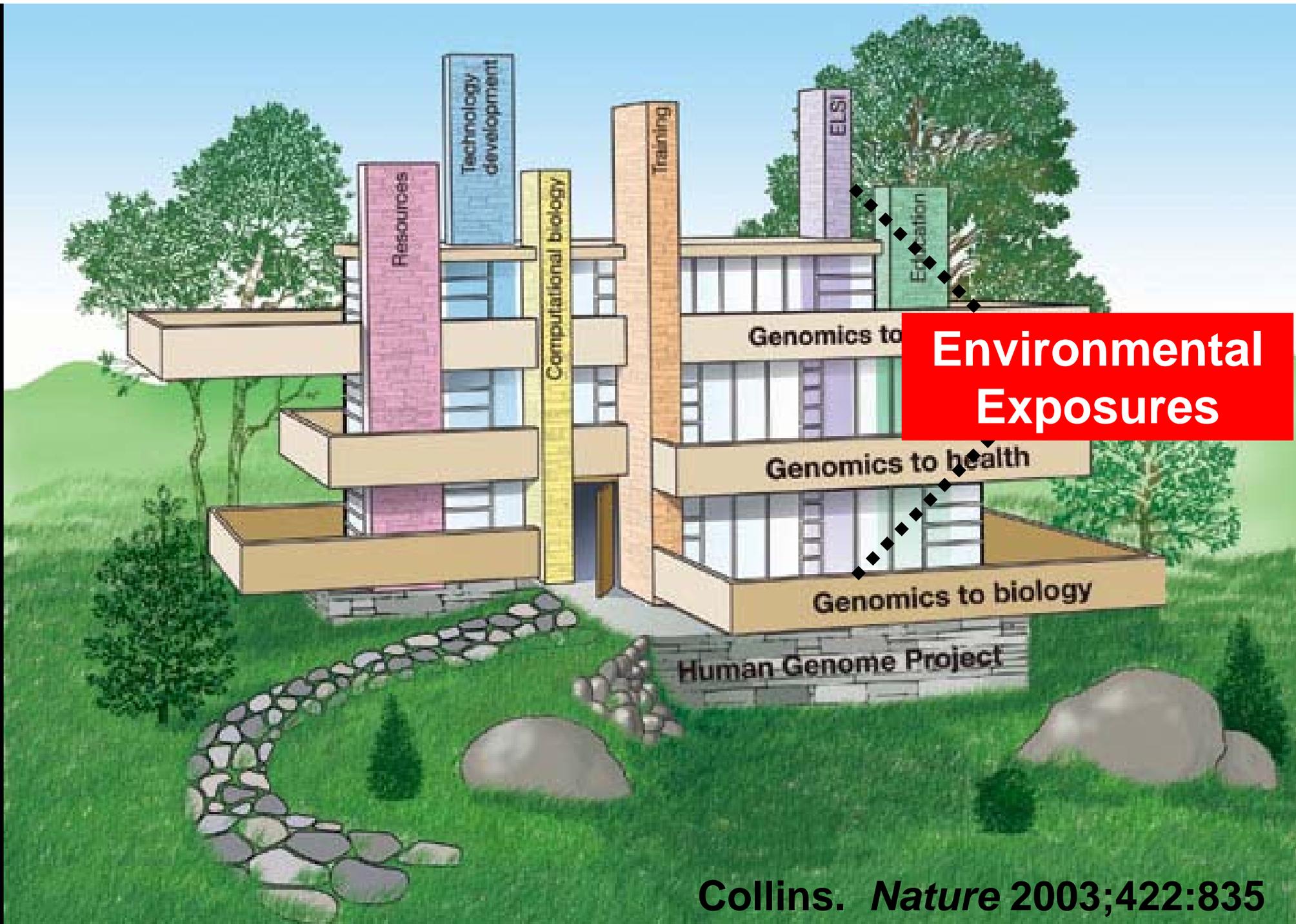


The Role of the Environment and Genes in Human Disease

**Presentation to the Secretary's Advisory Committee on
Genetics, Health and Society**

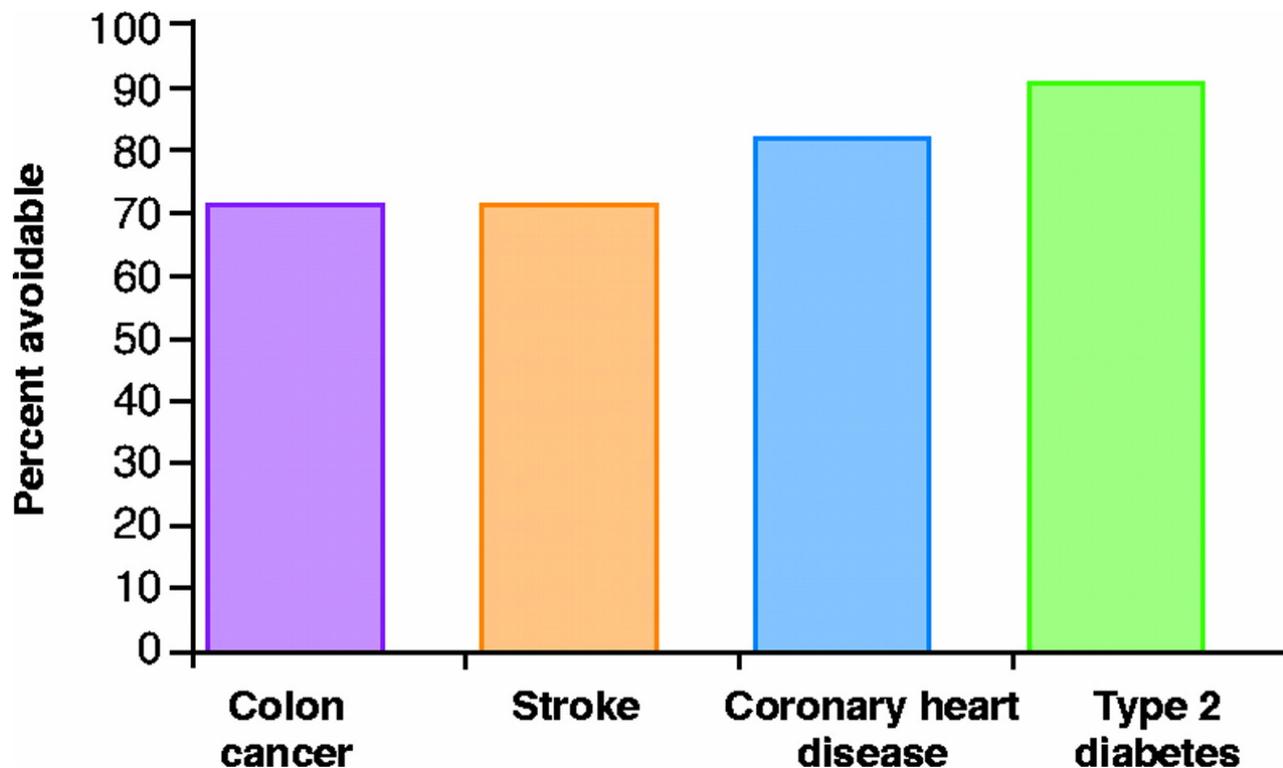
June 26, 2006





Collins. *Nature* 2003;422:835

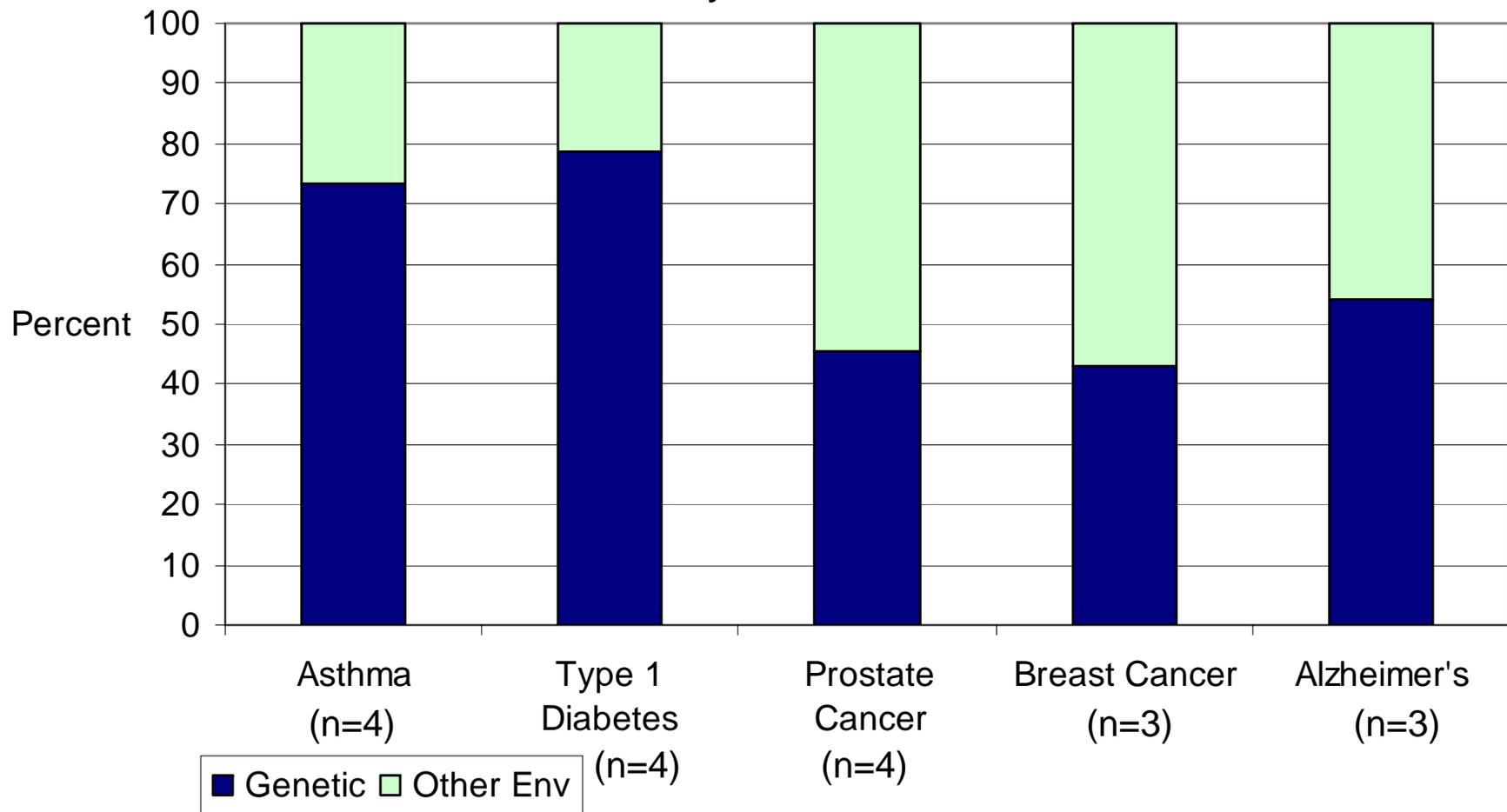
Etiology of Complex Human Diseases



- **70-90% of the major diseases in the USA are caused by reversible behaviors and exposures**
- **Single gene mutations are the major cause of cancers and CVD in < 5% of the cases**

Genetic and Environmental Contribution to Complex Human Disease

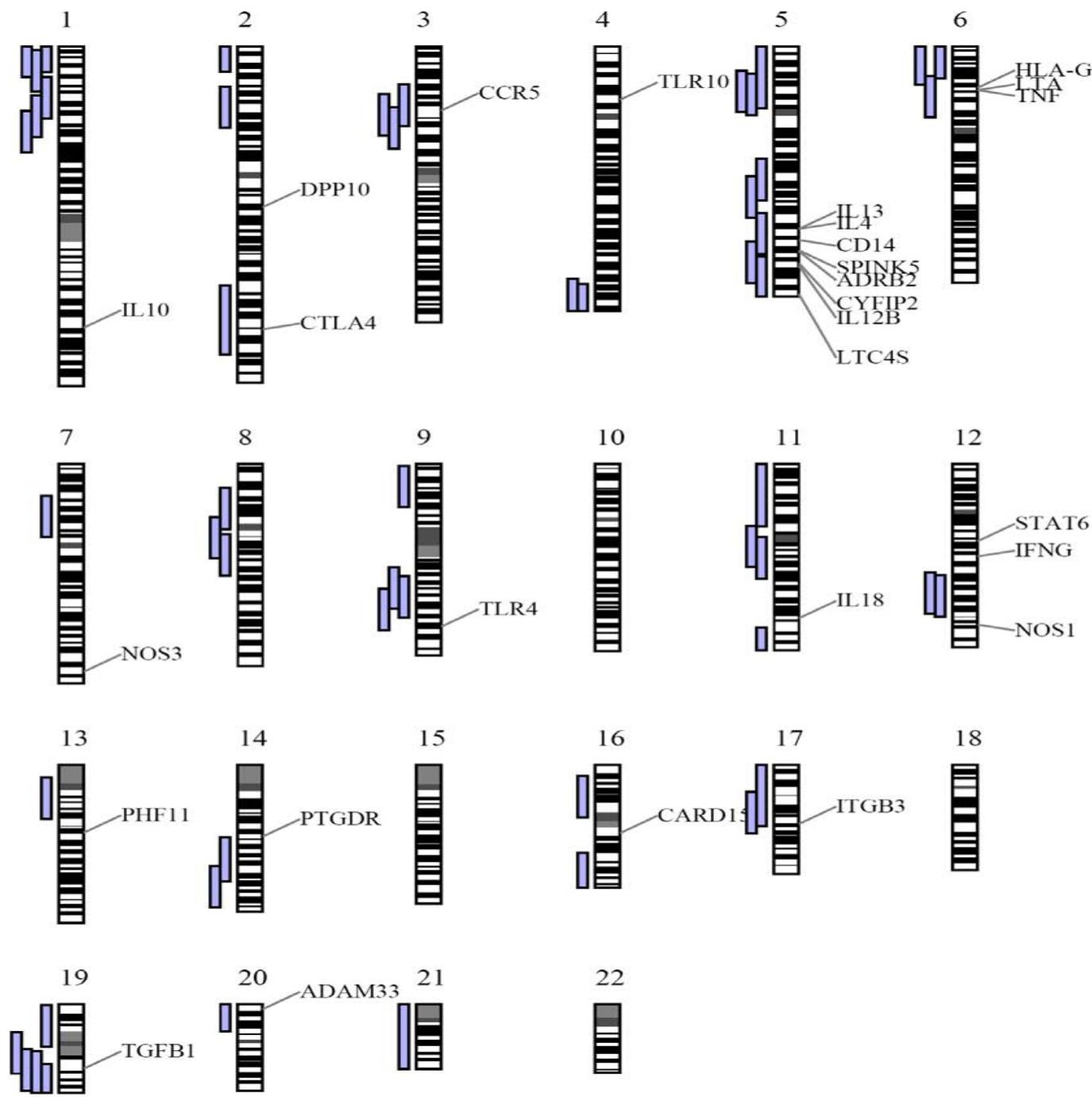
Meta-Analysis of Twins Studies*



* Population-based studies with records linkage and confirmed zygosity

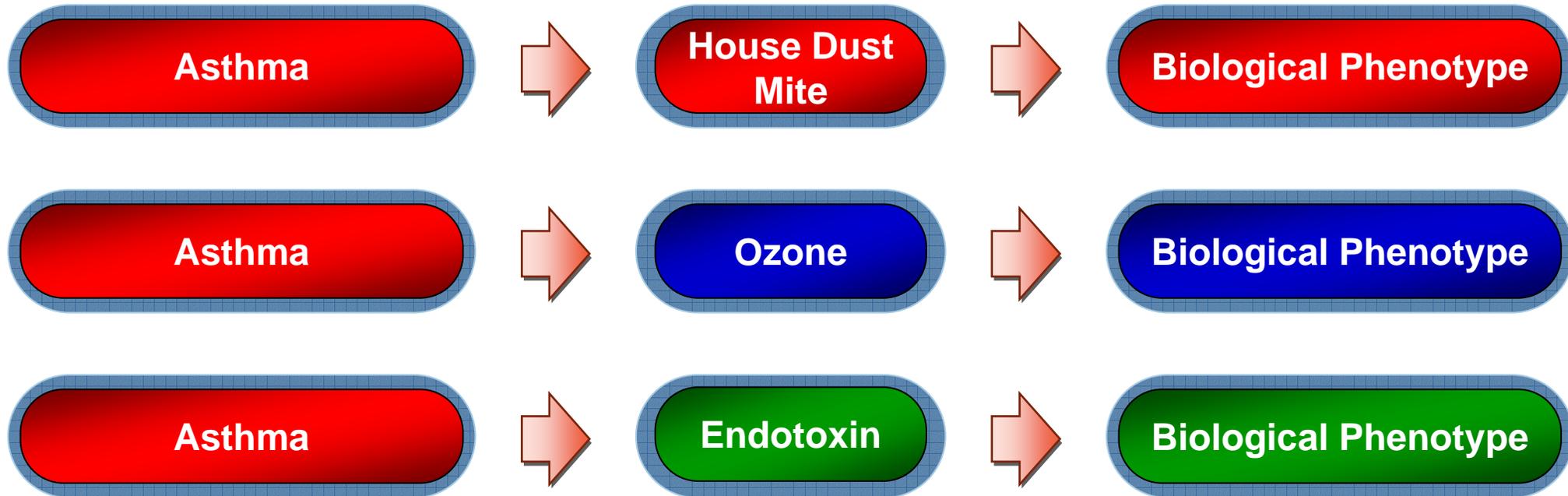
Many Loci and Genes are Associated with Asthma

- Multiple exposures
- Complex biology
- Many phenotypes



Styalinou I. "Comparative Genomics of Asthma." In: *Genetics of Asthma*. In press

Exposures Can Simplify Complex Diseases



Genes and Environment Initiative: Exposure Biology Program

**EXPOSURE BIOLOGY
PROGRAM**



**Develop technology
and biomarkers**

**WHOLE GENOME
ASSOCIATION STUDIES**

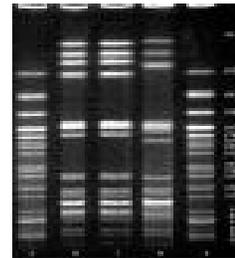
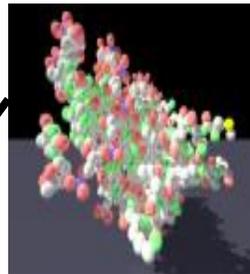


**Identify genetic
variants**

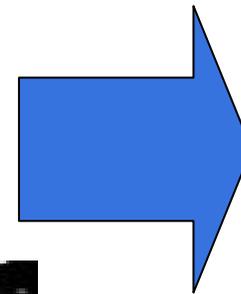
GXE

Exposure Biology Program: match precision of exposure measurements with genetics

Personal genetic analysis (SNPs)



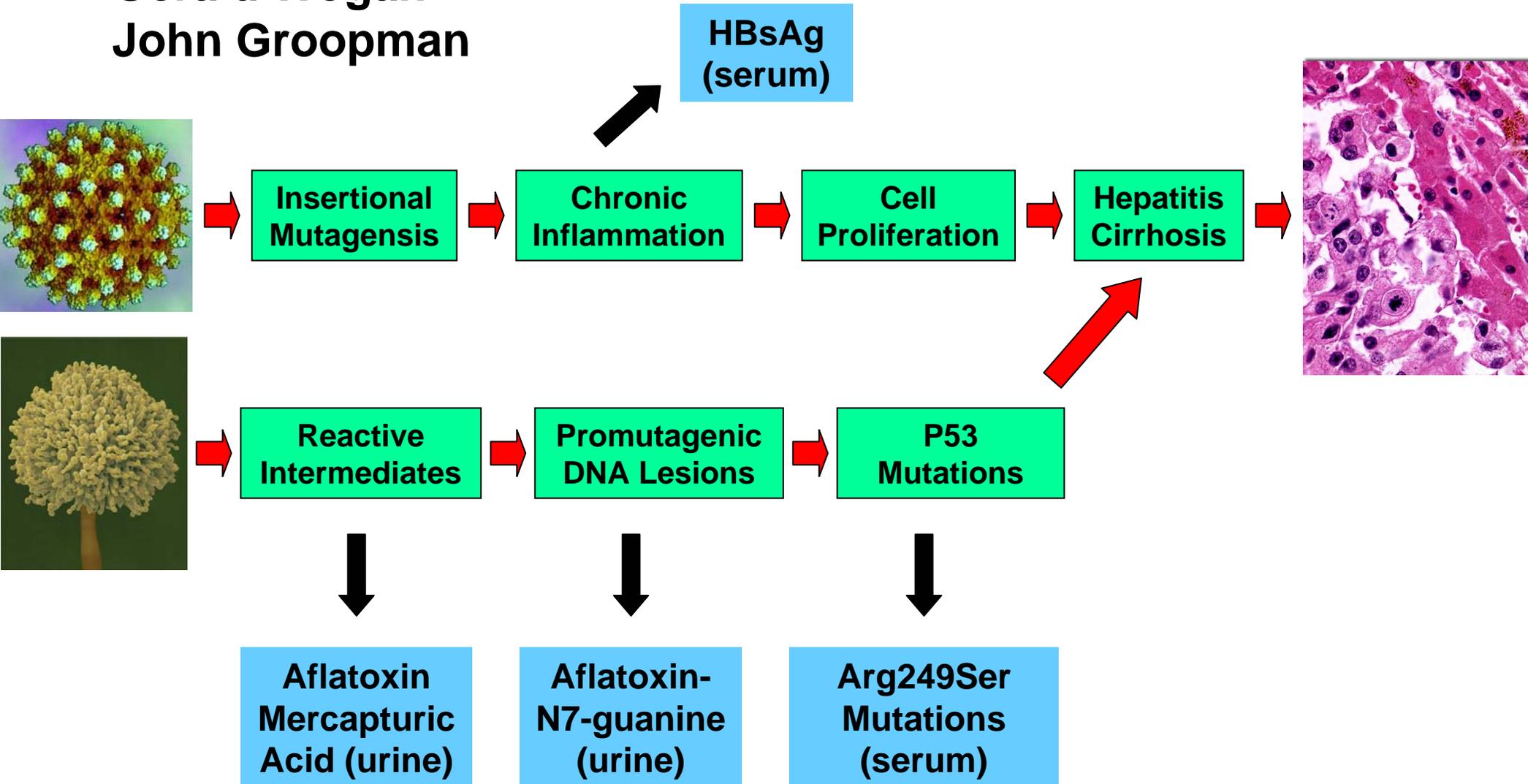
Personal exposure measurements



We need the same level of precision for genetic and exposure data to study GXE in disease

Etiology of Hepatocellular Carcinoma

Gerald Wogan
John Groopman

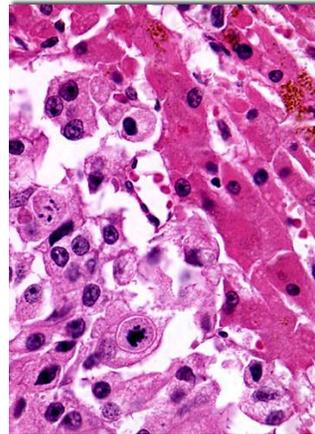
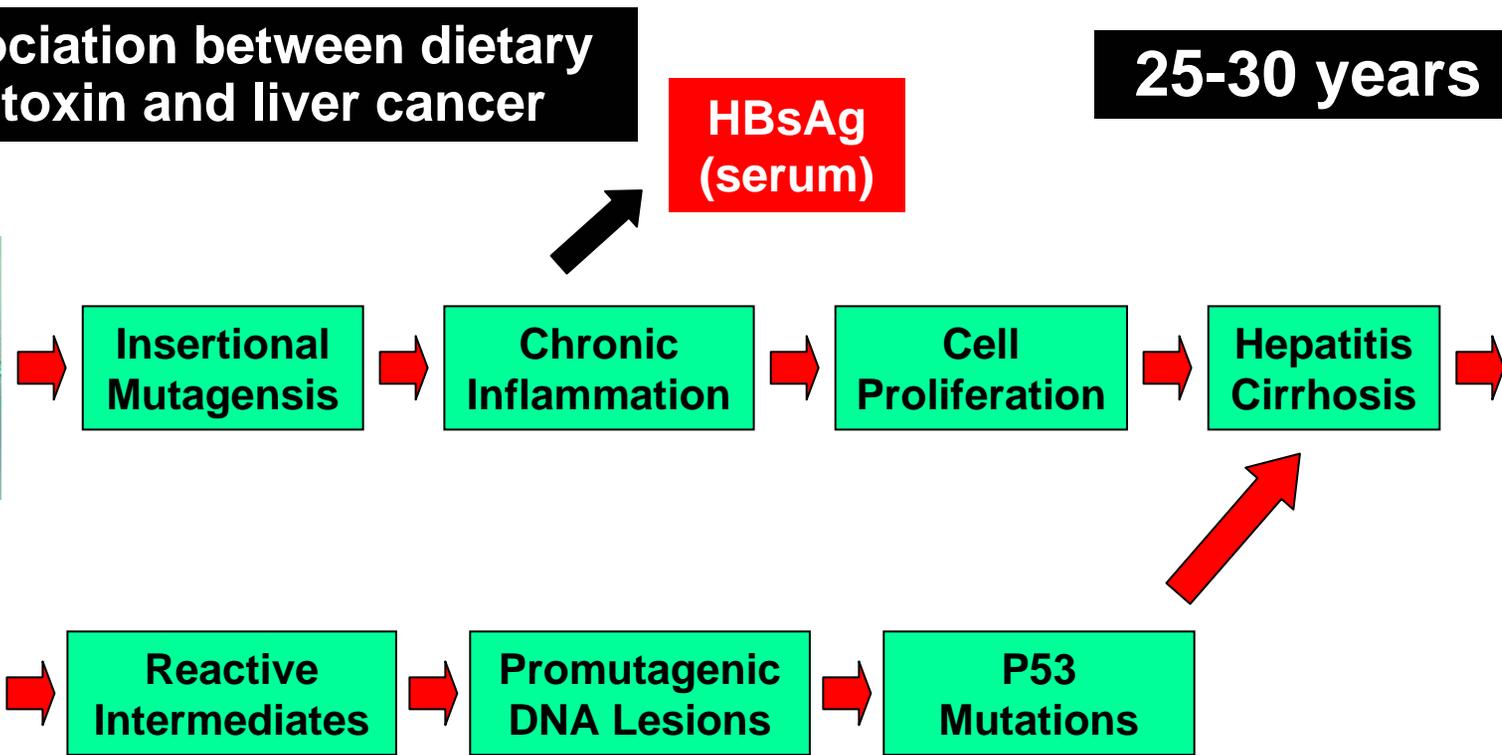
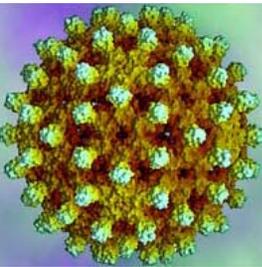


Etiology of Hepatocellular Carcinoma

No association between dietary aflatoxin and liver cancer

25-30 years

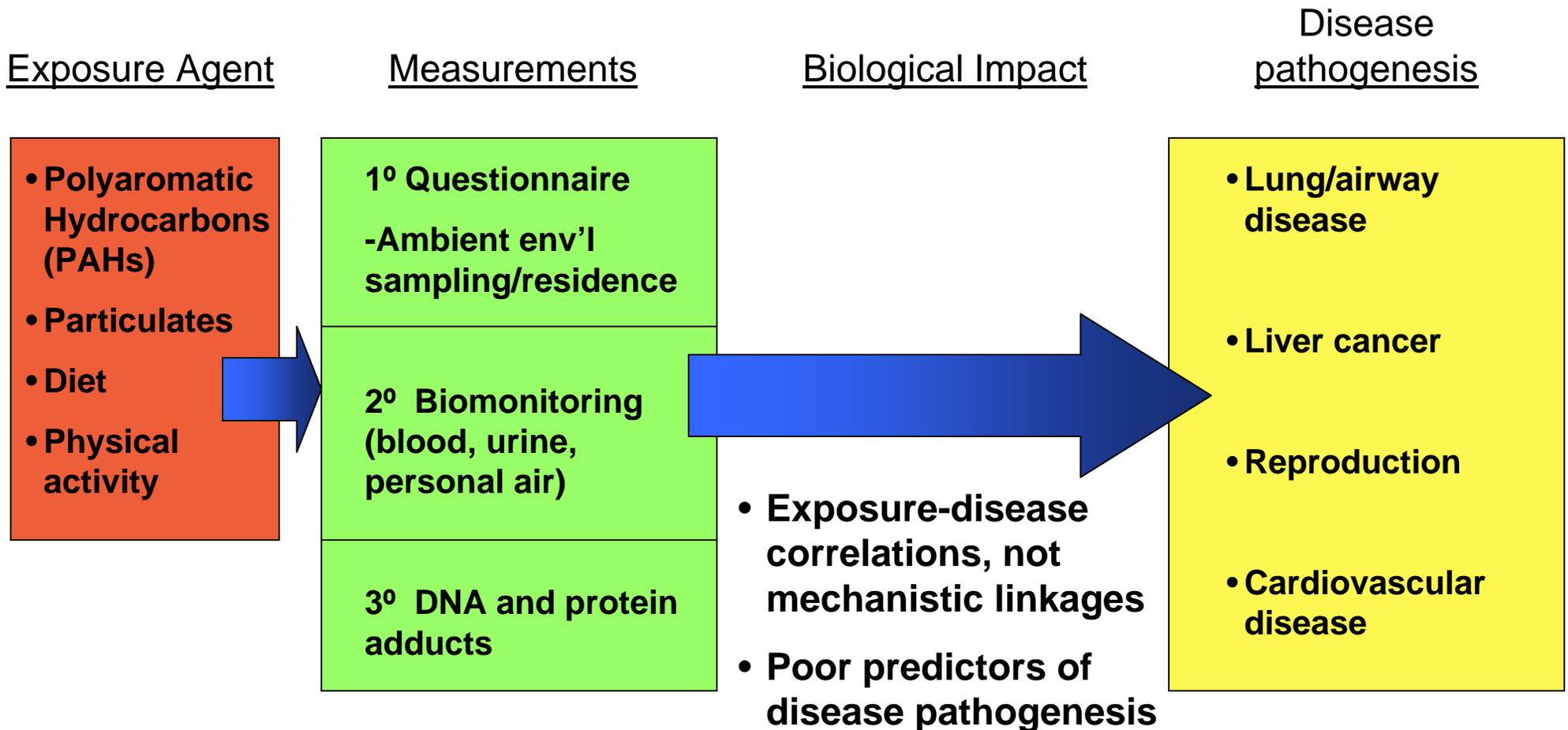
HBsAg
(serum)



↓	↓	↓
Aflatoxin Mercapturic Acid (urine)	Aflatoxin- N7-guanine (urine)	Arg249Ser Mutations (serum)

	<u>RR</u>
Aflatoxin	3.8
HBV	7.3
Aflatoxin + HBV	60.0

Human exposure: What we can we measure now

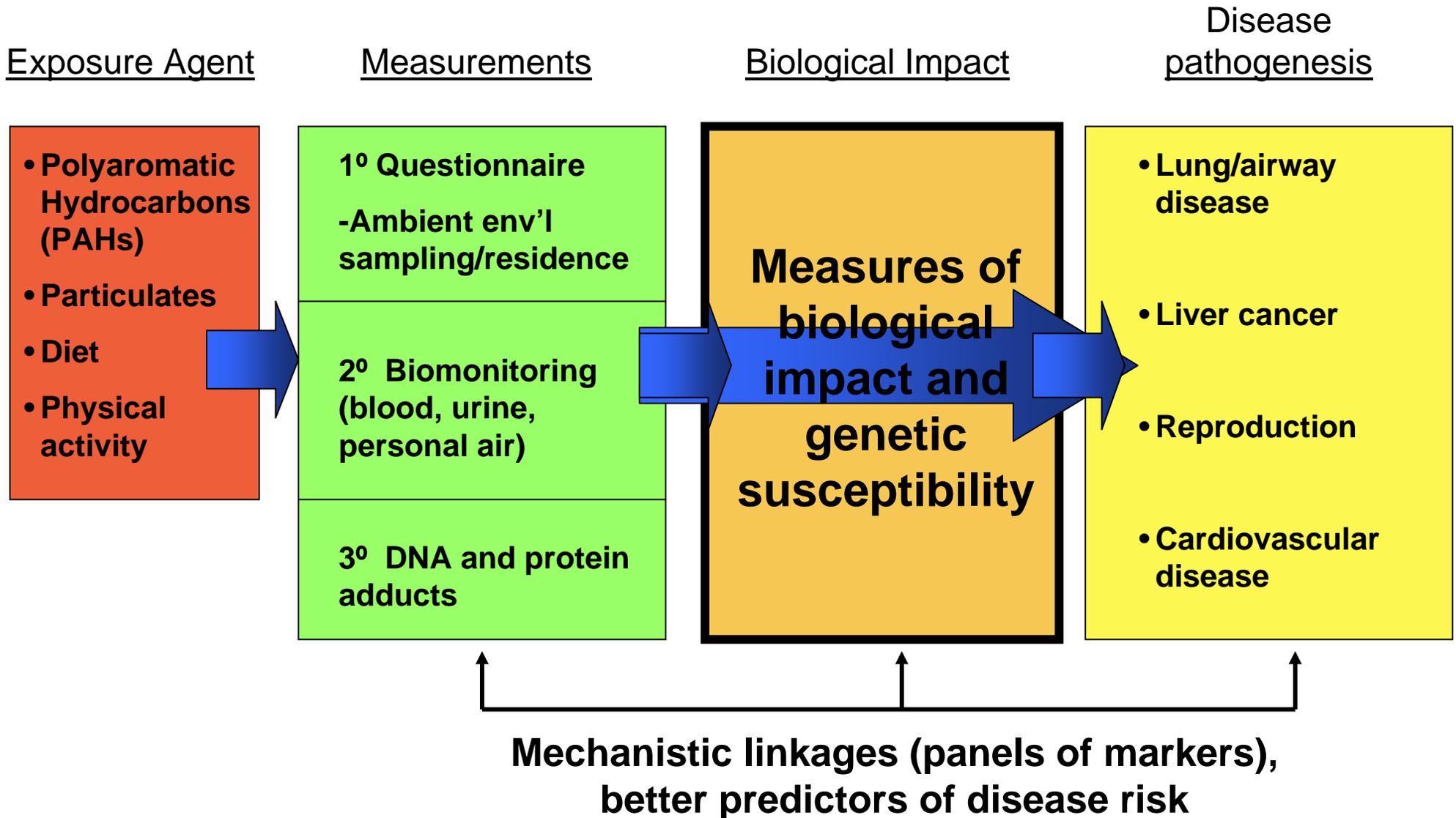


Current Limitations of Exposure Data

- Heavily dependent on questionnaire and environmental measurements
- Lack sensitivity and specificity
- Qualitative not quantitative – lack precision
- Environmental (ecological) not personal measurement
- Does not address contribution of diet or lifestyle

Limits the power to make definitive conclusions about relationships between exposure-genes and human disease

Human exposure: What we think we can measure



Interface between GEI and Large Population Based Study



1. New technology development (≥ 3 yr):

- Biological sensors (microfluidics, molecular imaging, epigenetics)
- Integrated remote sensing devices for real-time, multiplexed measuring (temporal, spatial resolution)

Large Population Based Study

2. Adapt existing technology (≤ 3 yr):

- Point of contact measures
- Physical activity measures (hand-held, remote sensing)
- Improved dietary measures
- Molecular signatures (gene expression, proteins, metabolites, DNA modifications)

Genes and Environment Initiative

Policy Considerations for Exposure Assessment

- **Ensure privacy and confidentiality of data**
- **Foster public involvement before, during, and after the study**
- **Develop clear, consensus policies for data access and sharing, public and private dissemination, and communication upfront**
- **Gauge level of public participation beforehand**

Interface between GEI and Large Population Based Study

