National Institute of Environmental Health Sciences
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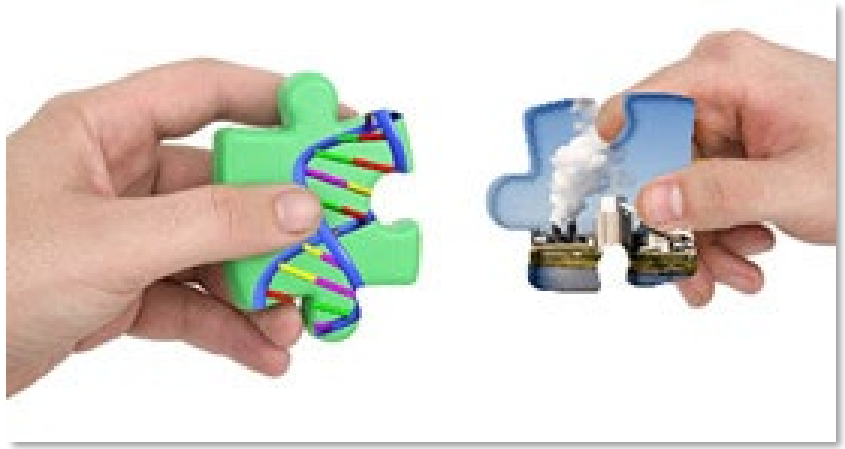
Overview of NIEHS Extramural Research Efforts in Gene-Environment Interaction (GxE) Studies



Kimberly McAllister
Program Director
National Institute of Environmental Health Sciences

Outline of Presentation

- **Overview** of G x E portfolio/research extramural efforts at NIEHS
- **Challenges** related to G x E in human studies for complex disorders
- **Recent NIEHS initiatives** to address these challenges
- Other recent related efforts:
  - **Multi-omics**
  - Impacts of exposures on **Mendelian diseases**
  - **G x E ELSI** (Ethical, Legal, and Social Implications)
- Introduction for **invited speaker talks** for this afternoon

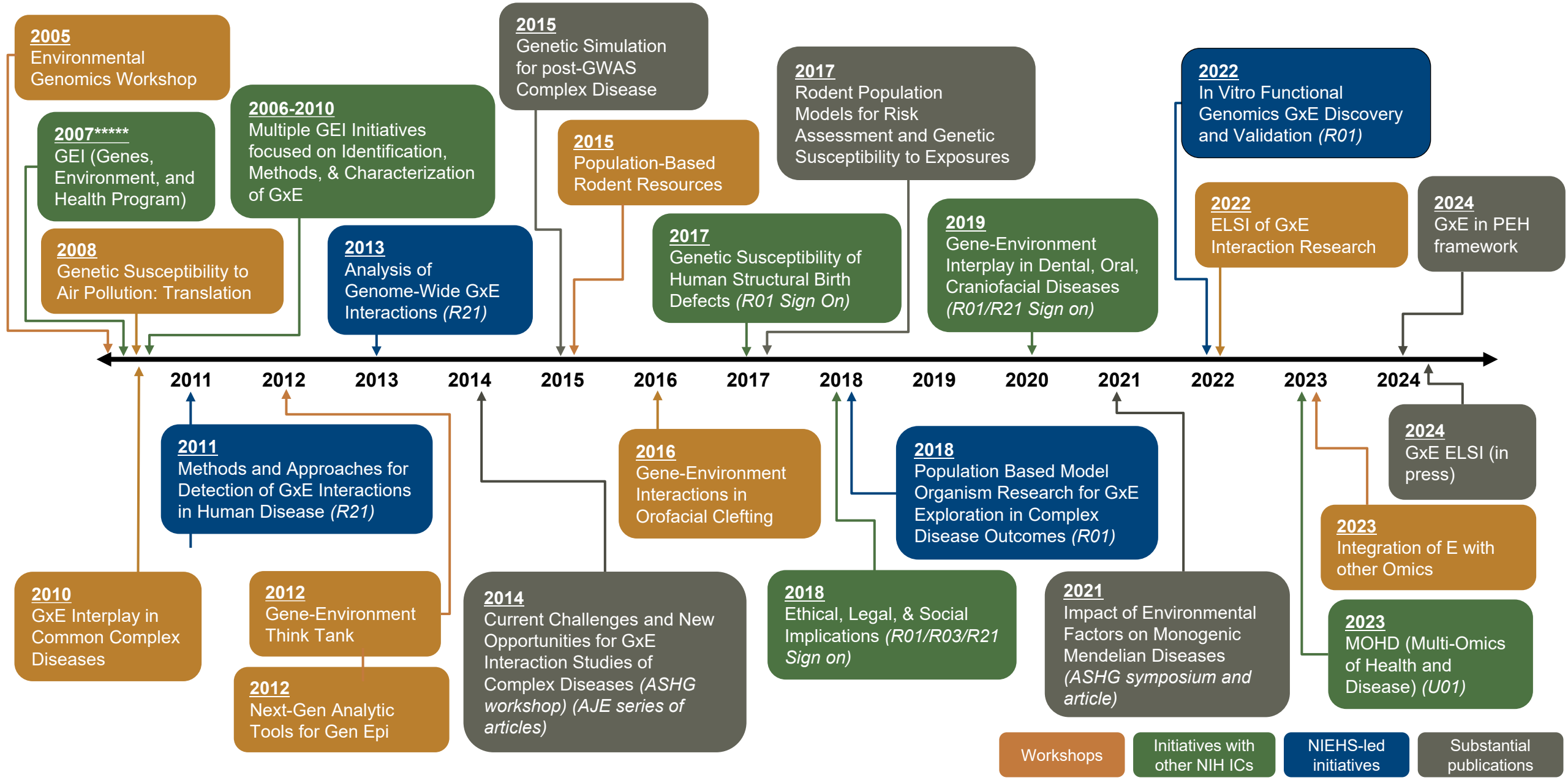
Why Study G x E Interactions?

G x E (Gene-Environment) Interaction:

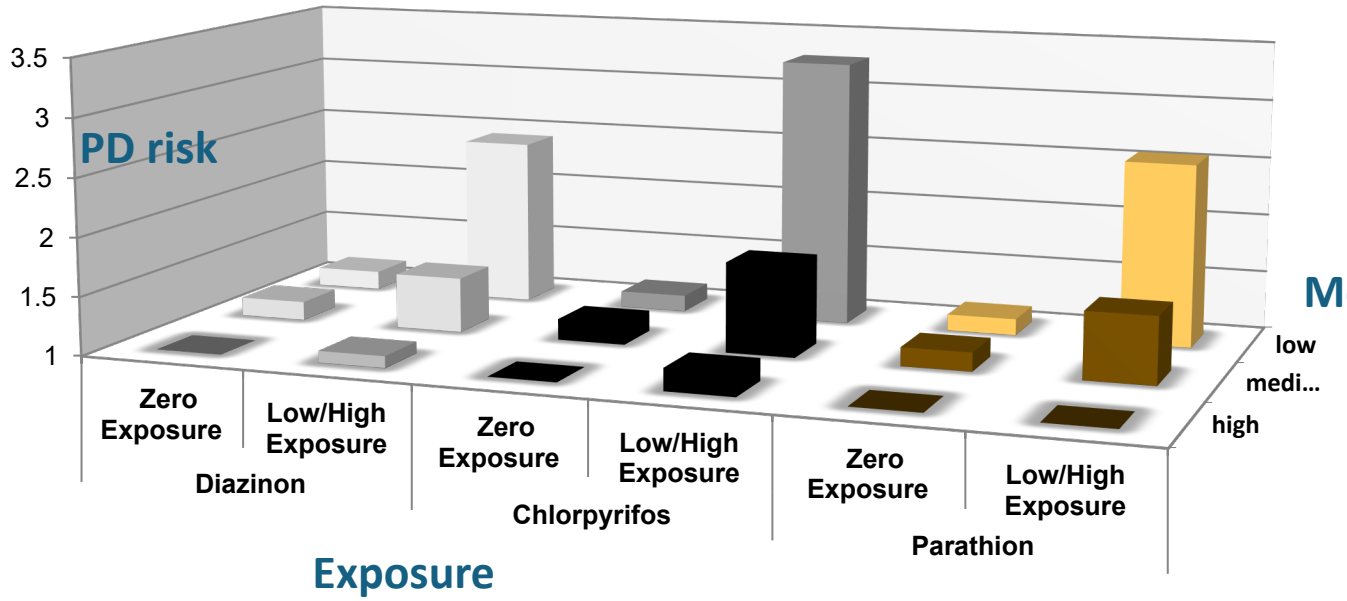
A varying effect of an environmental exposure(s) depending on genetic background of an individual.

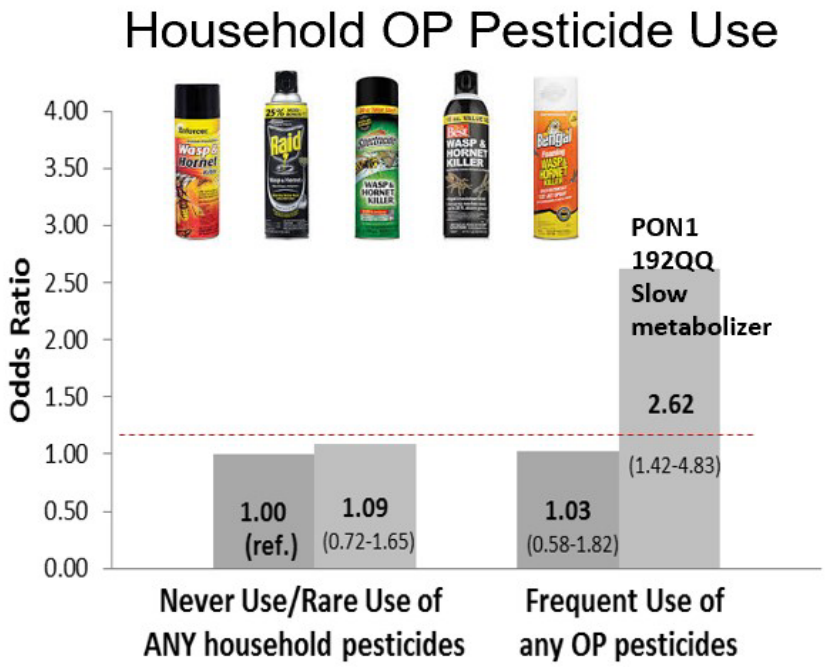
- Understanding biological mechanisms and pathways
- Risk prediction for complex disease
- Identify the most genetically susceptible individuals to exposures to ultimately adapt prevention/intervention strategies to protect (precision environmental health)

NIEHS Investments in GxE Research in Partnership with Other NIH Institutes (esp. NHGRI and NCI)



PD Risk by PON1 Metabolizing Status & OP-Pesticide Exposure





Functional paraoxonase 1 variants modify the risk of Parkinson's disease due to organophosphate exposure

Pei-Chen Lee [a,b], Shannon L. Rhodes [a], Janet S. Sinsheimer [c], Jeff Bronstein [d], Beate Ritz [a,d,*]

Environ Int 56 (2013) 42-47

Household organophosphorus pesticide use and Parkinson's disease

Shilpa Narayan,[1] Zeyan Liew,[1] Kimberly Paul,[1] Pei-Chen Lee,[1] Janet S Sinsheimer,[2] Jeff M Bronstein[3] and Beate Ritz[1,3]*

Int J Epidemiol 42 (5) (2013) 1476-1485

Past PARs: Development and Application of Statistical and Bioinformatics Methods/Approaches for GxE Discovery (in *Partnerships with Many Other NIH ICs)*

G x E Interaction Methods Initiative (1st PAR): PAR11-032

- Objective: Develop and Test Designs, Algorithms, and Analytical Approaches for Identifying G x E in Complex Disease
- Other participating ICs: NLM, NIDA, NIDCR, NCI, NHLBI, NHGRI, NIBIB
- Two Step Approaches for GxE with Simultaneous Software Programs (University of S. California efforts- David Conti-guest speaker)

Analysis of Genome-Wide Gene-Environment (GxE) (2nd PAR): PAR13-382

- Objective: Continued Development of Innovative Analytical Methods and Application of these GxE Methods in an Existing Human Consortia or GWAS
- Other participating ICs: NCI, NHGRI, NIAMS, NIDA, NLM, NHLBI
- Consortium Meta-Analysis/ "Mega-Consortium": harmonized datasets/longitudinal measures of E

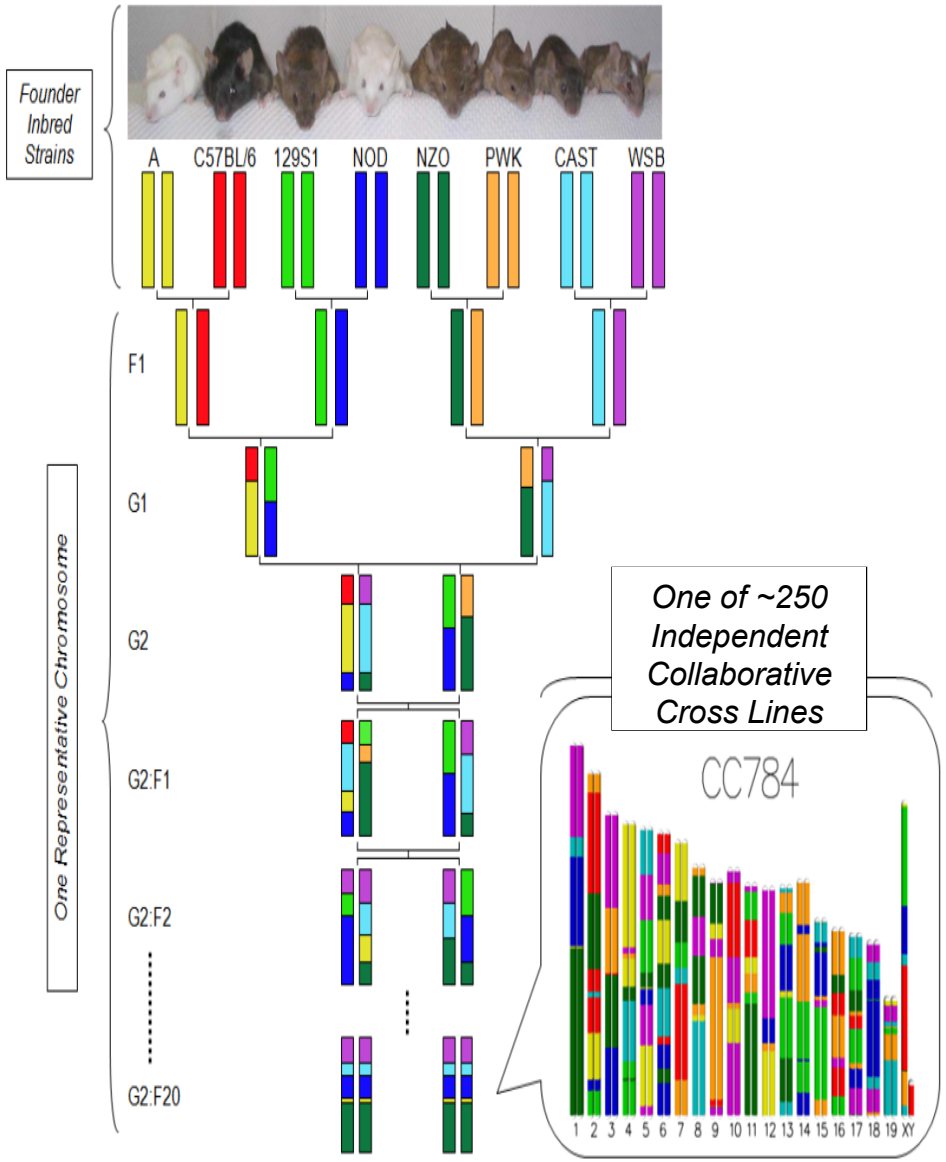
(Peter Kraft-guest speaker)

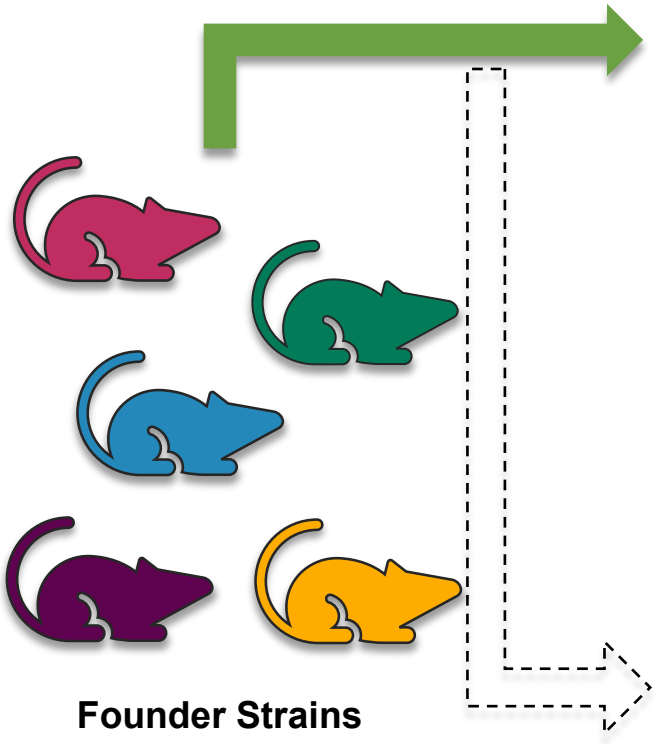
Challenges with Identifying New GxE Findings in Human Population Studies or Validating Existing Ones:

- Underpowered studies → **Need 4x numbers** compared to main effect study
- Complexity of measuring environmental exposures (ex. mixtures, dose, temporality) and harmonizing exposures across consortium
- Limited range of genetic and/or environmental variation
- Most genetic variants in non-coding regions → **need tissue-specificity and regulatory context**
- Secondary epidemiology studies with comparable G and E to validate may not exist

In Recent Years, NIEHS has Explored Alternative Approaches for GxE Discovery and/or Validation….

Population-based Mouse Models for GxE





Collaborative Cross (CC)

- **Genetically distinct lines**
- **Genetically identical within lines**

Diversity Outbred (DO)

- **Genetically unique individuals**
- **Genomic heterozygosity**

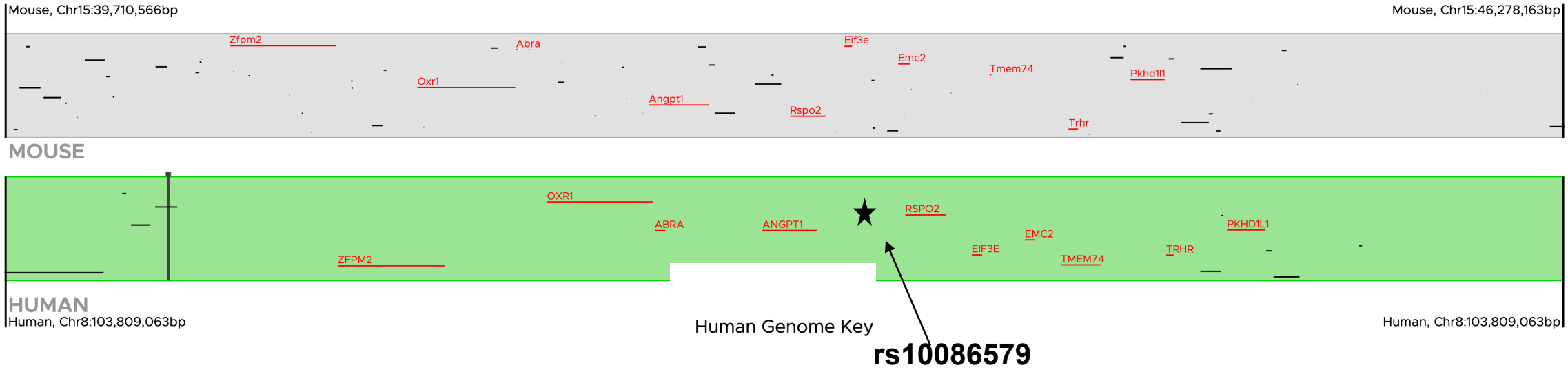
Adapted from Harrill and McAllister, 2017, *EHP*

Population Based Model Organism Research for GxE Exploration in Complex Disease Outcomes (R01), RFA-ES-17-009.

Orthologous Locus in Humans Exhibits GxE with Air Pollution in Emphysema (from Dr. Samir Kelada's lab, UNC)

Mouse QTL region (Chr15)

Orthologous region in human genome (Chr8)



B012 THE AIR OUT THERE: INVESTIGATIONS IN AIR POLLUTION / Mini Symposium

American Thoracic Society Abstract

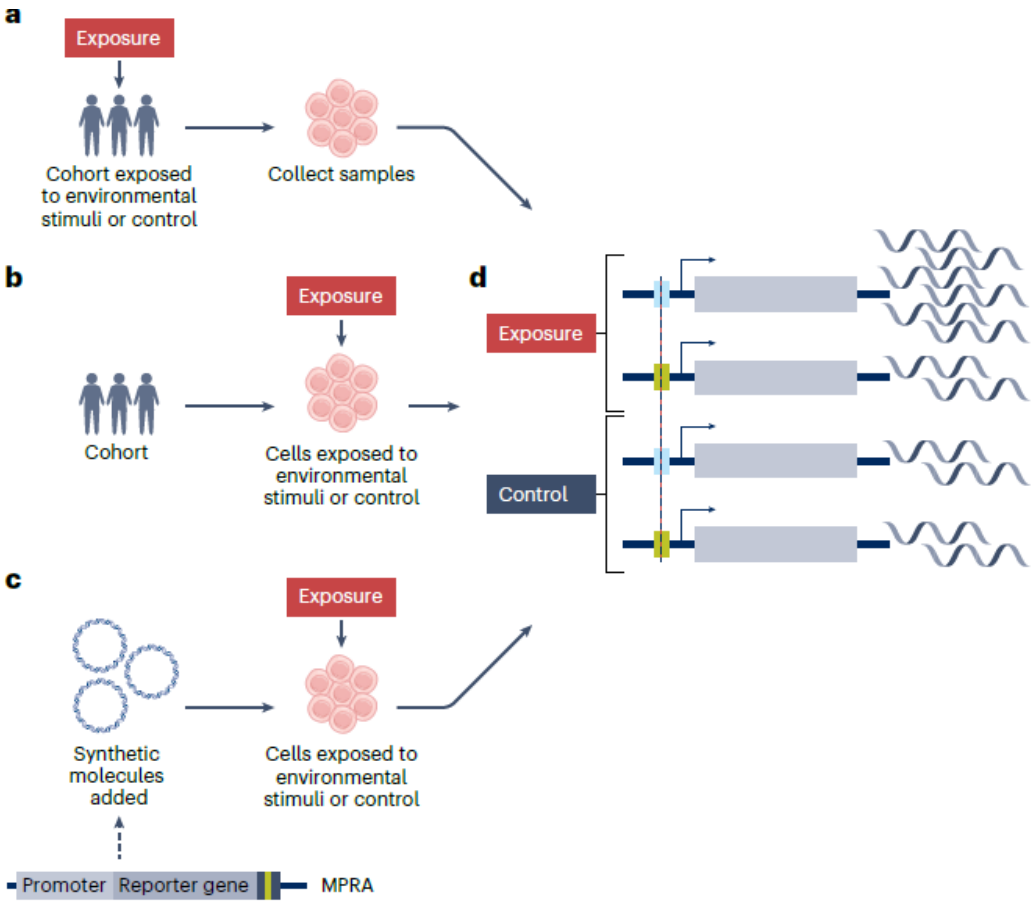
Air Pollutant Exposure-by-Gene Interactions Associated with Emphysema, Lung Structure, and Lung Function in SPIROMICS

New Advances for *In Vitro* and *In Silico* Approaches Could Allow Functional Validation/Discovery and Mechanistic Understanding of G x E Findings:

- ***In Vitro* Functional Genomics Advances for GxE, RFA-ES-20-018, using innovative tools/technologies:**
  - ❖ Genome/epigenome editing tools (**CRISPR/Cas9,** etc.)
  - ❖ Single cell analyses and embryonic stem (**ES**) cells and/or induced pluripotent stem cells (**iPSCs**) from relevant cell types-**allowing population-level studies to be performed *in vitro***
  - ❖ Organoid culture models (OCMs) and tissue-chip platforms-**allowing more accurate *in vitro* human models of disease**
- Nancy Cox chaired special emphasis panel review
- *"In Vitro* Functional Genomics Advances with E" webinar series launched in 2023

Lessons Learned From Functional Genomics of GxE

(Francesca Luca and Colleagues, *In Vitro* Functional Genomics RFA Recipient)

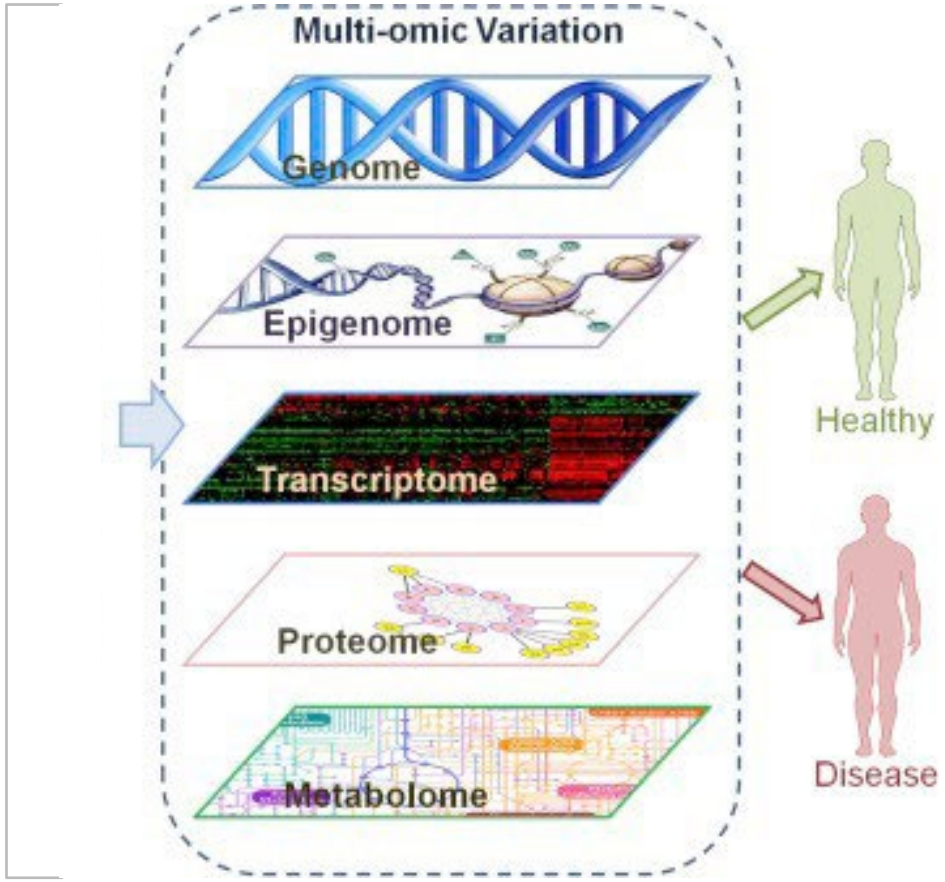


- Functional genomics approaches can identify molecular mechanisms underlying environmental effects on complex traits **with cellular and subcellular context**
- Context-aware genetic analysis of gene regulation identifies **latent environmental effects**
- One can identify and fine-map genetic variants that contribute to **inter-individual variation in the response to the environment**

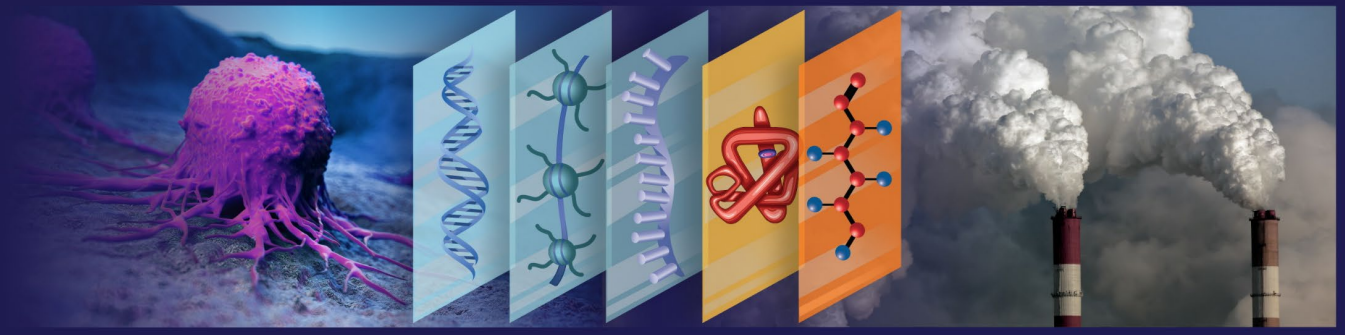
Boye et al, 2024, *Nat Genet*; Boye et al, 2024, *eLife*; Findley et al, 2019, *Genetics*; Findley et al, 2021, *eLife*; Moyerbrailean et al, 2016, *Genome Res*; Resztak et al 2023, *Nat Comm*; Resztak et al, 2021, *eLife.*

Integration of Environmental Data with other Omics Data (Beyond G) to Inform How E Alters Biological Pathways to Impact Disease Outcomes (G X E X Omics)

- Increased mechanistic insights
- Improved disease risk predictions
- Challenges:
  - Very few computational tools integrate complex environmental data well (heterogeneity, dose, timing, etc.)
  - Many of our environmentally-rich cohorts lack comprehensive omics data



National Institutes of Health



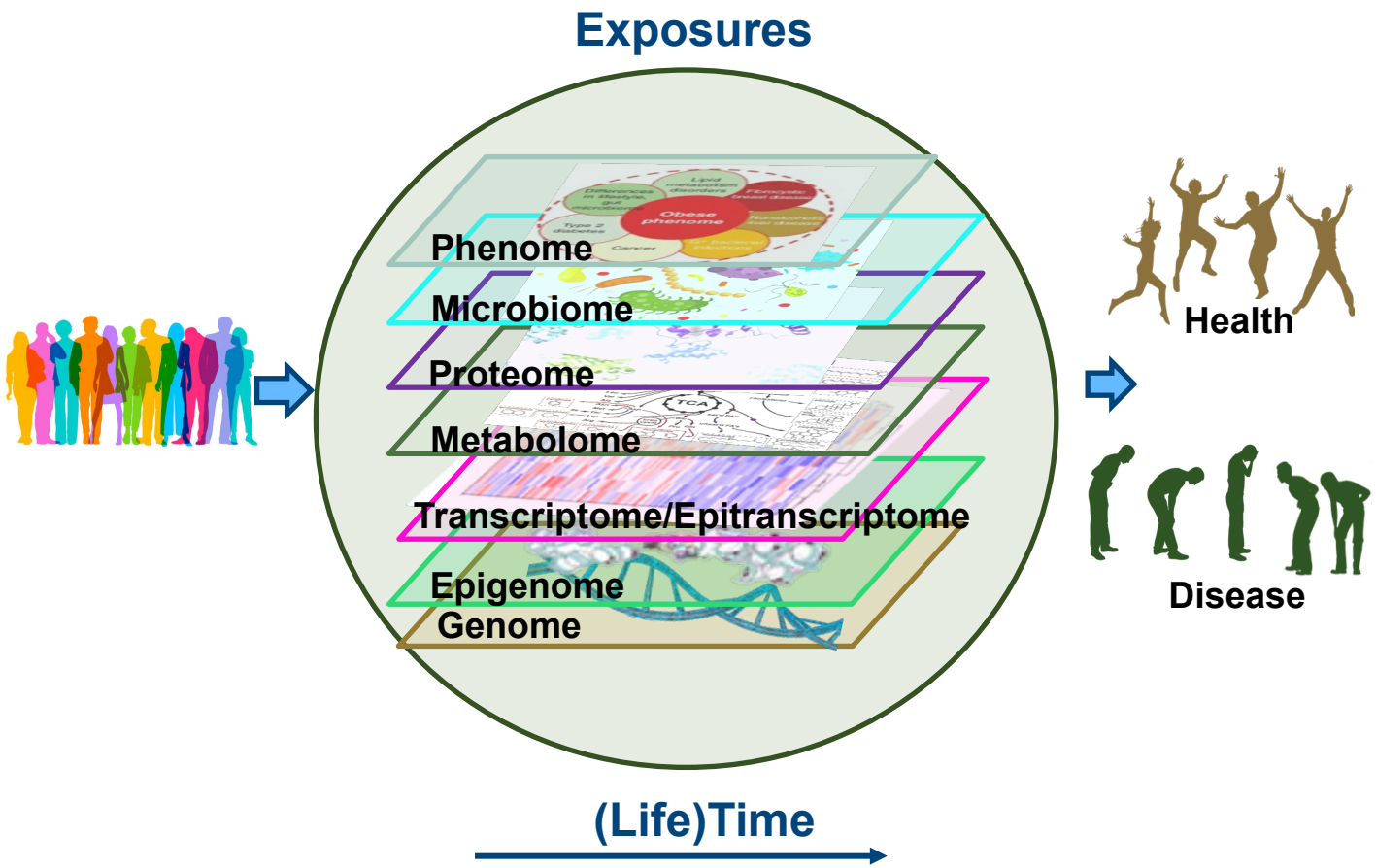
Integrating Environmental Data With Other Omics for Cancer Epidemiology (Feb 14-15, 2023)

Purpose: **Identify challenges and opportunities related to the integration of environmental exposure data with other omics data for human cancer population studies (especially exploring gaps in computational methods)**

Workshop Report:

https://www.niehs.nih.gov/sites/default/files/news/events/pastmtg/2023/environmental_data/integrating_environmental_data_workshop_report_508.pdf

MOHD (Multi-Omics for Health and Disease): NHGRI/NCI/NIEHS Initiative



Goals:

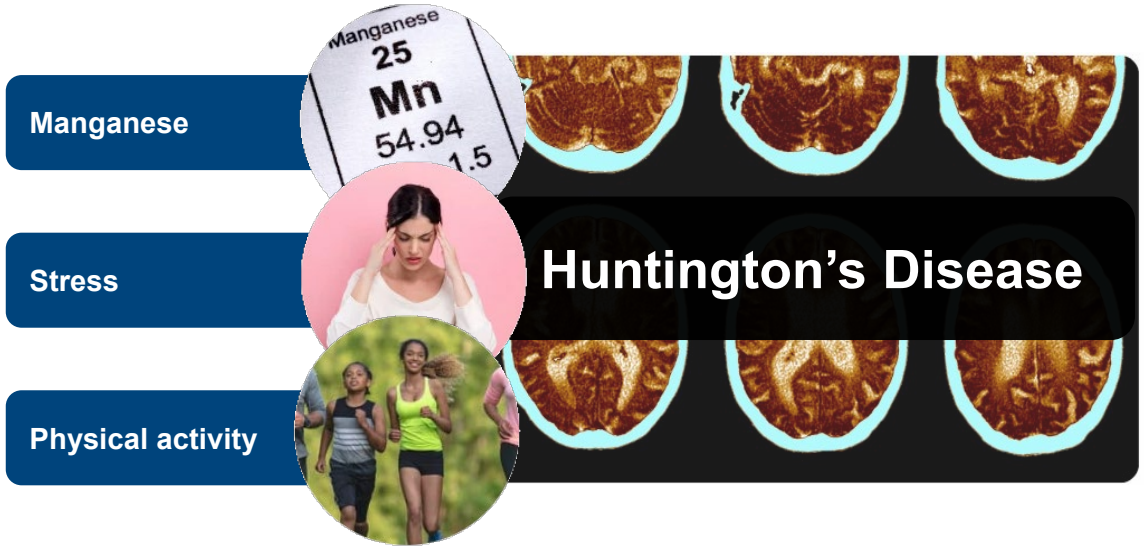
1. Multi-omics (with phenotypic and environmental exposure data) integration to identify molecular "profiles" for disease states
2. Develop generalizable data harmonization, integration, and analysis methods, and best practices and standards for multi-omics application
3. Create a public multi-dimensional dataset

Adapted from slides presented by:
M. Fornage's (UT Health Houston)
T. Lappalainen (NY Genome Center)

https://www.genome.gov/research-funding/Funded-Programs-Projects/Multi-Omics-for-Health-and-Disease

Mendelian Diseases and Environmental Risk Factors

(ASHG symposium and *Tox Sci* commentary, 2021*;* Charmaine Royal*)*



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Ethical, Legal, and Social Implications (ELSI) of Gene-Environment Interaction (GxE) Research

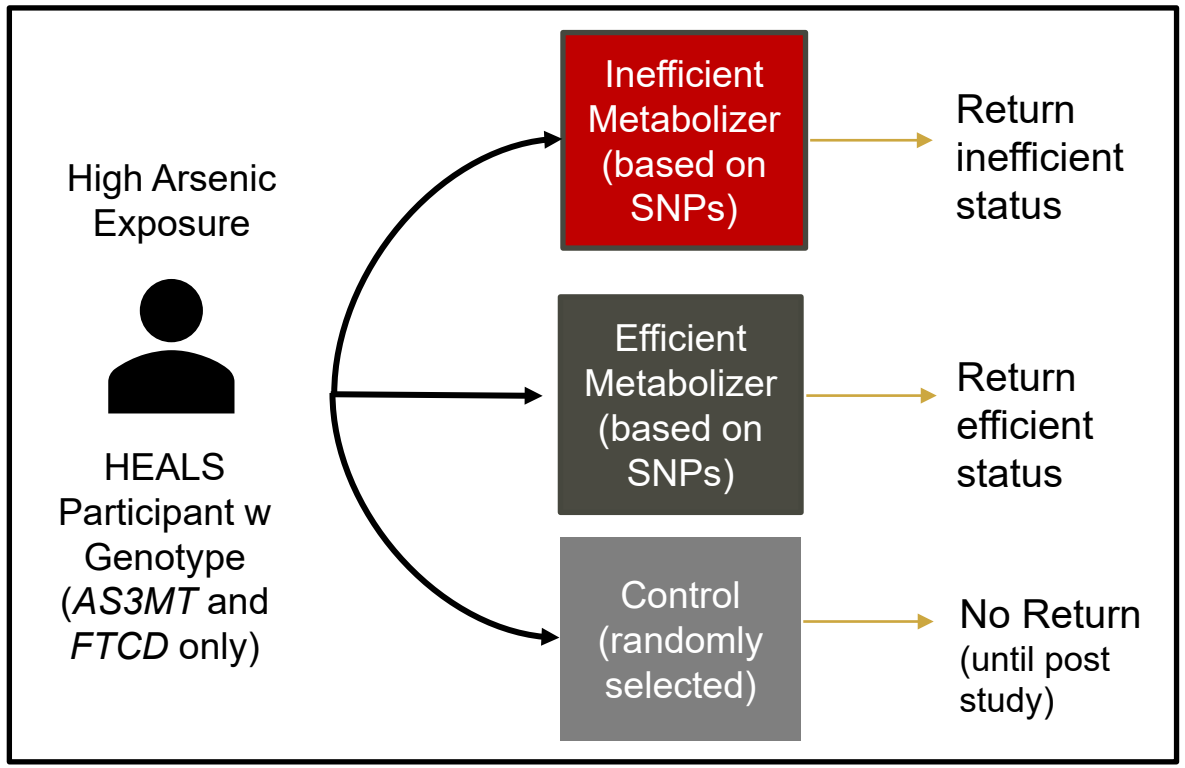
NIEHS/NHGRI Workshop** (January 2022)**:

What are the ELSI issues specifically related to genetic susceptibility to environmental exposures? **Report Back** (Return of Research Results to research participants), etc.

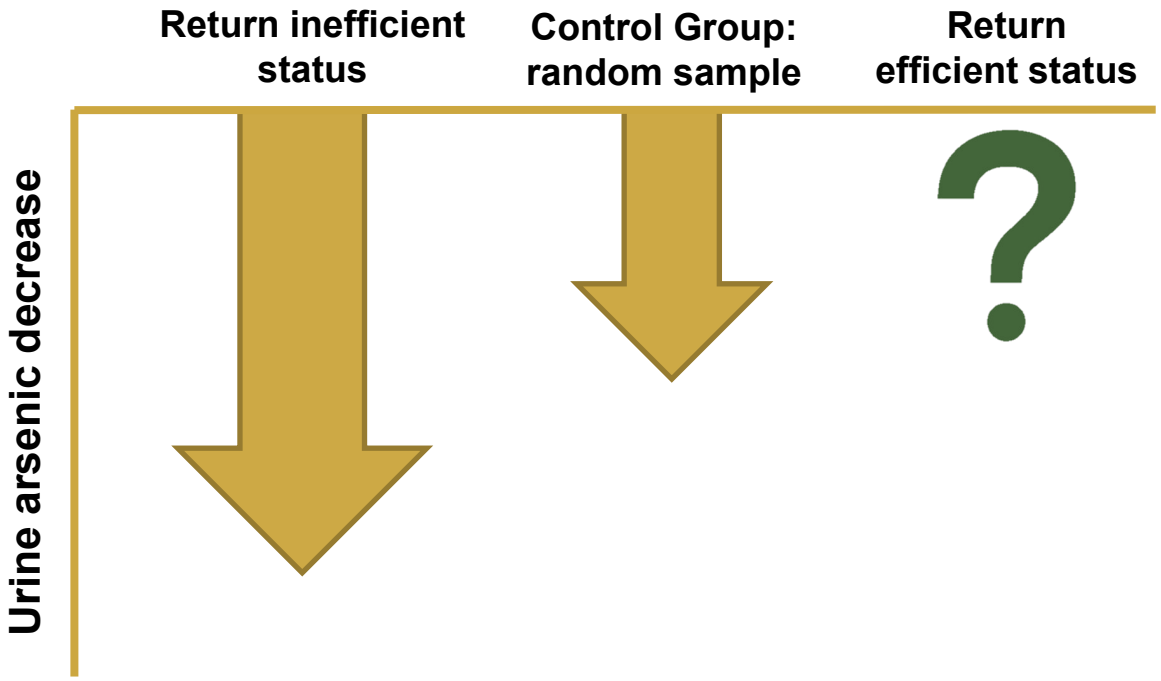
***Strategies for Responsibly Reporting Back Environmental Health or GxE Research Results** (**RFA-ES-23-006,** NIEHS/NHGRI/OSP): 8 new awards just made

***Ongoing PAR-23-293:** ELSI Research (NHGRI-led), exploring GxE report back, epigenomics ethics, etc.

Report Back Study for GxE



Hypothesis: Returning "Inefficient" status will result in a larger decrease in urine arsenic levels compared to the control group (after 6 months)



All participants receive one-on-one **informational intervention** on arsenic effects and exposure reduction

Tamayo, et. al. (2024). *Environmental Research* 240 (Pt 2), 117482

GxE Mini-Symposium

Dr. Peter Kraft,
NIH/National Cancer Institute

Dr. Charmaine Royal,
Duke University

Dr. David Conti,
University of
Southern California

Dr. Nancy Cox,
Vanderbilt University
Medical Center