The Exposome and Cancer

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AACR

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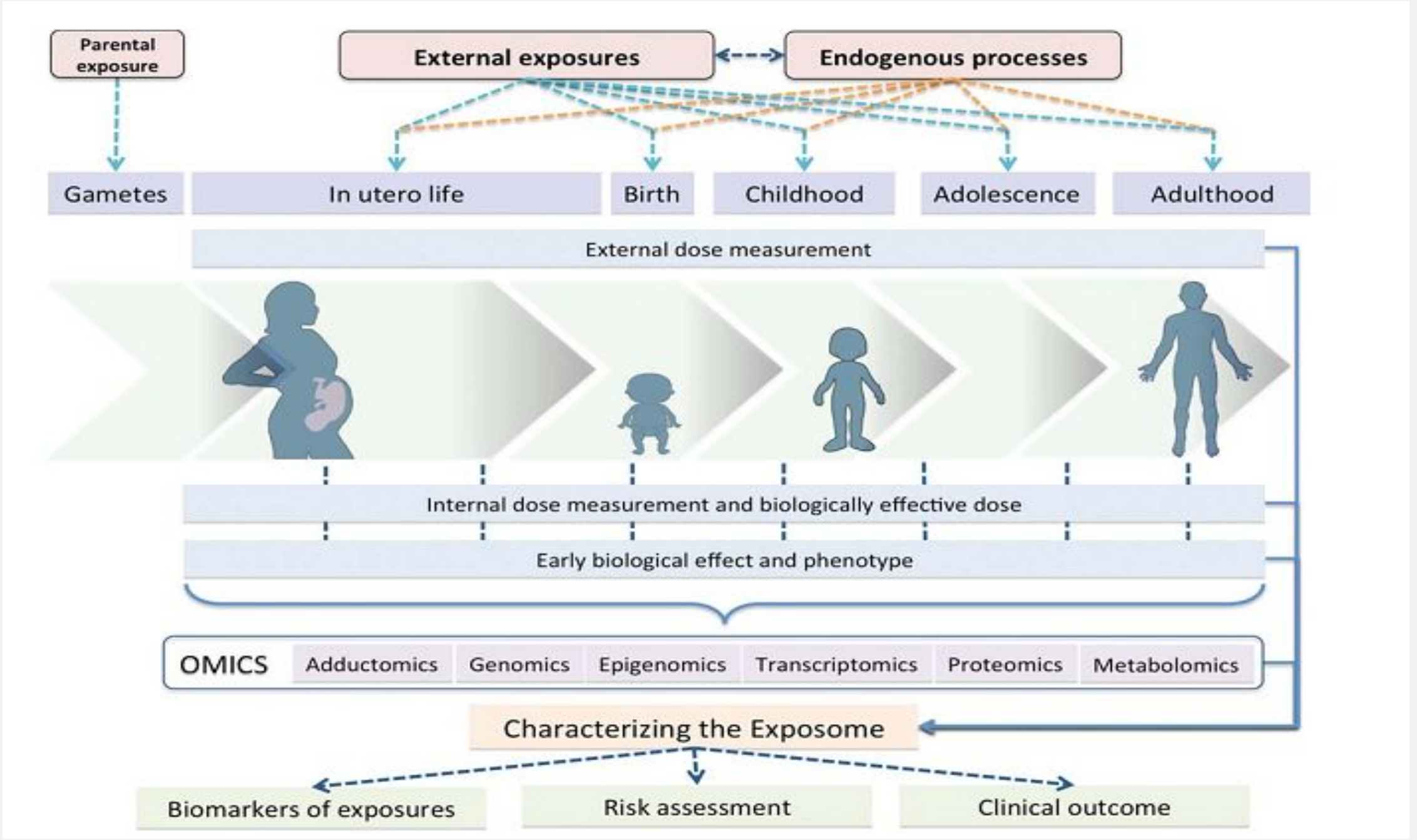
Exposome

Exposure to all exogenous environmental agents, socioeconomic conditions, lifestyle, and diet along with markers of endogenous processes across the life-time of an organism or community of interest. (Wild, 2005)

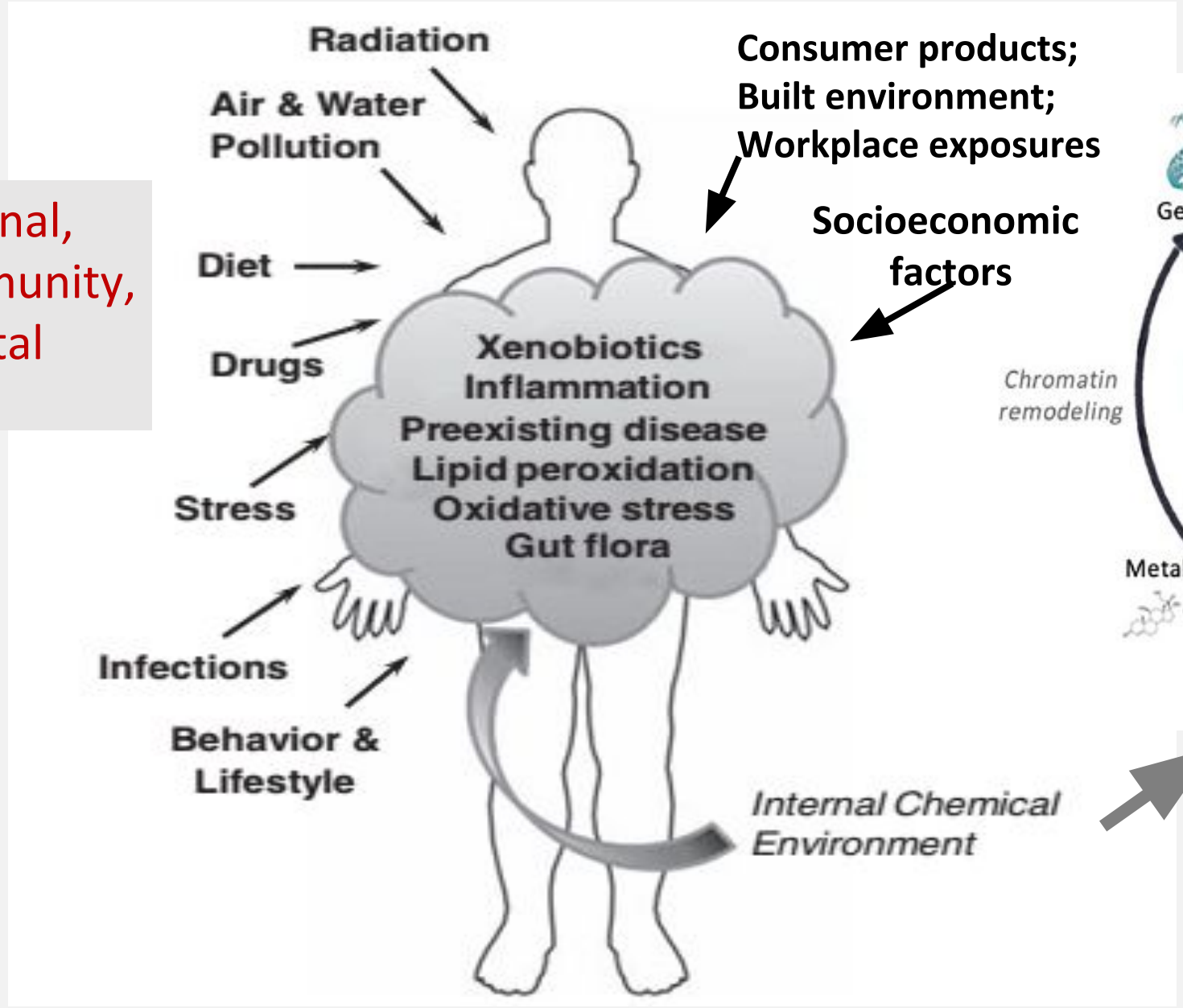
Rationale:

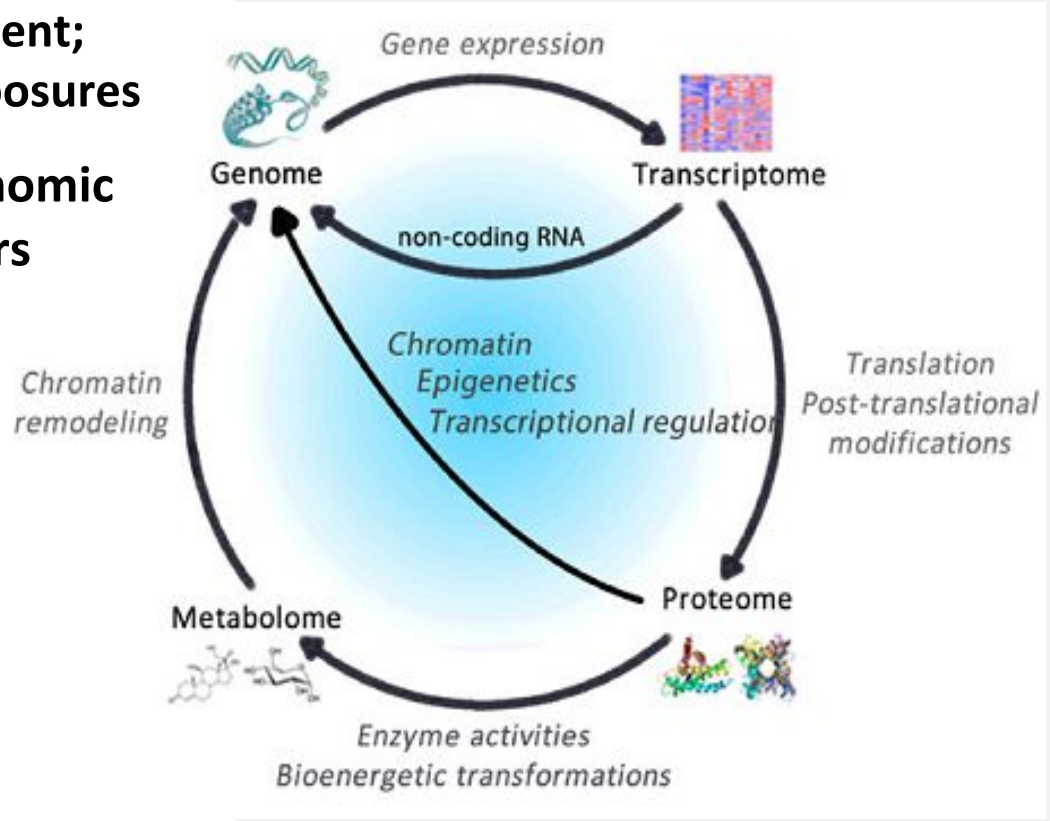
- To acknowledge the reality and complexity of chemical and non-chemical exposures
- To link external exposures to internal body burden, and internal body burden to biologic responses and disease outcomes.



Wild, EMM, 2013

Personal, Community, Societal





Rappaport, 2011 (modified)

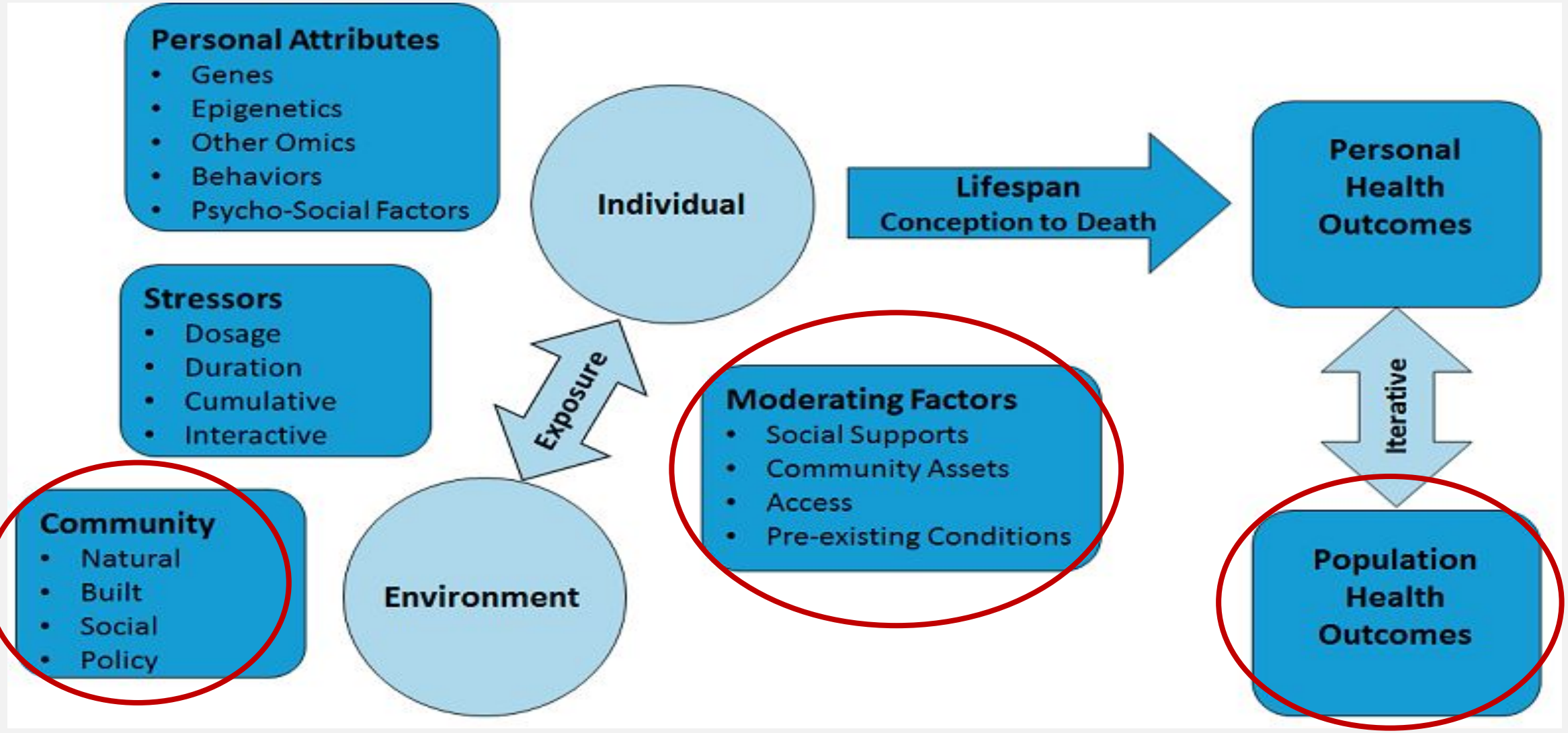
Public health exposome

A framework that helps identify and compare relationships between differential levels of exposure at critical life stages, personal health outcomes, and health disparities at a population level

- Includes mediating and moderating factors at both the individual and population health levels.

Juarez, Int. J. Environ. Res. Public Health 2014

Public health exposome conceptual model



Juarez et al., 2014

General external exposures

- Chemical
  - Air, water, soil, food, consumer products
  - Built environment: home, work, school, community

- Social environment
  - Poverty, education, employment, segregation, discrimination, racism, adverse childhood experiences (ACEs), control in life and on the job, etc.
  - Access to resources and opportunities; measures of resilience

- Policy environment: Federal, state, local

Approaches

- Top down
  - Untargeted biologic monitoring of individuals; over time
  - “omics” (e.g. genome, epigenome, transcriptome, metabolome); intermediate, integrated bio-signatures of exposures
  - Dependent on analytic capabilities; what we can measure

Approaches

- Bottom up
  - Quantifying specific chemicals in air, water, food and other sources of exposure; targeted biomonitoring.
  - Techniques: geospatial monitoring, personal bio-monitors, hand-held computers, mobile phones
  - Could include specific multi-level stressors; e.g. neighborhood- or community-level (e.g. discrimination, racism, income disparities)
  - Cannot be all-inclusive
  - Misses essential features of the internal chemical environment caused by interactions, gender, stress and endogenous processes

Integrating exposome with cancer

Top-down:

- Can help to identify signatures, biomarkers, networks of adverse outcome pathways are important in the pathogenesis of various kinds of cancer
- Why and how might they vary between individuals or communities?
- But, “intermediate” variables (e.g. –omics biomarkers) may be on a causal pathway or confounders (or both/neither)

Bottom-up:

- Which external exposures, alone or in combination, influence cancer risk?
- Which exposures, exogenous or endogenous, are associated with which mutational signatures? With key characteristics?

Hybrid: Meet in the Middle Approach

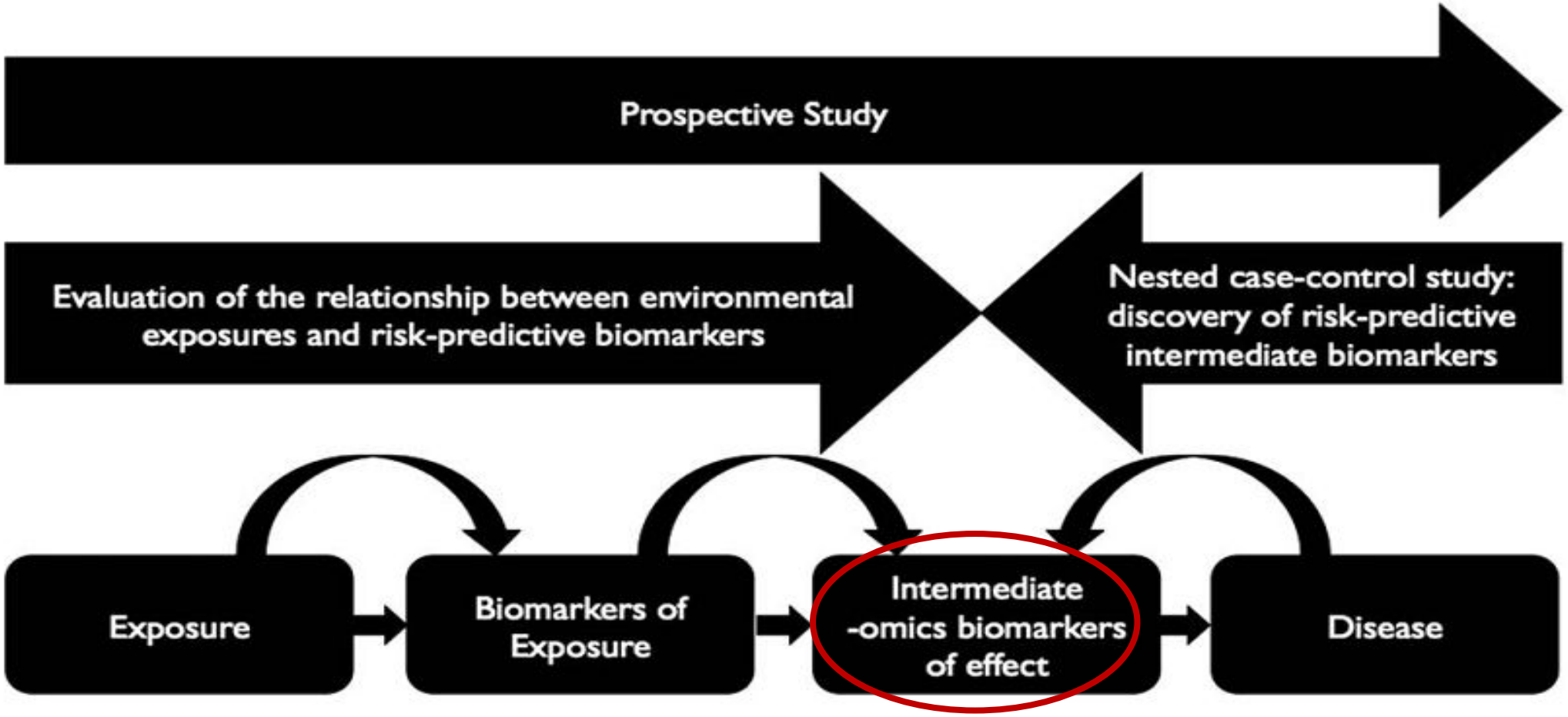


Fig. 1. The "meet-in-the-middle" approach. In prospectively collected cohorts, biological samples are characterized using omics platforms (e.g., transcriptomics, proteomics, and metabonomics) to identify molecules that represent intermediate markers of early effect. These are used to link exposure metrics/biomarkers of exposure with disease endpoints.

Chadeau-Hyam, 2011; Vineis, 2013

Integration challenges

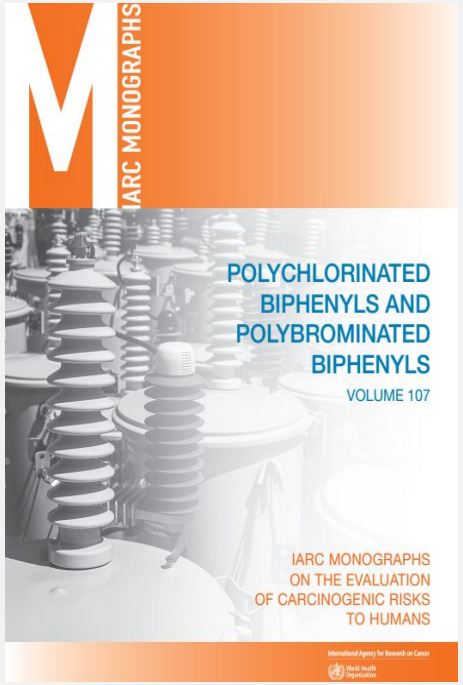
- What biologic changes associated with measures of the exposome are adaptive or adverse? When do adaptive responses become adverse?
- What mixtures of chemical and non-chemical stressors combine to influence the expression of the key characteristics of carcinogens? For example, mixtures resulting in combinations of inflammation, epigenetic modification, hormone alteration, and genotoxicity.
- Which key characteristics are more important in cancer development and therefore need more attention in exposome-related research?
- Answers rely to some extent on biologic assumptions about cancer origins as well as known risk factors for particular cancers

PCBs—Group 1 carcinogen IARC

- Mechanistic data: some but not all of the 209 congeners cause:
  - Genotoxicity
  - Metabolism-associated generation of ROS
  - Endocrine disruption: thyroid, ER, AR
  - Activation of AhR and other receptors
  - Enzyme induction
  - Immunotoxicity
  - Inflammation
  - Reduction in apoptosis

"Overall, PCBs can induce formation of ROS, genotoxic effects, immune suppression, inflammatory responses, and endocrine effects to various extents and through different pathways."

"PCBs are *carcinogenic to humans (Group 1)*….However, the carcinogenicity of PCBs cannot be attributed solely to the carcinogenicity of the dioxin-like PCBs."

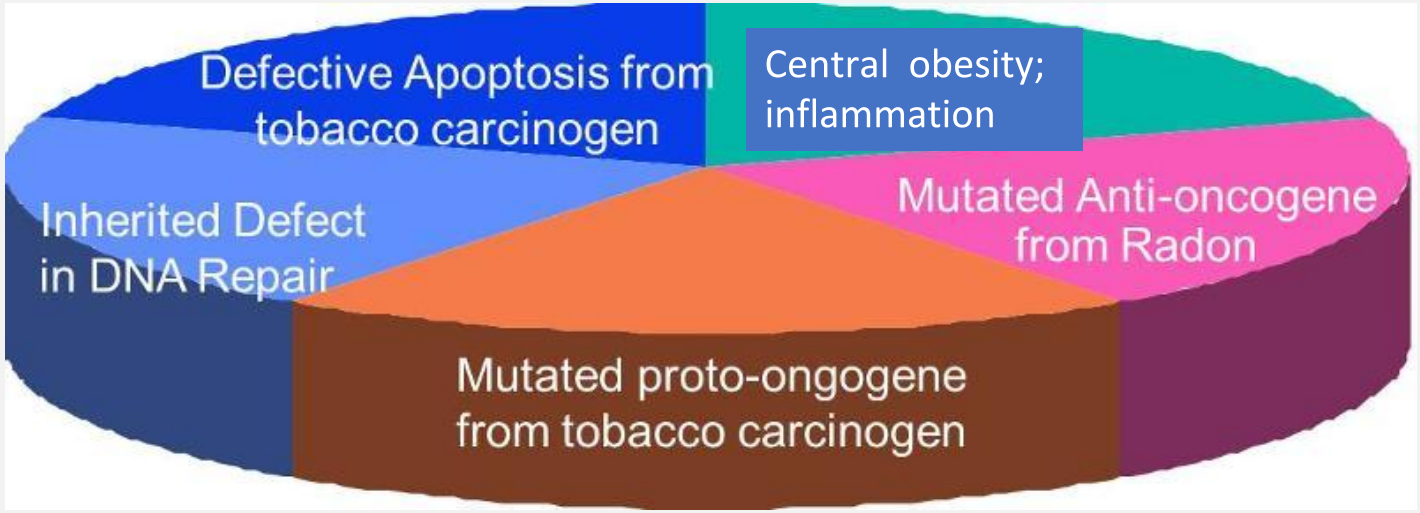


2016

Rothman's Sufficient Causal Model and the Exposome

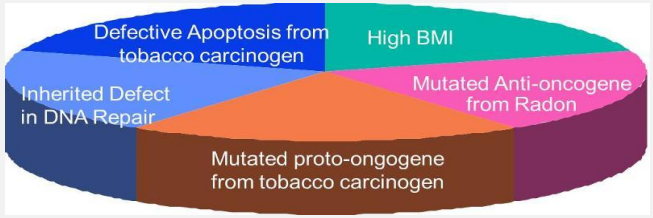
A cause is not a single component, but a minimal set of conditions or events that produces the outcome in an individual person. Interactions among component causes are a primary feature

One sufficient causal "pie" for lung cancer



Which causal pathway <u>combinations</u> are sufficient to result in cancer development over time? Role of promoters? What are the implications for cancer prevention? "Intercepting" cancer before "sufficiency" is completed?

Sufficient Causal Model



- Combinations of other component causes can also be sufficient; i.e., various sufficient causes for lung cancer
- Tobacco is important but, what else? (proportion of never-smokers among patients with NSCLC increasing 1990-2013. (Pelosof, 2017))

Criteria air pollutants; diesel exhaust; dozens of hazardous air pollutants; industrial chemicals, metals; asbestos; silica; radon; radiation; etc.

(IARC; Field, Clin Chest Med, 2012)

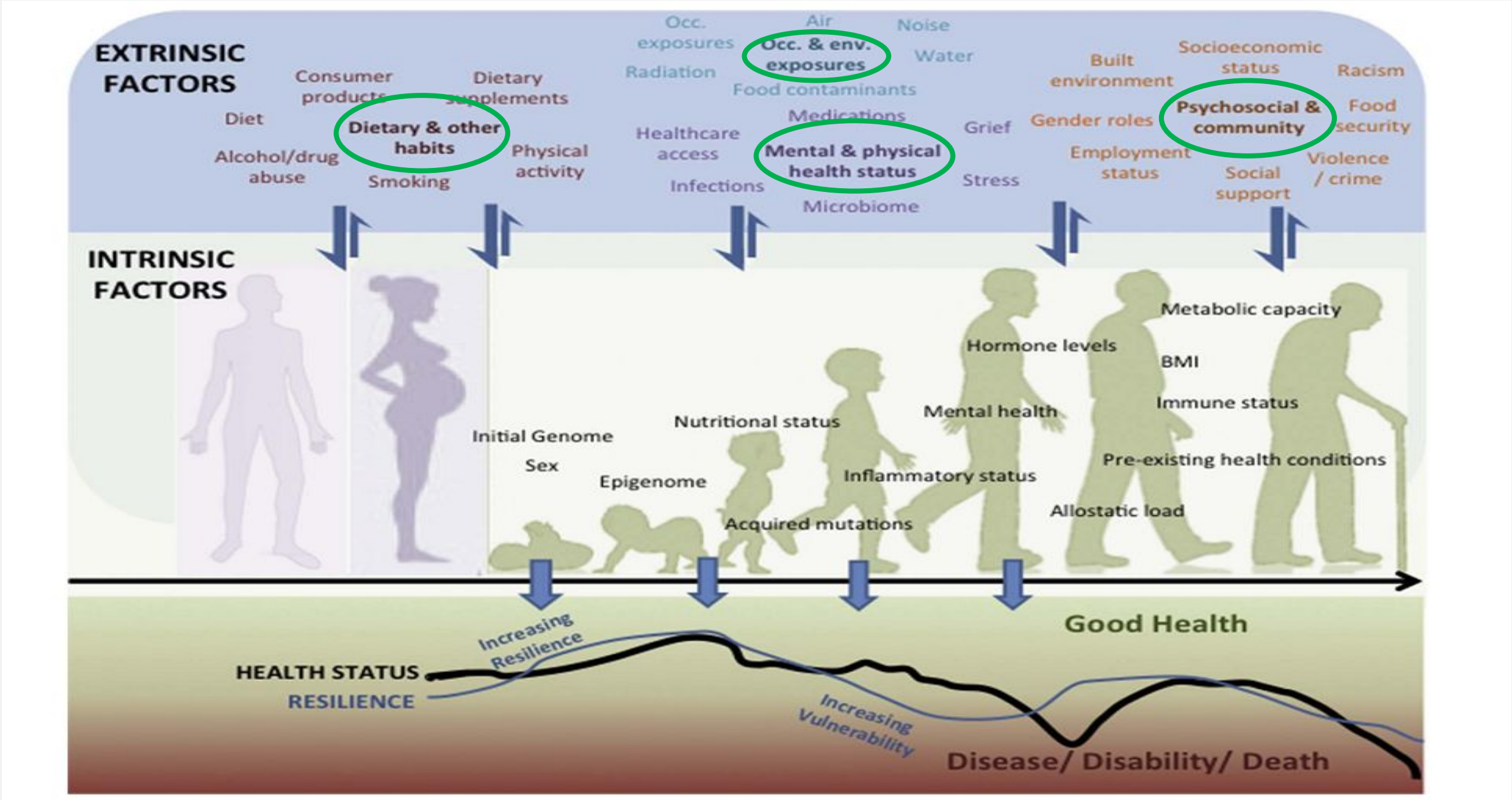
Interactions (effect modification) among causal risk factors, over the life course, make it very difficult to determine valid etiologic or population attributable fractions for many kinds of cancer

Summary

The exposome framework:

Explicitly acknowledges that multiple chemical and non-chemical stressors, over the life course, can influence cancer risk in individuals and populations
(a quintessential “mixture” problem)

Suggests opportunities for integrating multiple and cumulative exposures, over the life-course, with biologic responses relevant to carcinogenesis



Moving from G x E to I x E (Individual, community, societal level variables) McHale; Mutat Res, 2018

Future needs and questions

- More routine integration of social sciences, epidemiology, laboratory sciences; multi-level exposure assessments
- In addition to understanding mutational signatures associated with specific exposures, look for changes in mutational signatures or epigenetic patterns of tumors over time as potential risk factors change; e.g. gliomas and cell phone use
- Which key characteristics, apart from increasing mutational load, are more important in cancer development and therefore need more attention in exposome-related research? Need valid biomarkers
- Systematic attention to timing of exposome assessments; windows of vulnerability

Future needs and questions

- What is the relevance of transcriptome and metabolome to past exposures? What is their value in non-target tissues?
- How stable are epigenetic markers associated with cancer risk? Does that vary over the lifecourse? When and how can they be used as markers of exposure?
- Further development of bioinformatics and biostatistical methods (collecting, curating and analyzing complex “big data”)

Ongoing exposome projects

- EU: Human Early-Life Exposome (HELIX)
- EU: Health and Environment-wide Associations based on Large population surveys (HEALS; http://www.heals-eu.eu)
- EU: EXPOsOMICS (http://www.exposomicsproject.eu)
- NIH: Exposome Research Center (http://emoryhercules.com)
- NIEHS: Children's Health Exposure Analysis Resource (CHEAR; 2015; http://www.niehs.nih.gov/research/supported/exposure/chear/)