# On the Origins of the Exposome

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# On the Origins of the Exposome

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

....the prompt

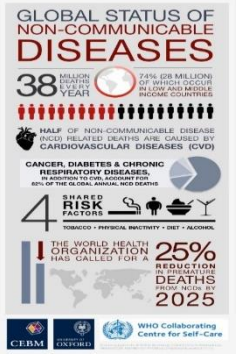
# The global cancer burden: necessity is the mother of prevention

- 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

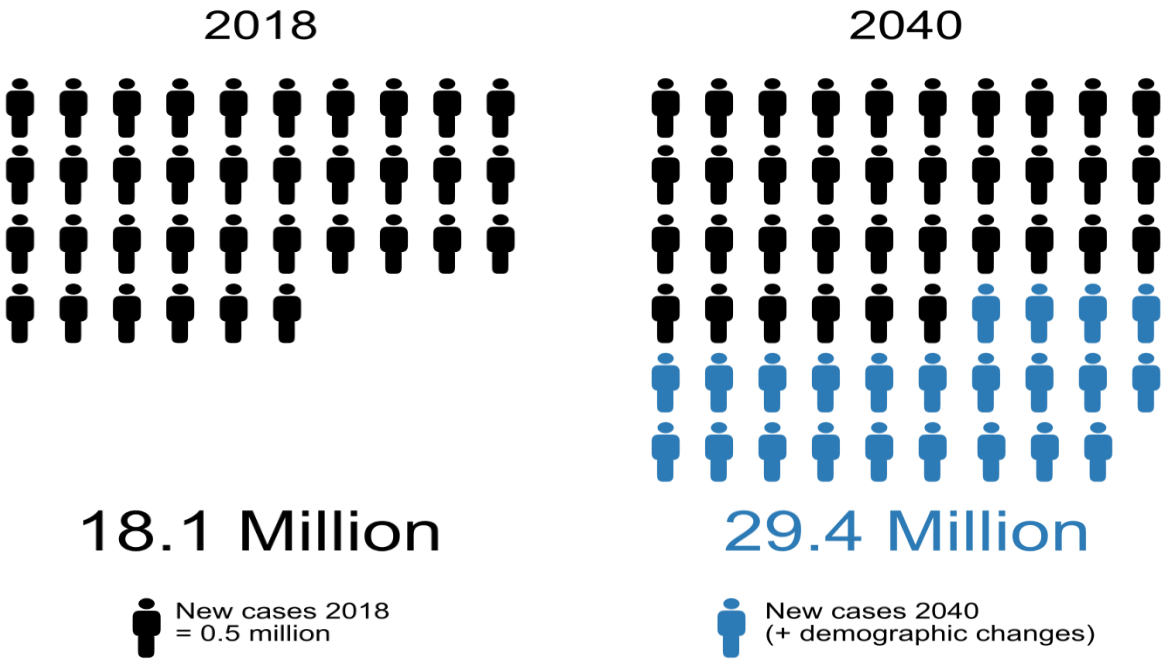
# Cancer is a disease of uncontrolled growth

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

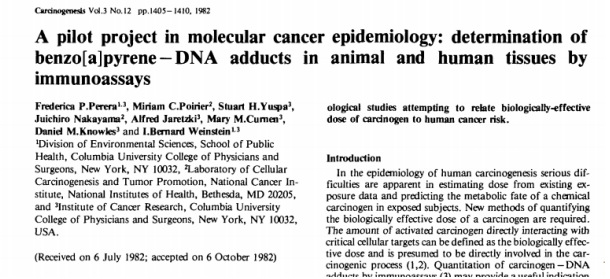
[1]Hanly P et al., (2015) Int. J. Cancer 136: E136-145

[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[2], Mary M.Cumen[3], Daniel M.Knowles[3] and I.Bernard Weinstein[1,3]

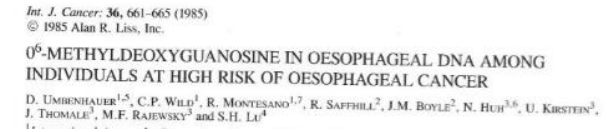
[1]Division of Environmental Sciences, School of Public Health, Columbia University College of Physicians and Surgeons, New York, NY 10032, [2]Laboratory of Cellular Carcinogenesis and Tumor Promotion, National Cancer Institute, National Institutes of Health, Bethesda, MD 20205, and [3]Institute of Cancer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

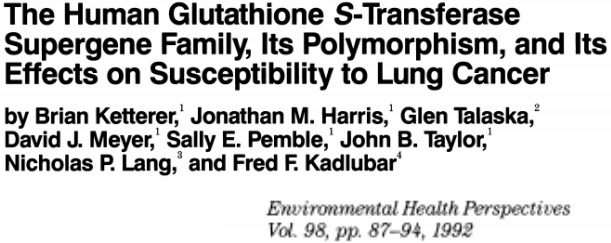
In the epidemiology of human carcinogenesis serious difficulties are apparent in estimating dose from existing exposure data and predicting the metabolic fate of a chemical carcinogen in exposed subjects. New methods of quantifying the biologically effective dose of a carcinogen are required. The amount 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]



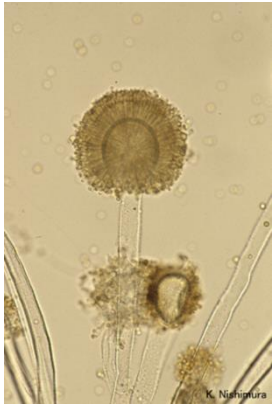
**The Human Glutathione *S*-Transferase Supergene Family, Its Polymorphism, and Its Effects on Susceptibility to Lung Cancer**

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]

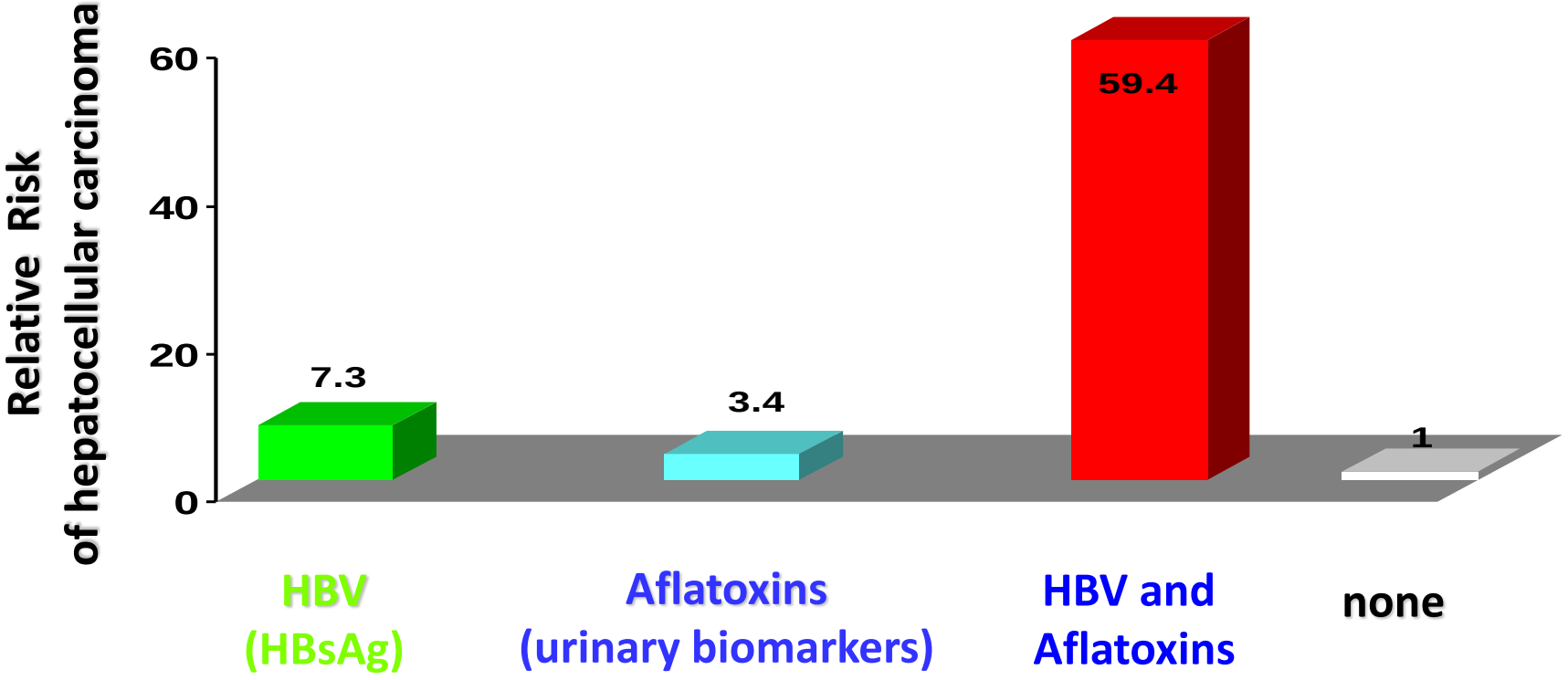
*Environmental Health Perspectives*
*Vol. 98, pp. 87–94, 1992*

# 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

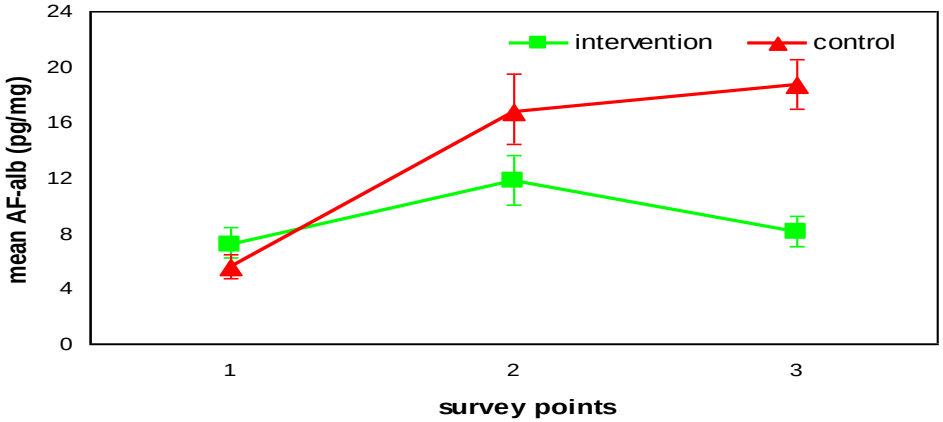



# Aflatoxin biomarkers: interaction between HBV infection and aflatoxins in liver cancer in China




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

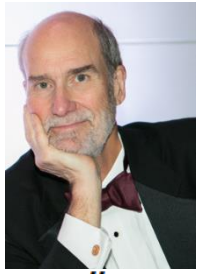
## The image

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

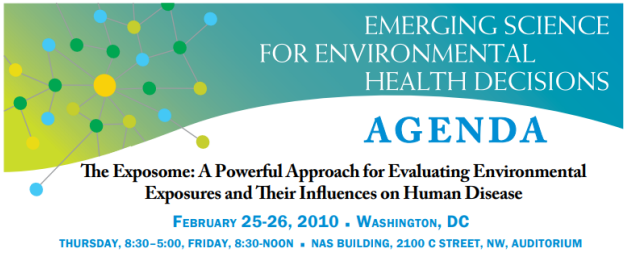
- Paper turned down by a number of leading journals – not reviewed
- Submitted in my role as co-editor-in-chief of CEBP. Dr John Potter comment: *"this is out there"*
- An anonymous childhood – no citations or follow-up for 5 years
- Resuscitated by the US National Academy of Sciences, Engineering and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

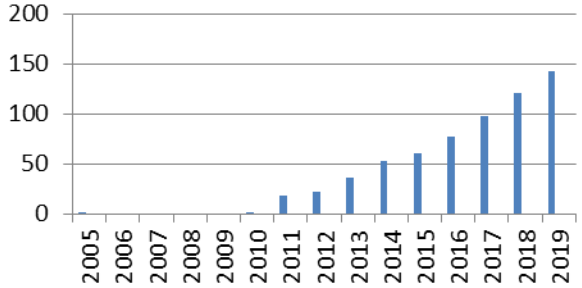
*Editorial*

**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



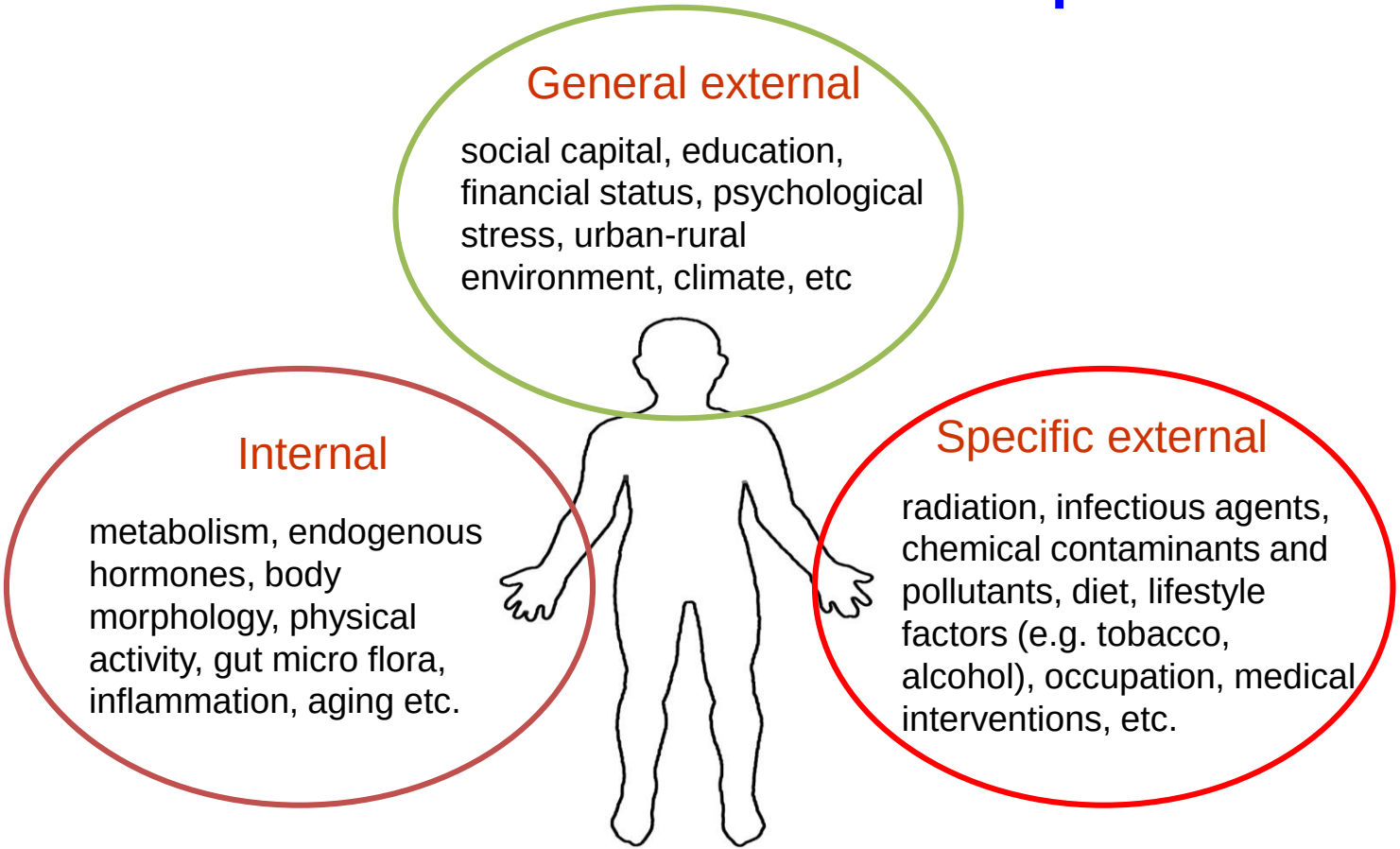



# Exposome - the definition

- 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

**EXPOSOME**

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

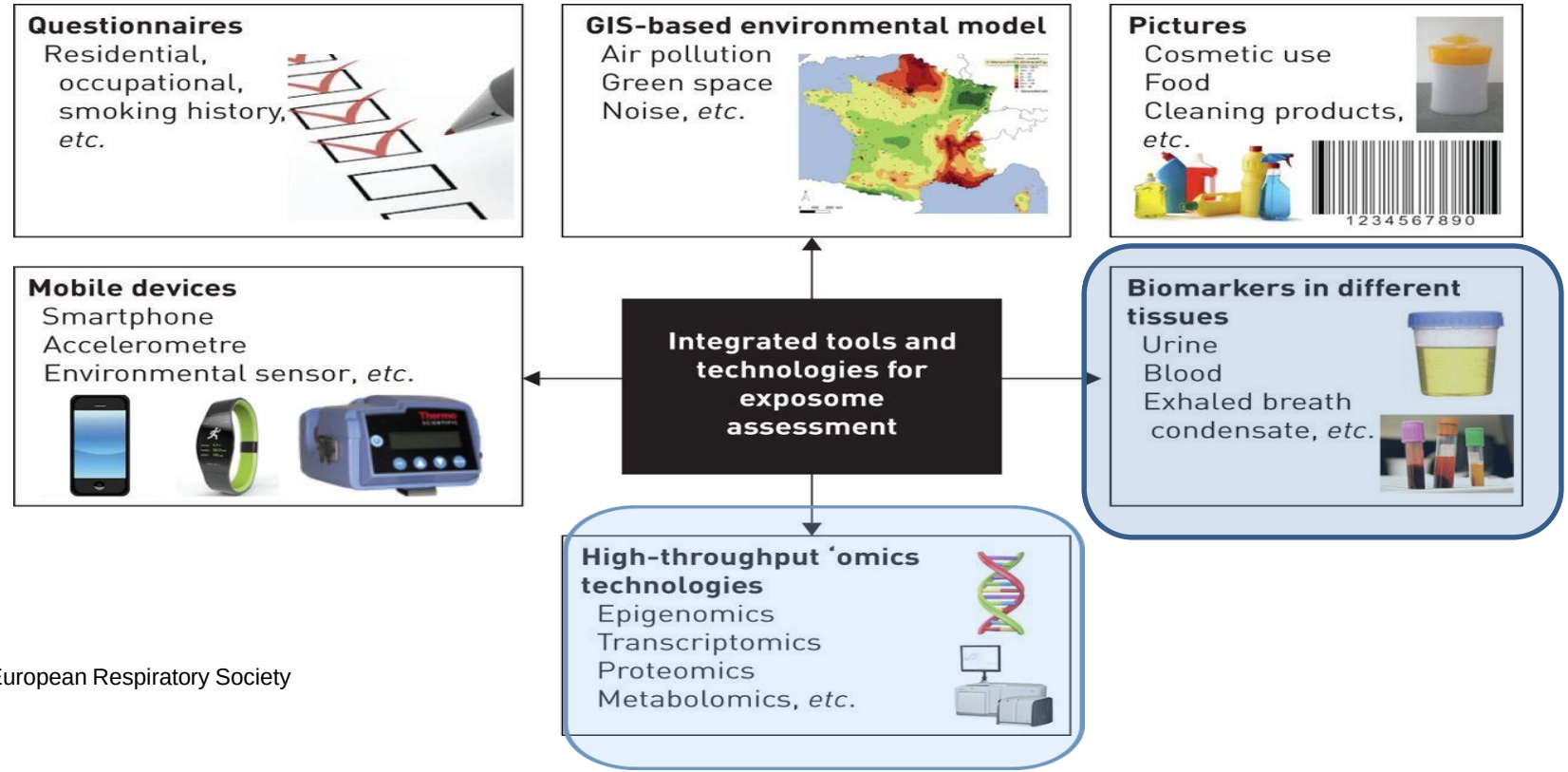
# An opportunity for scientific innovation: in the questions framed

- 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



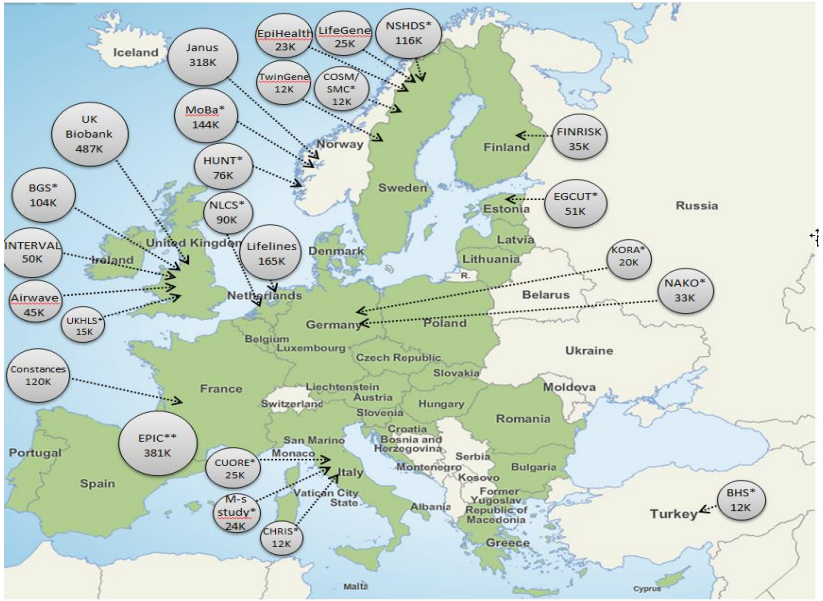



Valérie Siroux et al. Eur Respir Rev 2016;25:124-129

# 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

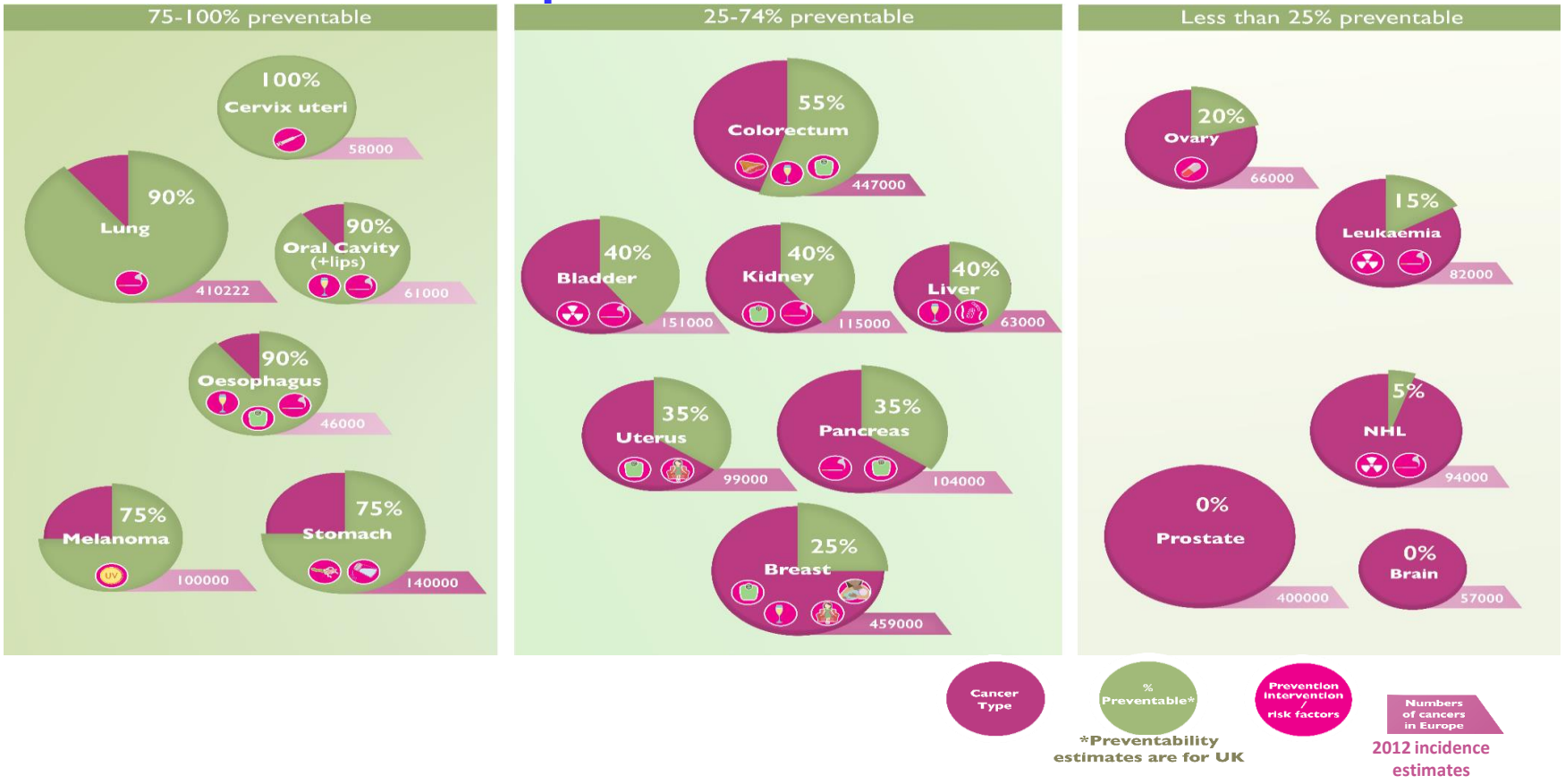
**Chronic disease research in Europe and the need for integrated population cohorts**

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!