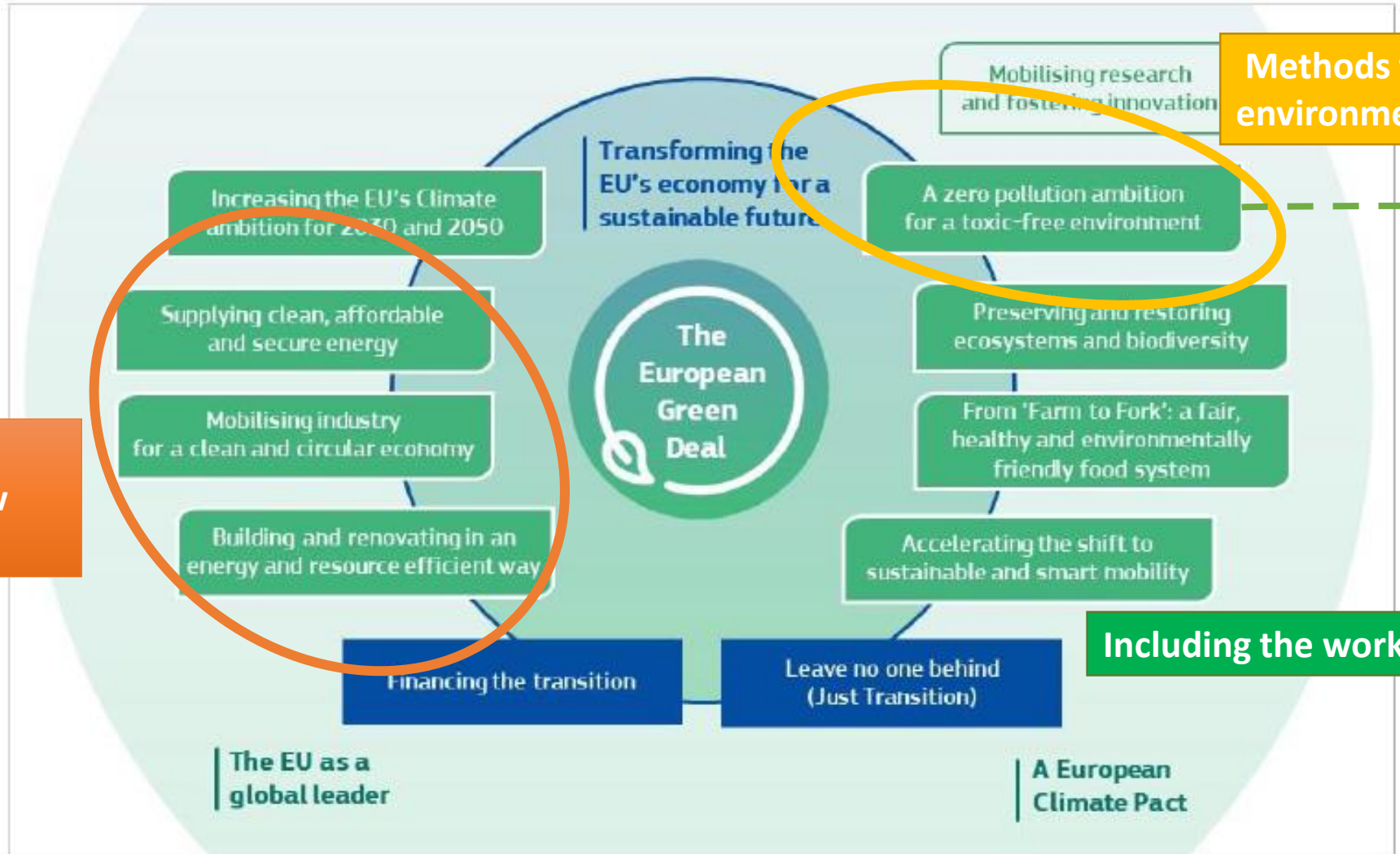
What are the critical needs for success

- Stakeholder interactions on their needs
  - Stakeholder advisory board:
    - ETUI, ICOH, NIOSH, EU EOSHA, ECETOC
  - 4 Stakeholder consultations

- European Human exposome Project interactions
  - Joint communication and dissemination strategy
  - Exchange of knowledge:
    - Technical, e.g. data storage and analyses, sensors, internal exposome
    - Other: ethical aspects, making available and implementation of tools etc



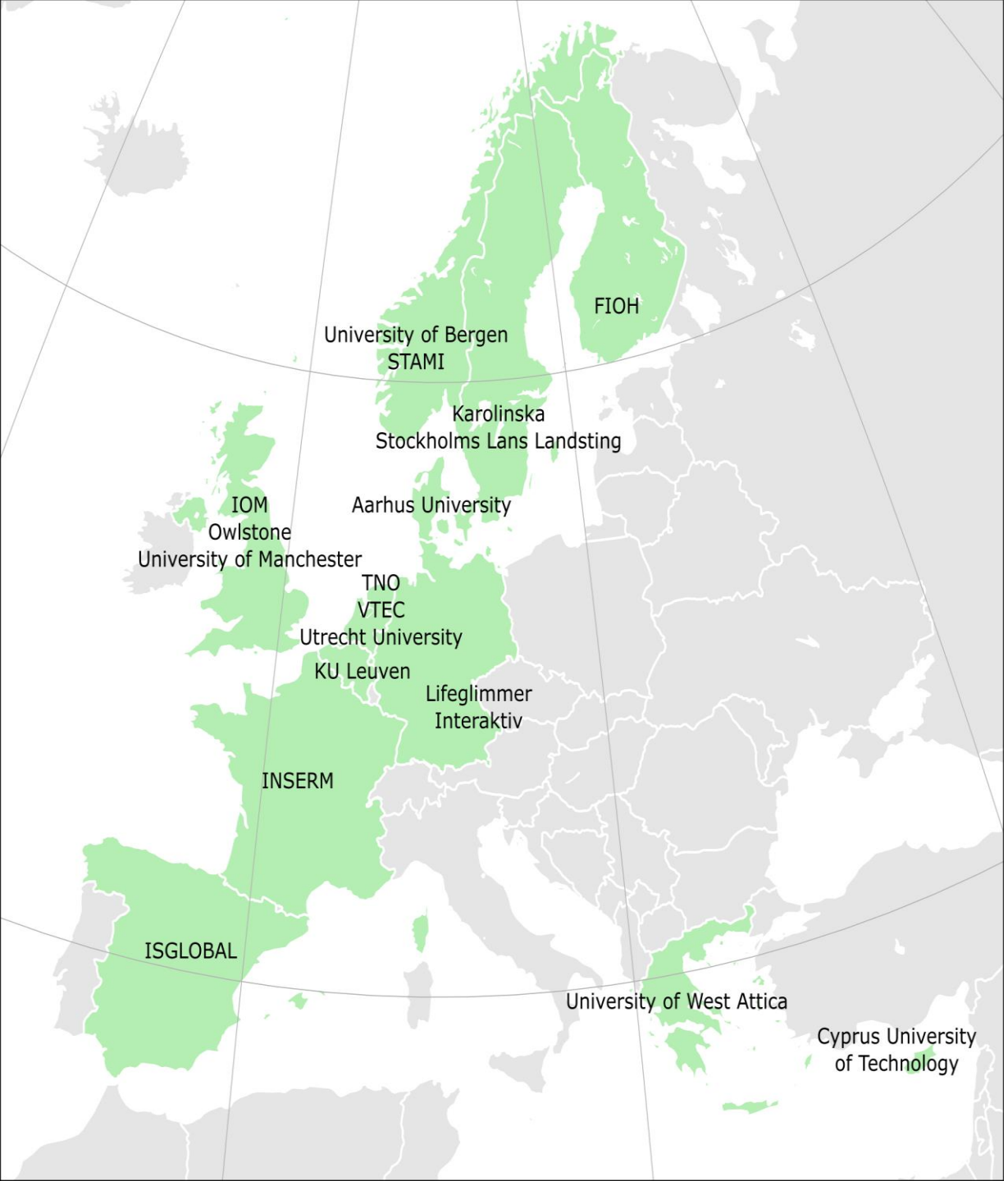
How will EPHOR contribute to reaching the goals of the Green Deal



Methods for monitoring of environmental levels

Dealing with emerging risks (e.g. recycling,new energy sources)

Including the work environment



EPHOR Exposome tools for a healthy working life

Acknowledgements

WP Leads	Other partners
TNO, NL (coordinator)	INSERM, FR
Institute for Occupational Medicine, UK	Finnish Institute of Occupational Health, FI
Karolinska Institutet, SE	University of West Attica, GR
Katholieke Universiteit Leuven, BE	VTEC-Engineering BV, NL
Universiteit Utrecht, NL	Universitetet i Bergen, NO
Statens Arbeidsmiljoinstitutt, NO	Lifeglimmer, DE
Aarhus Universitet, DK	Owlstone Medical Limited, UK
ISGLOBAL, ES	Interaktiv GmbH, DE
University of Manchester, UK	Cyprus University of Technology, CY
	Stockholms Lans Landsting, SE

This project has received funding from the European Union's Horizon 2020 research and innovation programme under grant agreement No 874703

Audience participation in the panel discussions

Go to www.menti.com
and use the code
86 98 50

Social media

Relevant hashtags:
#**Exposome**
#EUHealthResearch
#H2020
#HumanExposome

EC Twitter tags:
@EUScienceInnov
@EU_H2020

Panel: Exposome and the Green Deal

Moderator: Anya Sitaram, Rockhopper Media, IE

- **Gary Miller**, Vice Dean of Research Strategy and Innovation, Columbia University Mailman School of Public Health, US
- **Natacha Cingotti**, Senior Policy Officer, Chemicals and Health Programme, Health and Environment Alliance, BE
- **Pierpaolo Mudu**, Technical Officer, World Health Organization, European Centre for Environment and Health, DE
- **Vicente Franco**, Policy Officer, Unit Clean Air, DG Environment, BE

- **Joakim Dillner**, Professor of Infectious Disease Epidemiology, Karolinska Institute, SE
- **Sophie Lanone**, Research Director, French National Institute of Health and Medical Research, FR
- **Anjoeka Pronk**, Senior Scientist, Netherlands Organisation for Applied Scientific Research, NL

Concluding remarks

- **Anna Lonnroth**, Head of Unit, Healthy Lives, DG Research and Innovation, EC

European Commission

The European Human Exposome Network invites you to a Reception

Please fill-in our survey:

https://ec.europa.eu/info/events/launch-event-european-human-exposome-network-2020_en

Research and Innovation