Discovering Gene-Environment Interactions

Alison Motsinger-Reif, PhD

Branch Chief, Senior Investigator

Biostatistics and Computational Biology Branch

Research Overview

- Applied and methodological research

PEGS
Personalized Environment & Genes Study
Powerful science for integrating genetics and environmental data

All of Us RESEARCH PROGRAM
The Future of Health Begins With You

Team Members


Dr. Farida Akhtari


Dr. Dillon Lloyd


Dr. John House


Jasmine Mack


Dr. Ryan Campbell


Dr. Joe Breeyear


Cristina Justice

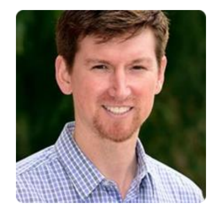

Dr. Kwangmi Ahn

Other Key Co-Conspirators

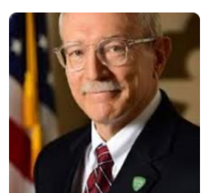

Dr. Jan Hall


Dr. David Fargo


Dr. Charles Schmitt


Dr. Kyle Messier

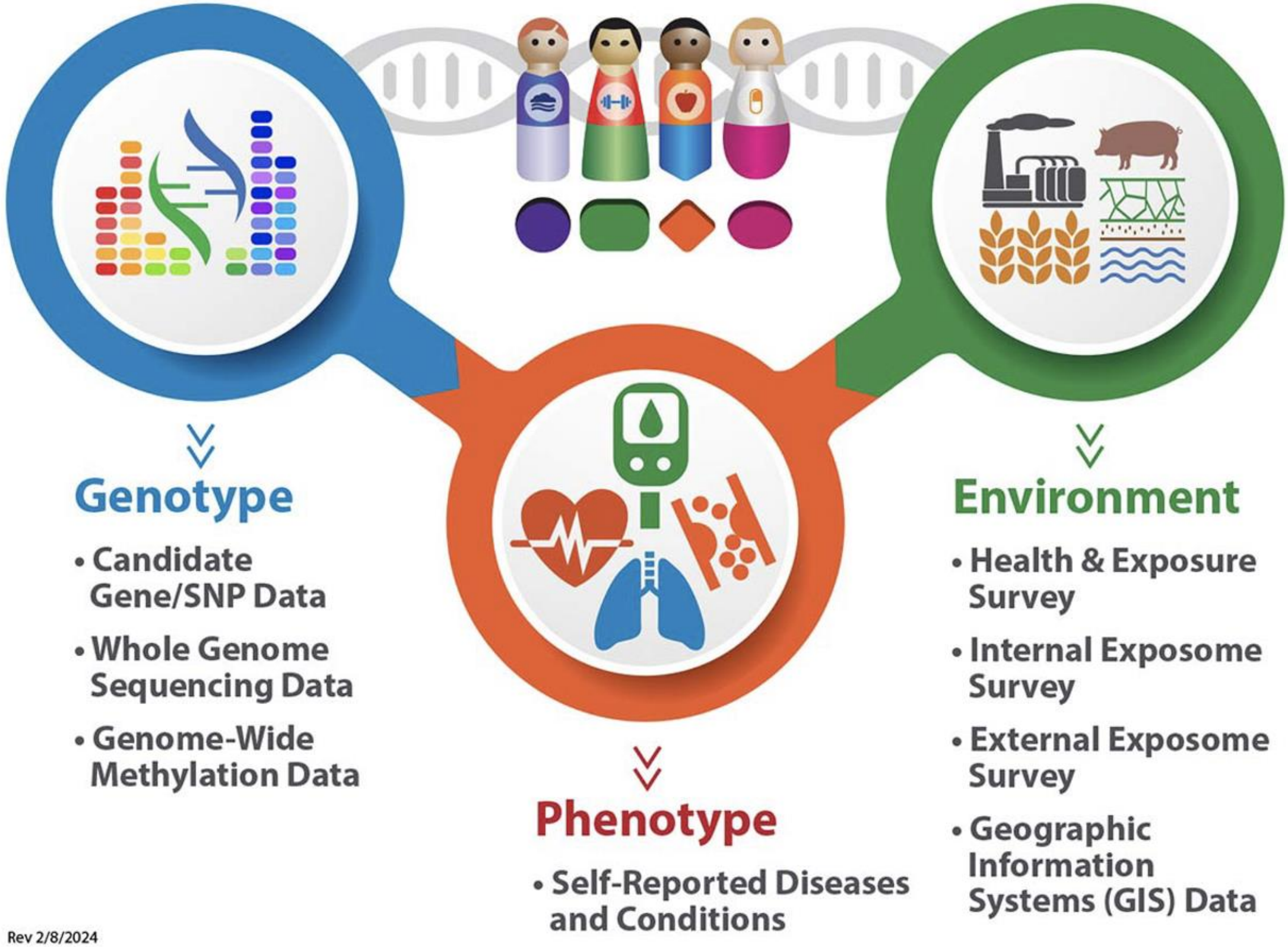

Dr. Geoff Ginsburg


Dr. Rick Woychik


Dr. Larry Kirschne

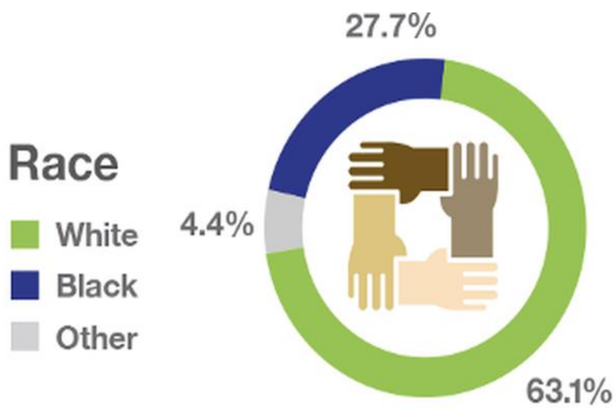

Dr. Josh Denny

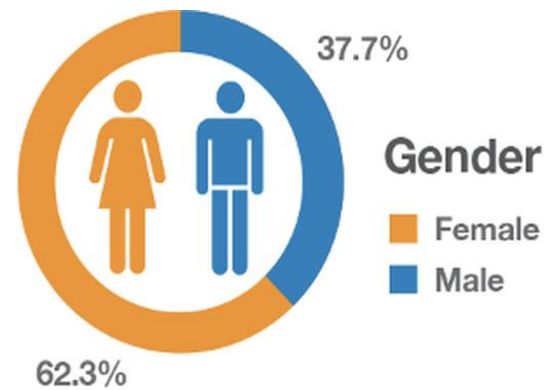
Personalized Environment and Genes Study

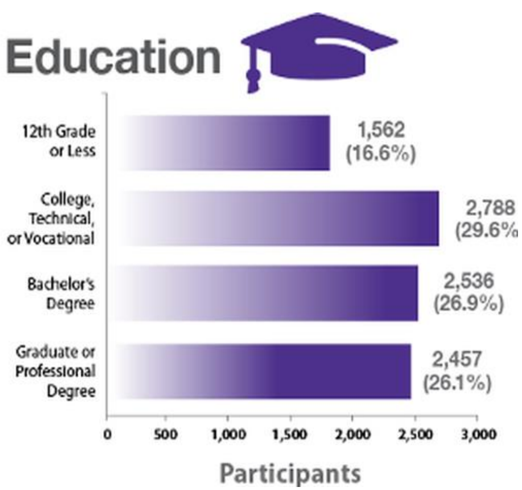


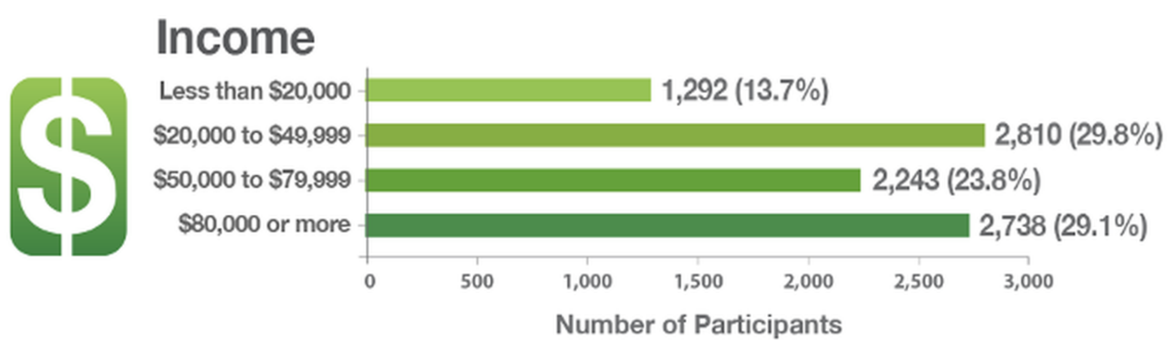
PEGS
Demographics

Average Age: 49.7

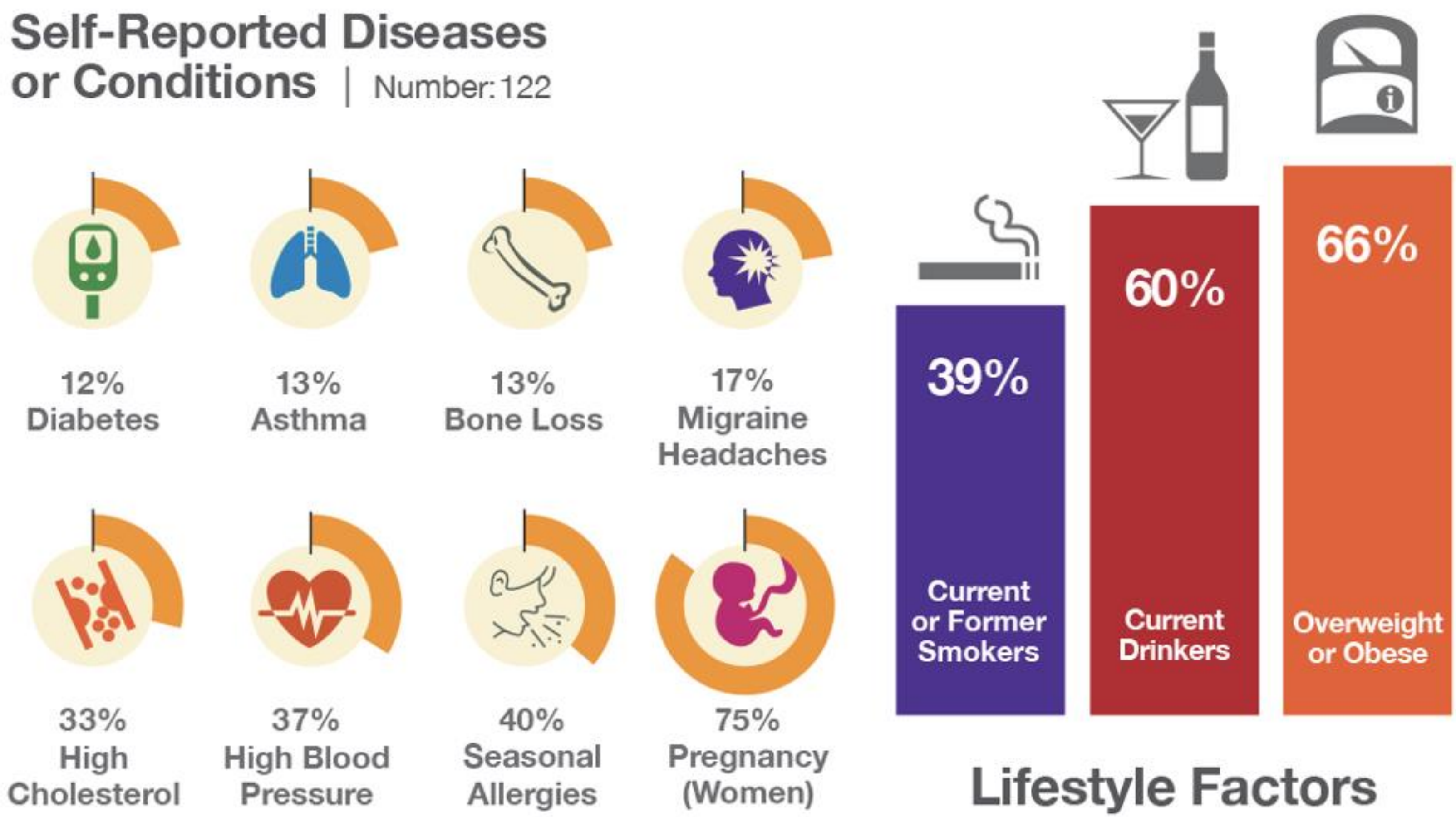








Health and Exposure Survey



Exposome Surveys

Part A: 'External Exposome'

- Characteristics of current and past homes
- Workplace characteristics
- Chemical and metal exposures at work
- Hobby exposures
- Ultraviolet light exposures

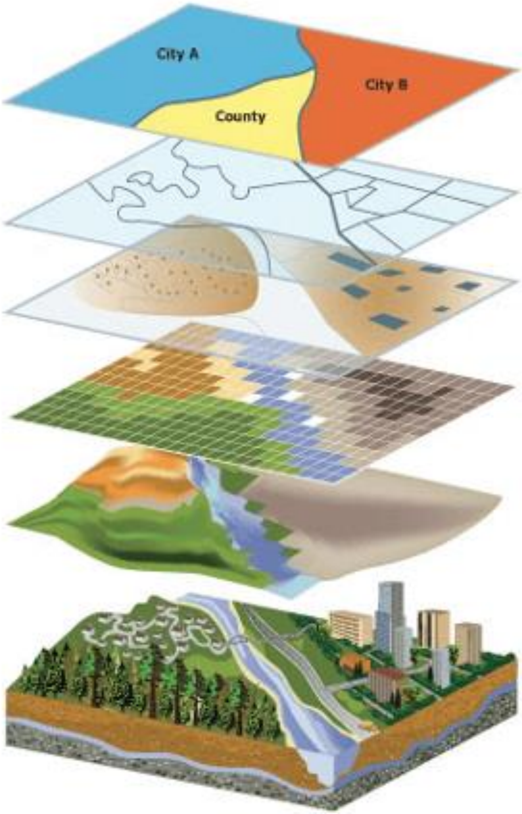
Part B: 'Internal Exposome'

- Medications
- Vitamins, minerals, dietary supplements
- Chemotherapy/radiation therapy
- Physical activity
- Stress
- Infection
- Sleep
- Dietary behavior
- Dietary intake
- Siblings/twins/birth order
- Genetic history

GIS Data

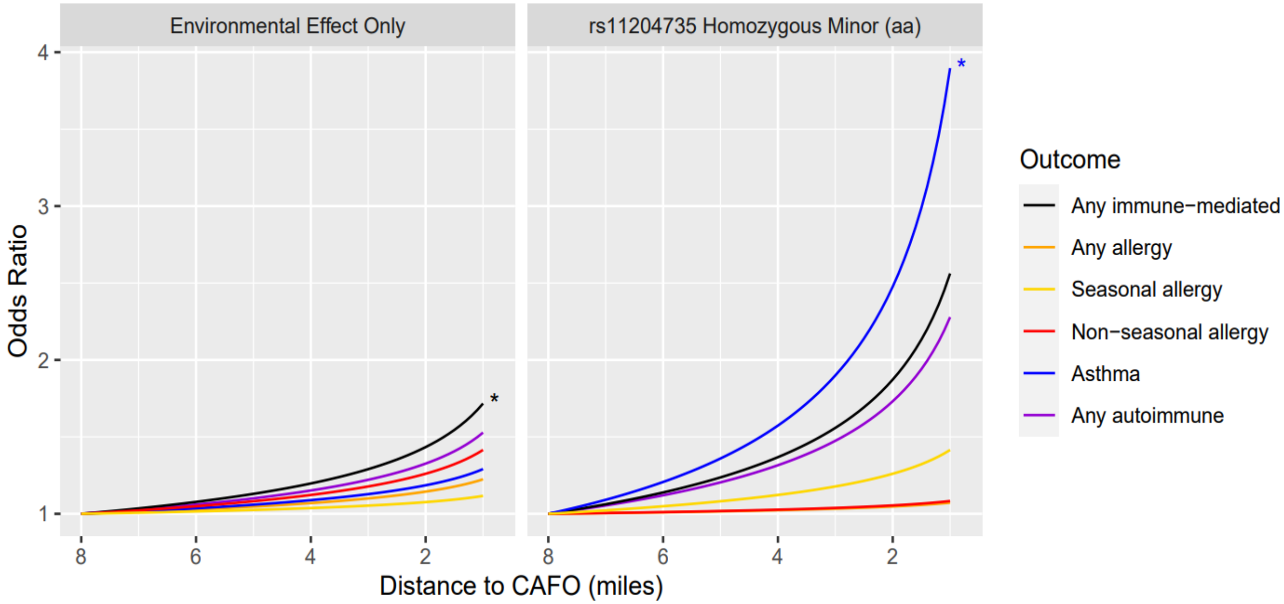
Growing Number of Data Layers

- Airports
- CAFOs
- Cellular towers
- Drinking water
- Dry cleaners
- Hazardous waste
- Highways
- Nuclear sites
- Wastewater
- Population info
- Power lines
- PR landfills
- Railroads
- Spills
- Sanitary landfills
- Superfund sites
- Toxic release sites,
- Etc.



Address at the time of survey completion and longest lived childhood address

Caged Animal Feeding Operations and IMD



Logistic regression adjusted for sex, race, age, income, and smoking status. * Indicates significant effect.

Summary

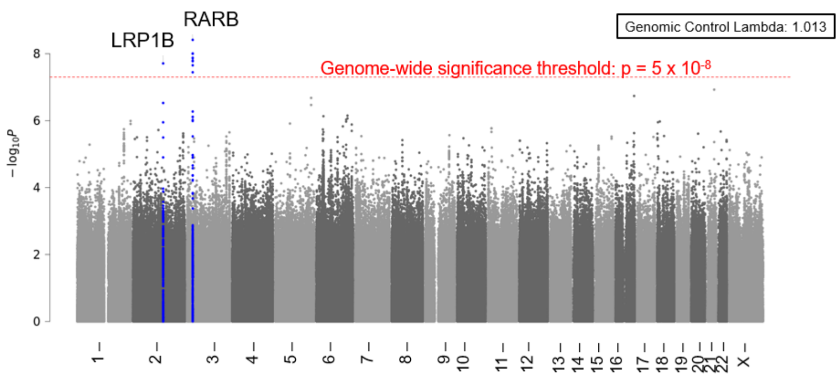
- CAFO proximity was associated with multiple IMD phenotypes suggesting possible shared disease mechanisms
- Multiple PTPN22 and AHR pathway gene interactions with CAFO exposure were identified

Exploring Landscape of Gestational Hypertension

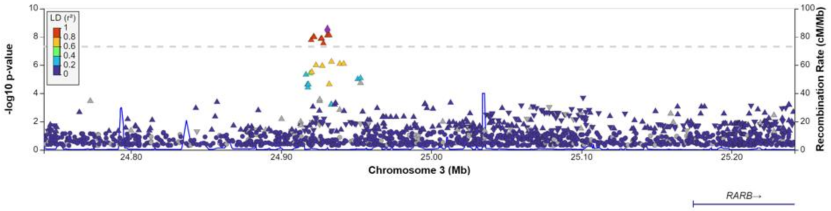
Significant genetic variant association near *LRP1B* (chr2) and *RARB* (chr3)

- 202 cases and 1,569 controls- Racial/ethnic groups: 71% White, 20% Black, 3% Hispanic/Latino, 2% Asian, and 4% Other
- Retinoic acid (RA) signaling gene RARB replicated in UKBB
- RARB Shown to be associated with the severity of proteinuria in the preeclamptic fetal genome

Jasmine Mack

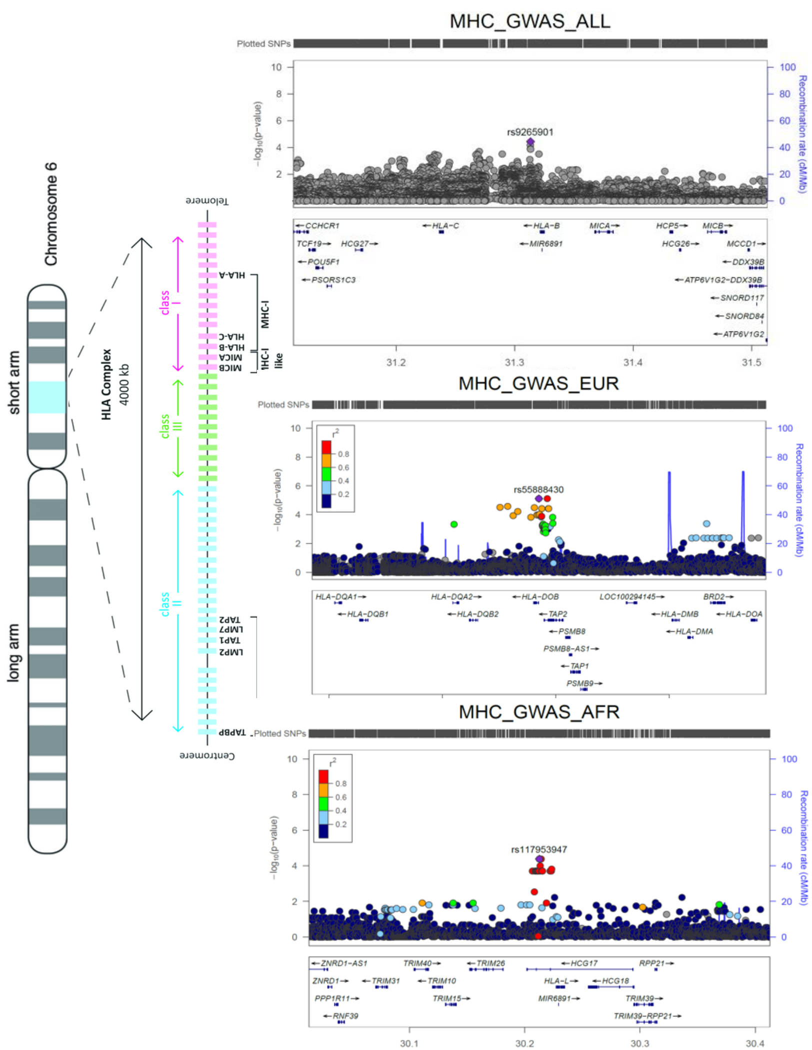


Regional Plot of Candidate Region near *RARB*



- The Lead SNP is at chromosome 3 (rs61176331): of cases, 20.9% are heterozygous at this locus, while 7.7% of controls are heterozygous.

MHC Region Mapping and Adult-Onset Asthma



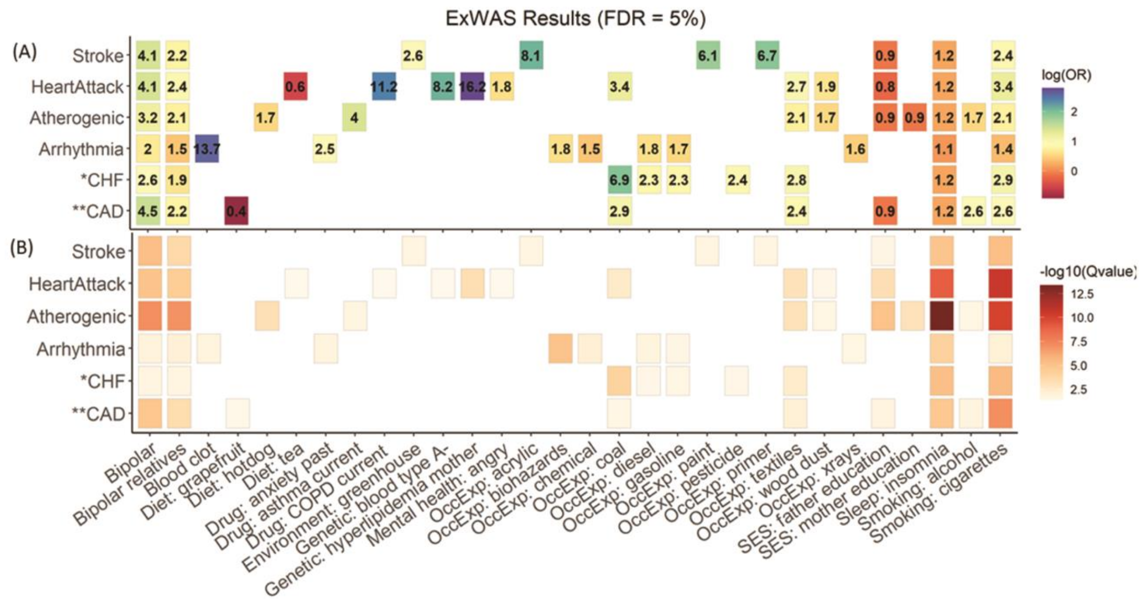
Study Objectives

- Tested population-specific SNP and HLA associations

Findings

- **MHC-wide Association Study (MWAS)**
  - SNPs with evidence of functional elements : *rs9265901/HLA-B (pooled), rs55888430/HLA-DOB (EUR subjects), rs117953947/HCG17* (AFR subjects)
- **HLA Analysis**
  - Class I HLA genes (B and C) for participants with EUR ancestry
  - Class II HLA gene (DRB1) for participants with AFR ancestry – HLA-DRB1*0301 associated with childhood asthma (Hanchard et al., 2010)

ExWAS Analysis of Cardiovascular Disease



Study Objective

- Identify **unique** and **overlapping** **nongenetic** risk factors associated with **CVD**-related outcomes

Main Results

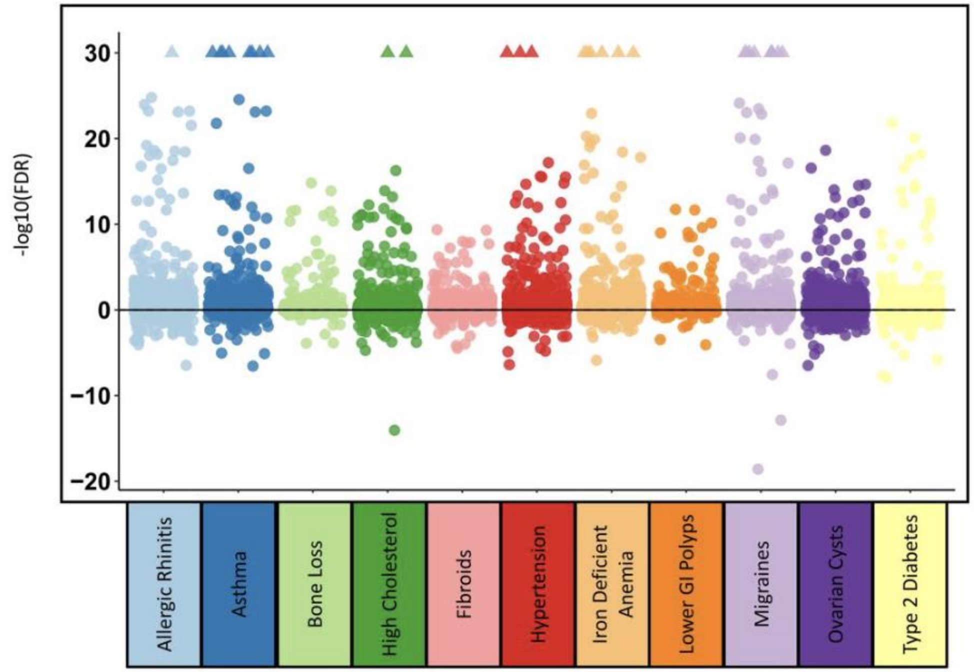
- Blood type A (Rh-): heart attack
- Paint-related exposure (acrylic paint, primer): stroke
- Biohazardous materials : arrythmia
- Paternal education level : stroke, heart attack, CAD, combined atherogenic outcome

Dr. Eunice Lee

Exposome Wide Association Studies

ExWAS of High-Prevalent Traits

- Significant associations were found with:
  - lifestyle and socioeconomic factors
  - exposures such as asbestos, dust, biohazards, and textiles
- Both shared and unique signals
- AI-driven literature review identified both known (e.g., smoking, sleep) and novel (especially occupational) exposure-disease associations

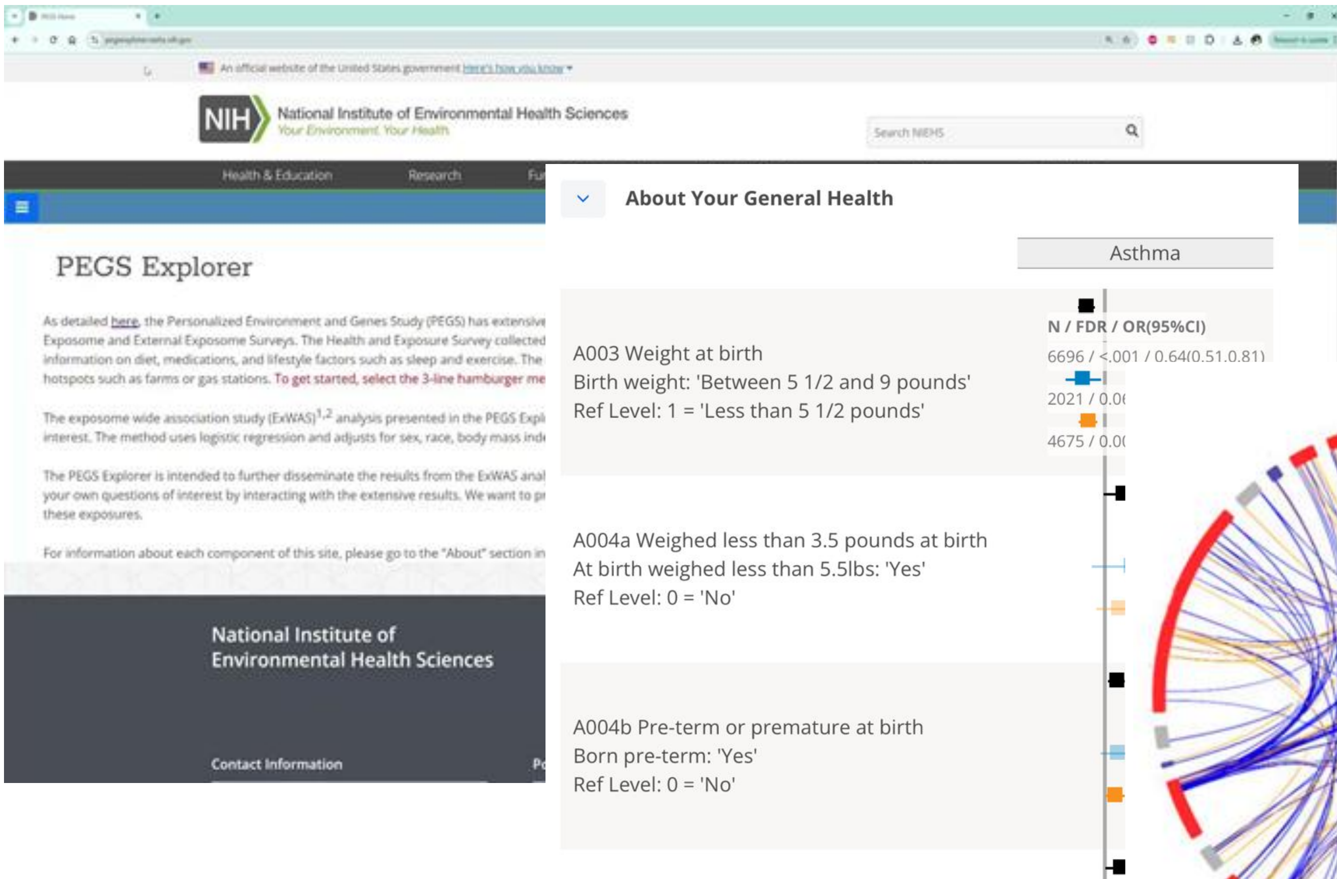


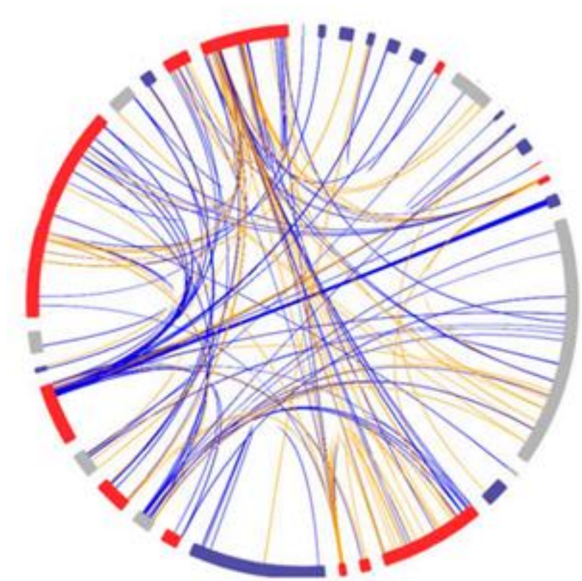
Miami plot of ExWAS results

Lloyd et al. Exposome 2024

Dr. Dillon Lloyd

Results Dissemination





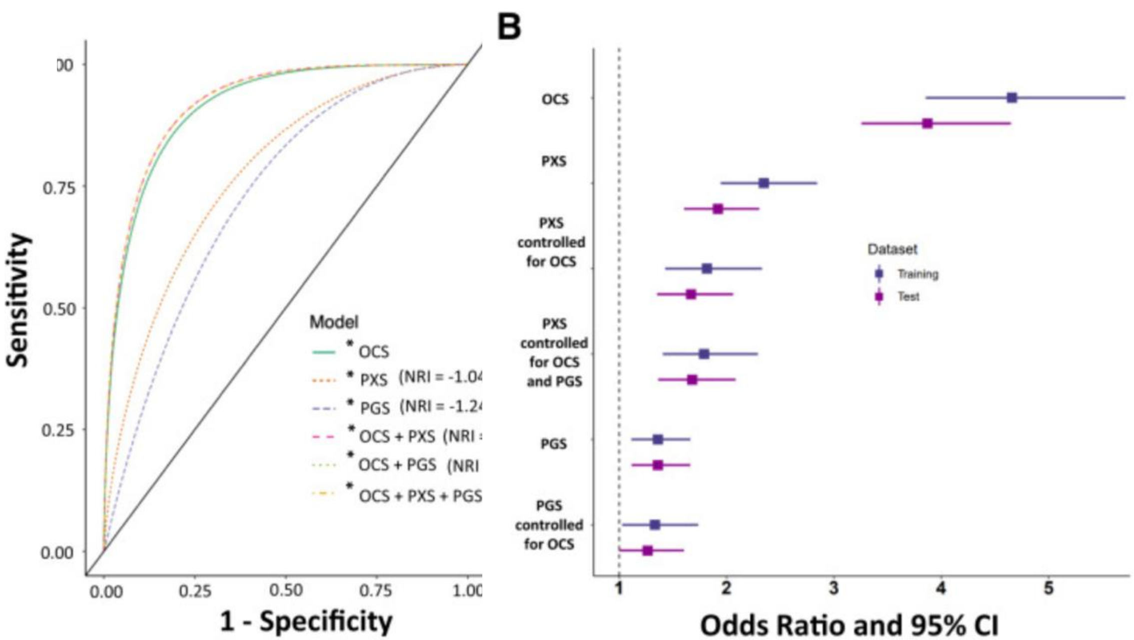
https://pegsexplorer.niehs.nih.gov/

Polyexposure Score (PXS)

- Aggregates multiple exposures into a single score
- Captures cumulative effects of diverse, potentially modifiable factors on health or other outcomes
- Emphasizes combined exposure patterns rather than any single risk source
- Includes intervenable exposures that can be modified through targeted action
- Examples of intervenable factors:
  - Occupational hazards (e.g., chemical exposure, ergonomic risks)
  - Hobbies or lifestyle choices (e.g., sports-related risks)
  - Stress exposures (e.g., work-related stress, chronic social stress)

Genetic and Environmental Scores and T2D

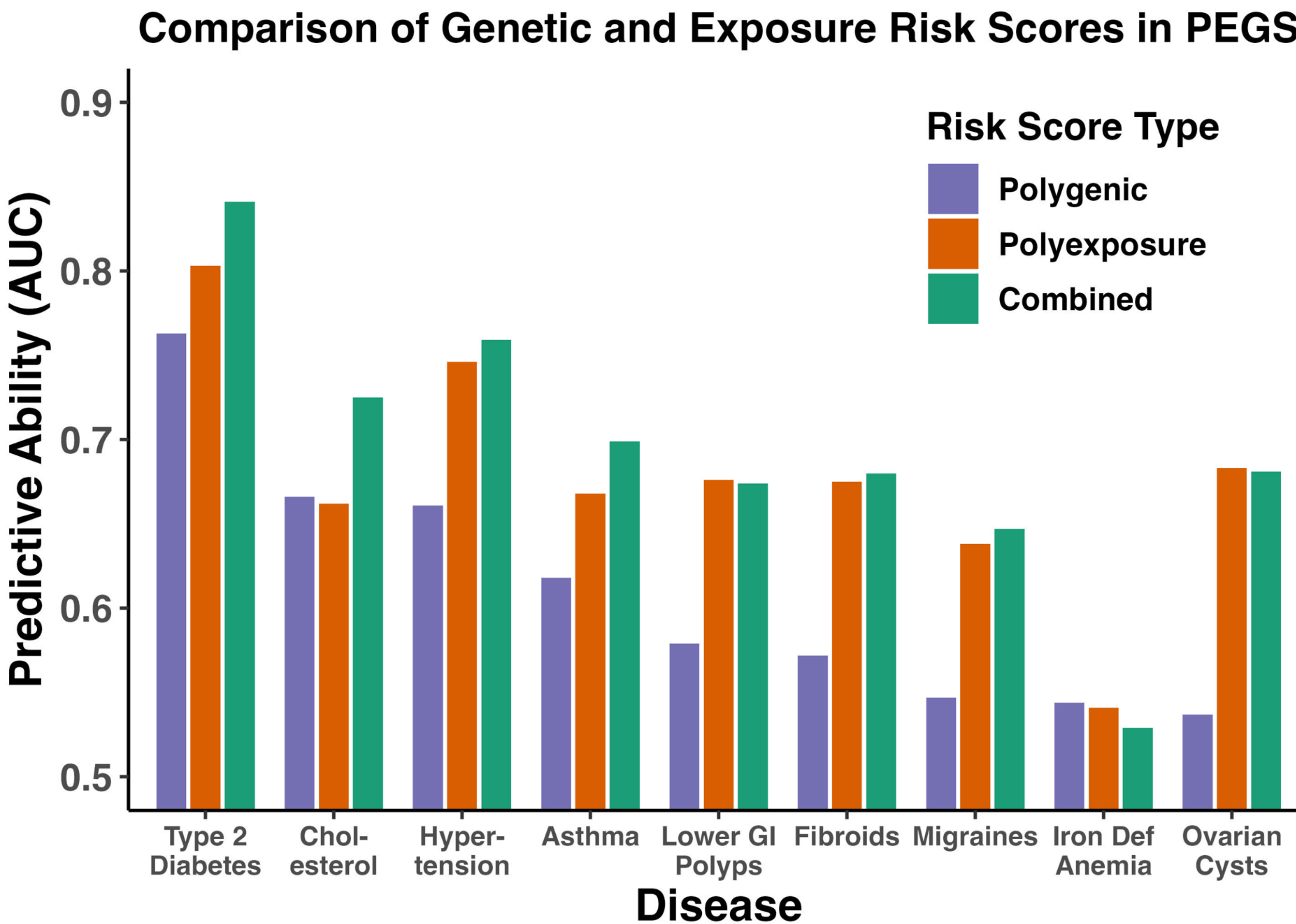
- Computed: Overall Clinical Score (OCS), polyexposure scores (PXS) and polygenic scores (PGS)
  - Rigorous train/test/validate approach
- PXS explained a larger proportion of variance compared to PRS
  - Added predictive value to OCS



Akhtari and Lloyd et al.
Diabetes Care 2023

Dr. Farida Akhtari

Dr. Dillon Lloyd


Comparison of Genetic and Exposure Risk Scores in PEGS
Predictive Ability (AUC)
0.9
0.8
0.7
0.6
0.5
Risk Score Type
Polygenic
Polyexposure
Combined
Type 2 Diabetes
Chol-esterol
Hyper-tension
Asthma
Lower GI Polyps
Fibroids
Migraines
Iron Def Anemia
Ovarian Cysts
Disease

Ongoing Work and Future Directions

- Separating exposures into two different polyexposure scores
- Incorporating advanced ML/AI methods to build exposure scores
- Understanding PGSs in Context of Exposure, building on Schaid et al. 2025

Polysocial Score (PSS)

- **Non-intervenable**, structural features – factors that are more difficult to change at an individual level

Examples:

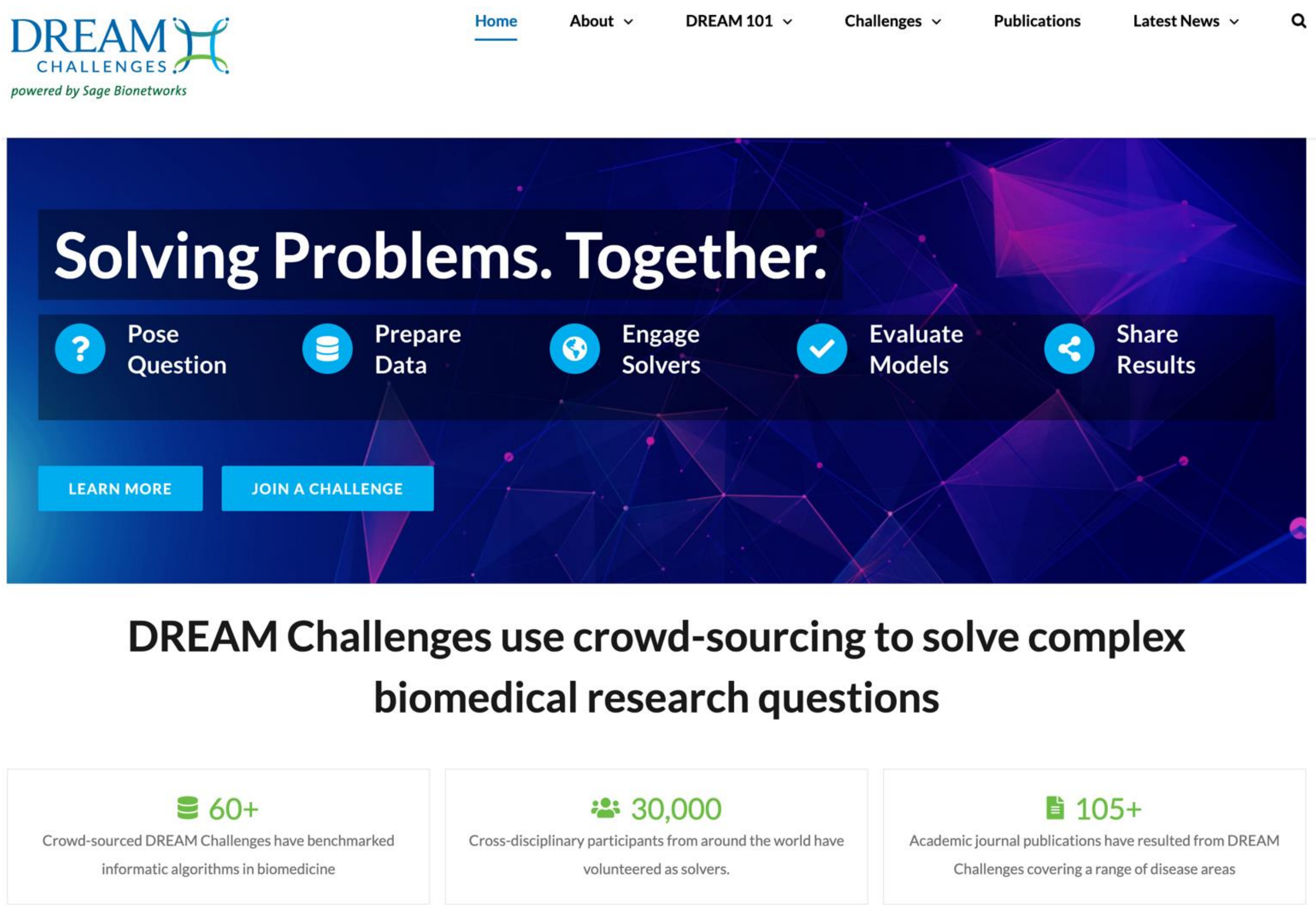
- Income or socioeconomic status
- Housing type or living conditions
- Social vulnerability indices

Polyexposure Score (PXS)

- **Intervenable** exposures – factors that can be modified or addressed through targeted interventions.

Examples:

- Occupational hazards
- Hobbies or lifestyle choices
- Stress exposures



https://dreamchallenges.org/

PEGS DREAM Challenge

Personalized Environment and Genes Study Challenge

Task 1: Disease Classification

- **Aim:** Classify hypercholesterolemia status using **any combinations** of the health, exposomics, geospatial, and genomic data available for the PEGS DREAM Challenge.

Task 2: Ideation Challenge

- **Aim:** Develop a novel hypothesis(-es) and/or generate model(s) using the **multi-dimensional** PEGS DREAM Challenge data to improve the understanding of the etiology of hypercholesterolemia beyond conventional clinical and genetic risk factors.

Ongoing Work

- GIS ExWAS
- EJI ExWAS
- Genetic correlation analysis
  - Genetic associations with exposures
- Epigenetic Wide Association Studies (EWAS)
- Epigenetic biomarkers of exposure and protein expression association studies
- Integrative ‘omics analysis (ex. TWAS)
- Expansion of PXS vs. PGS comparisons

All of Us Ancillary Studies

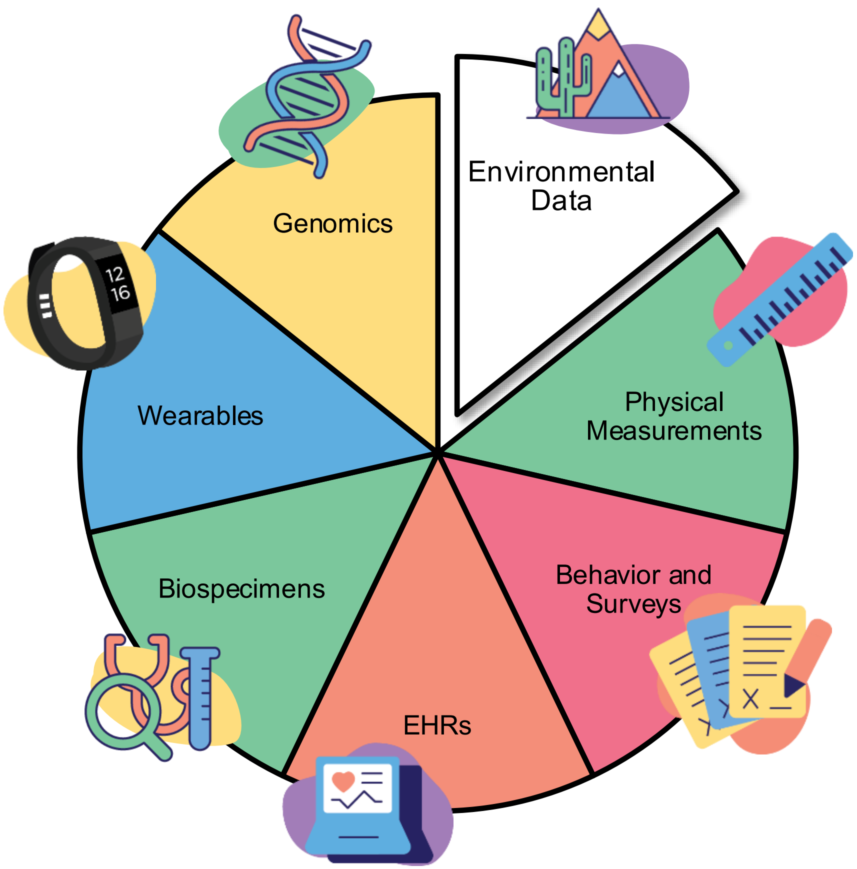
All of Us RESEARCH PROGRAM | The Future of Health Begins With You

The *All of Us* Research Program is a historic, longitudinal effort to **gather data from one million or more people** living in the United States **to accelerate research and improve health**. By taking into account individual differences in **lifestyle, socioeconomics, environment, and biology**, researchers will uncover paths toward delivering **precision medicine – or individualized prevention, treatment, and care – for all of us**.

"*All of Us* is among the most ambitious research efforts that our nation has undertaken!"

NIH Director Francis Collins, M.D., Ph.D.

Integrating Environmental Data into All of Us



To meet scientific priorities and goals for precision medicine, All of Us will need to integrate individual location and environmental exposure data.

This collaboration will lay the groundwork for investigating the health implications of interactions between the exposome and other data types available in the All of Us Researcher Workbench.

Far-reaching research potential of integrating environmental data

Risk & Prevention
What environmental biomarkers can help identify risk for future disease?

Health Equity
How do socioeconomic factors interact with environmental exposure to increase disease risk?

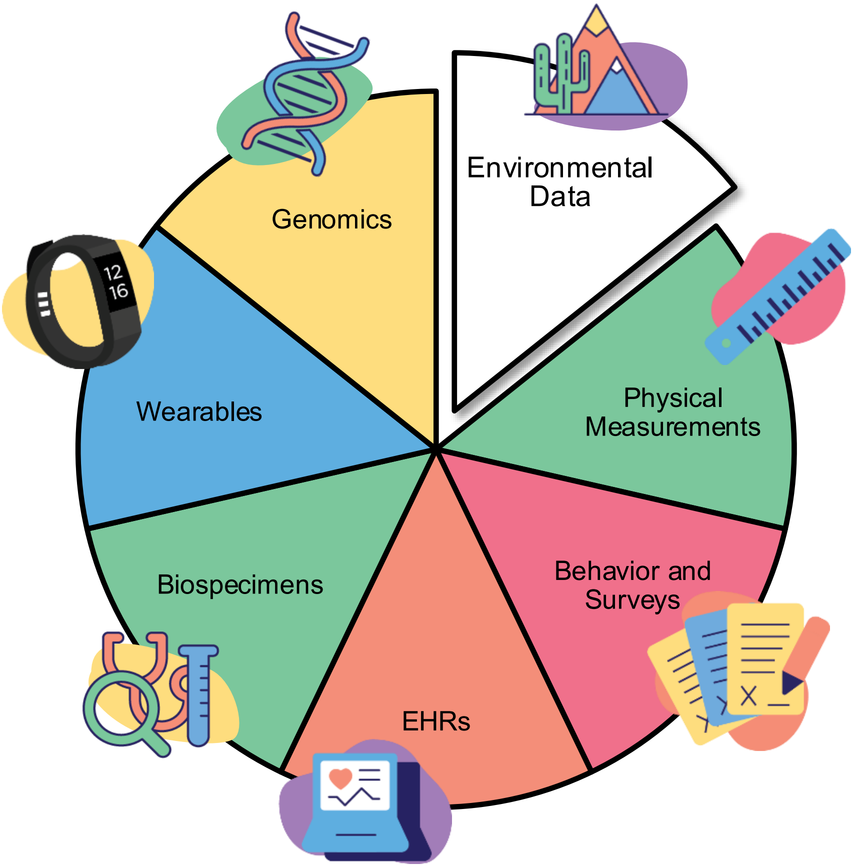
Diagnosis
What exposure signatures are typical of patients with different conditions?

Empowerment
How can returning information about environmental risks and exposures empower participants?

Treatment & Outcomes
How can we objectively assess whether a treatment or intervention will be effective?

All of Us Partnered Research Studies

- Exposomics
  - Case-cohort study of Type 2 Diabetes
  - Untargeted metabolomics on ~5,600 samples
- Environmental Exposures and Occupational Health Partnered Research Study
  - Two questionnaires
    - Residential history and exposures
    - Work history and occupational exposures



Encorporating the Environment into All of Us

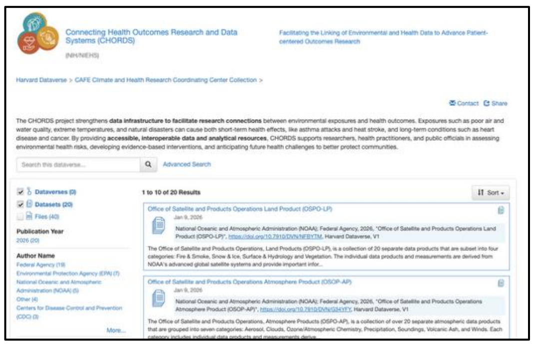
Phase 1: Location	Phase 2: Geospatial Environment	Phase 3: Health
Geocoded location information across the lifecourse Exposure survey *For the entire cohort*	Initial linkages to the Environmental Justice Index Additional linkages with PCORTF tools *For the entire cohort*	HHEAR untargeted assays on a case-cohort study of T2D *n~5600*

Supported by a contract through the Center for Linkage and Acquisition of Data (CLAD) and CHORDS

Supported by NIEHS

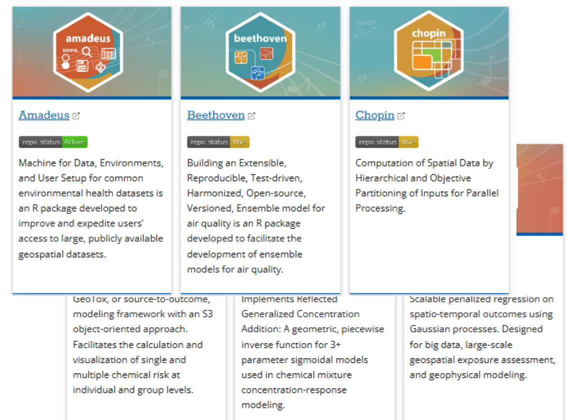
Connecting Health Outcomes Research Data Systems (CHORDS)

Deliverables



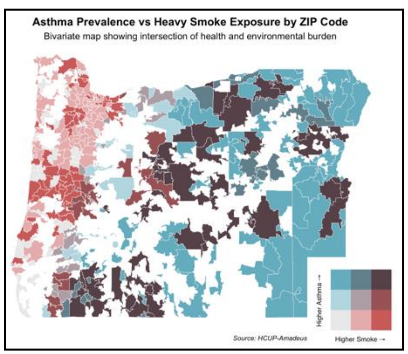
Data catalog with over 150 curated data resources.

*Hosted by **HEW Café** DataVerse (>1000 data sets avail.)*



Open source, validated, software packages and published data sets

6,979 Amadeus downloads, being used in CHORDS Use Cases & All of Us research project



Demonstration Use Cases

- AHRQ Healthcare Cost and Utilization Project (HCUP) National & State Databases
- NIEHS Personalized Environment and Genes Study (PEGS) Cohort
- NHLBI Cardia Cohort

Online tutorials, vignettes, & publications

CHORDS Products

amadeus

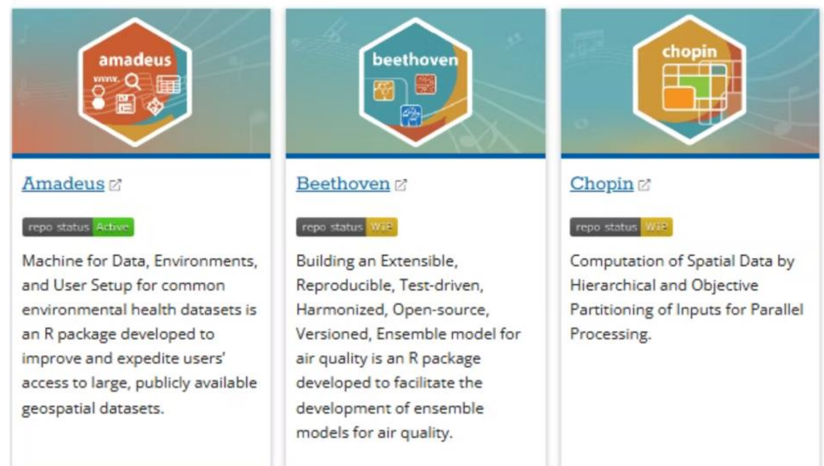
A mechanism for environmental data and user setup in R for CHORDS exposure analysis.

Large-Scale Downloads

Downloads environmental data from 20+ sources including NASA, NOAA, EPA, and USGS.

One Consistent Workflow

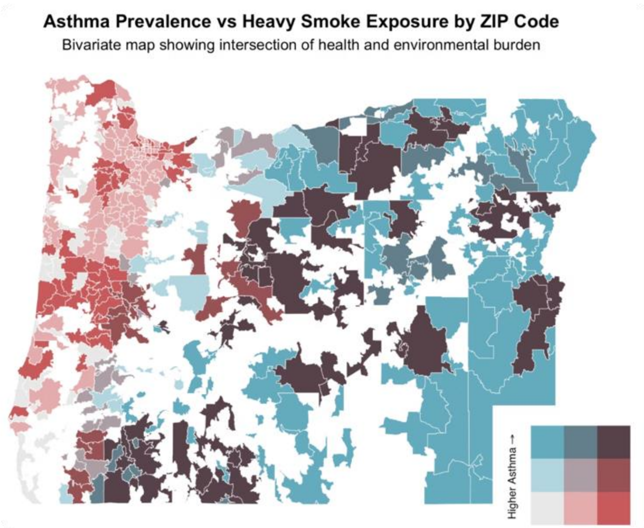
Automatically handles source-specific URLs, file names, formats, and metadata.



Dr. Kyle Messier

Asthma Demo: Wildfire Smoke Increases Rates

Using NOAA HMS smoke plumes (light, medium, heavy) for fire seasons **2014–2023**, linked daily at the ZIP3 level to **11,700–33,400 asthma participants/year** in *All of Us*.



Key Findings

- **2017–2022:** consistent, significant increases in ED/UC rates
- **Per smoke day:** ~1–5% higher visit rates
- **Per 100-unit PM proxy:** ~10–43% higher visit rates
- **Largest effects:** 2019 and 2021

Exposure Construction

Intensity-weighted $PM_{2.5}$ proxy: **5×light + 16×medium + 27×heavy** smoke days. Aggregated ZIP5 → ZIP3, linked by participant ZIP3 and event date.

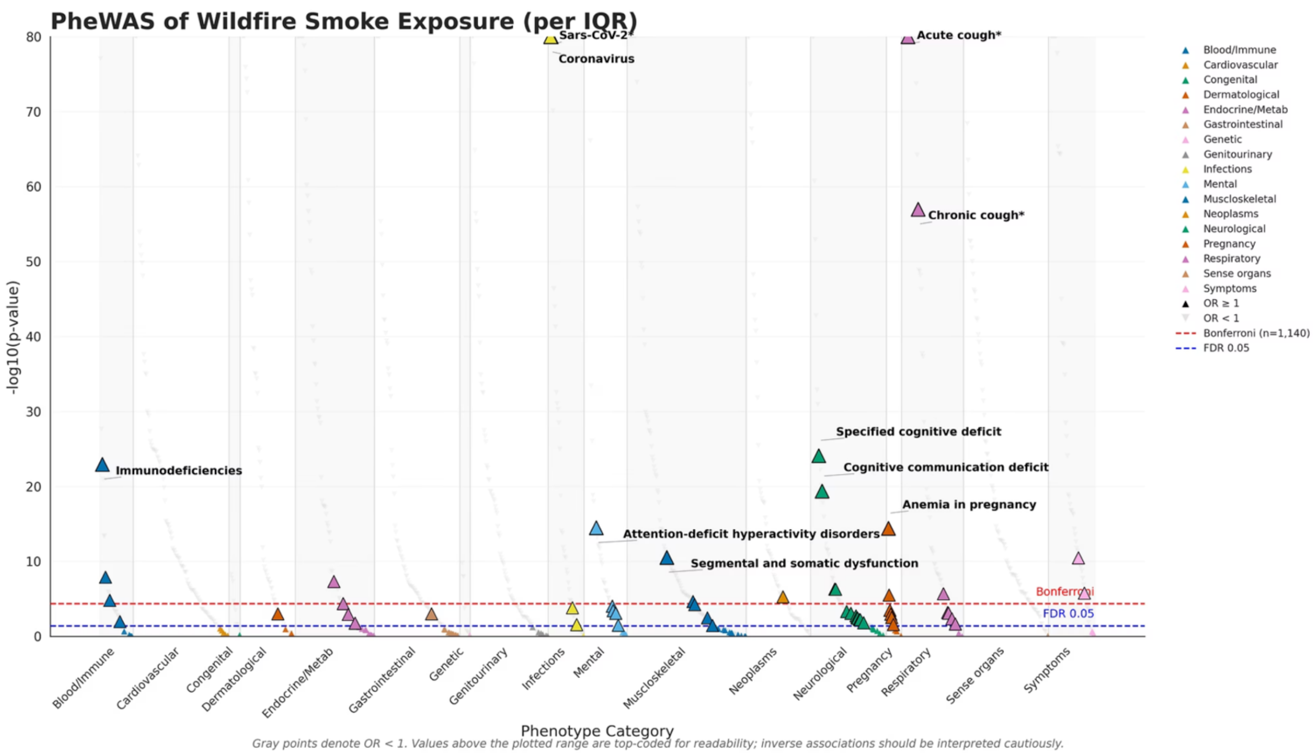
Outcome Model

Negative binomial model adjusted for age, sex, race/ethnicity, BMI, SVI, smoking, income, and EHR length offset.

ZIP3-level exposure recovers plausible clinical signals in *All of Us* at population scale.

PheWAS: Discovery-Scale Scan with Smoke

Using the same standardized pipeline, a phenome-wide association study tested **IQR-scaled $PM_{2.5}$ proxy** (1-year lag, 2014–2023) against incident phecodes in the adult *All of Us* EHR cohort — going beyond a single clinical endpoint.



Study Design

Incident disease defined as ≥2 encounters with same phecode; prevalent cases excluded via 2-year washout. Logistic regression per phecode.

Covariates

Age, sex, race/ethnicity, region, smoking, BMI, SVI, and healthcare use. Effect scale: odds ratio per IQR increase in wildfire-smoke exposure.

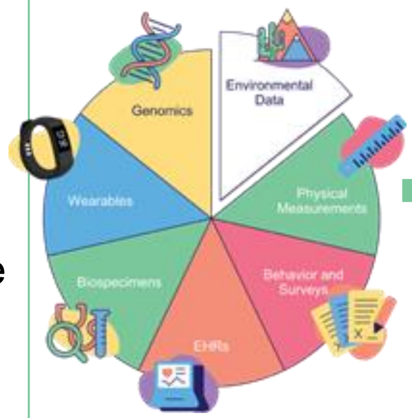
Key Findings

Positive associations for **respiratory, infectious, neurological, and symptom phenotypes.** Inverse associations likely reflect confounding, healthcare use, or selection effects.

All of Us Exposomics Partnered Research Study

Launched in July, this study is performing **untargeted metabolomics on >5,600 diverse participant samples** to measure environmental exposures.

Data on **environmental, pharmaceutical, dietary, and endogenous metabolites** will be added to existing *All of Us* data in 2026.



New research on environment, gene, and behavior interactions will **drive discovery across health conditions**.

Samples were selected to reflect the high diversity of the *All of Us* cohort and for overlap with the multi-omics pilot. In this cohort 86% represent at least one community previously underrepresented in research and 62% represent an underrepresented race or ethnicity.

Untargeted Exposomics through the Human Health Exposure Analysis Resource (HHEAR)

Endogenous: Host Metabolism (~1,043)

Amino acids, carboxylic acids, biogenic amines, polyamines, bases, nucleosides and nucleotides, bile acids, carnitine, sugars, mono- and disaccharides, fatty acids, lipids, steroids, and hormones, as well as *coenzymes and vitamins*

Food Metabolome: Includes Subclasses, such as:

Phytoestrogens
Aromatic Ketones
Benzoic Acids
Elegiac Acids
Flavonoids
Caffeoylquinic Acids
Catecholamines
Coumarins

Hippuric Acids
Hydroxytoluenes
Phenylamines
Stilbenes
Urolithins
Valerolactones
Xanthonoids

~Identified 550 compounds across ~50 subclasses via targeted analysis that are being transferred to untargeted platform

Environmentally Relevant Metabolites (~433)

AP Pesticides
PFAS
Phenols
Parabens
Phthalates
Tobacco-Related
VOCs
PBDEs, PCBs
PAH Metabolites
Pesticides

Candidate compounds and metabolites were derived from the National Health and Nutrition Examination Survey (NHANES) and literature reviews based on known identifications using quantitative targeted methods.

Parabens: food additives
Phthalates: food and water contaminants

Additional Categories

Drugs and Medicines (48)
Choline Metabolism (24)
Folate Metabolism (17)
Vitamins and Vitamin-Like Compounds (30)
Carnitines and Acylcarnitines (39)
Amino Acids (24)
Omega 3 and Omega 6 Fatty Acids (5)

EEOH Partnered Research Study

In collaboration between NIEHS and *All of Us*, we will integrate participant-reported survey data on environmental, residential, and workplace exposures into the *All of Us* dataset. The the *All of Us* dataset. The environments where people live and work profoundly affect their health across the lifecourse. This survey will go out to all All of Us participants. participants.

Home & Work Environment

Lifestyle & Behaviors

Social & Community Factors

Air & Environmental Pollution

Occupational Exposures

Diet & Chemical Exposures

Status

Questionnaires have been approved, translated, and are going through final rounds of burden testing.

Will launch to all All of Us participants in November 2026.

EEOH Partnered Research Study

In collaboration between NIEHS and *All of Us*, we will integrate participant-reported survey data on environmental, residential, and workplace exposures into the *All of Us* dataset. The environments where people live and work profoundly affect their health across the lifecourse. This survey will go out to all All of Us participants.

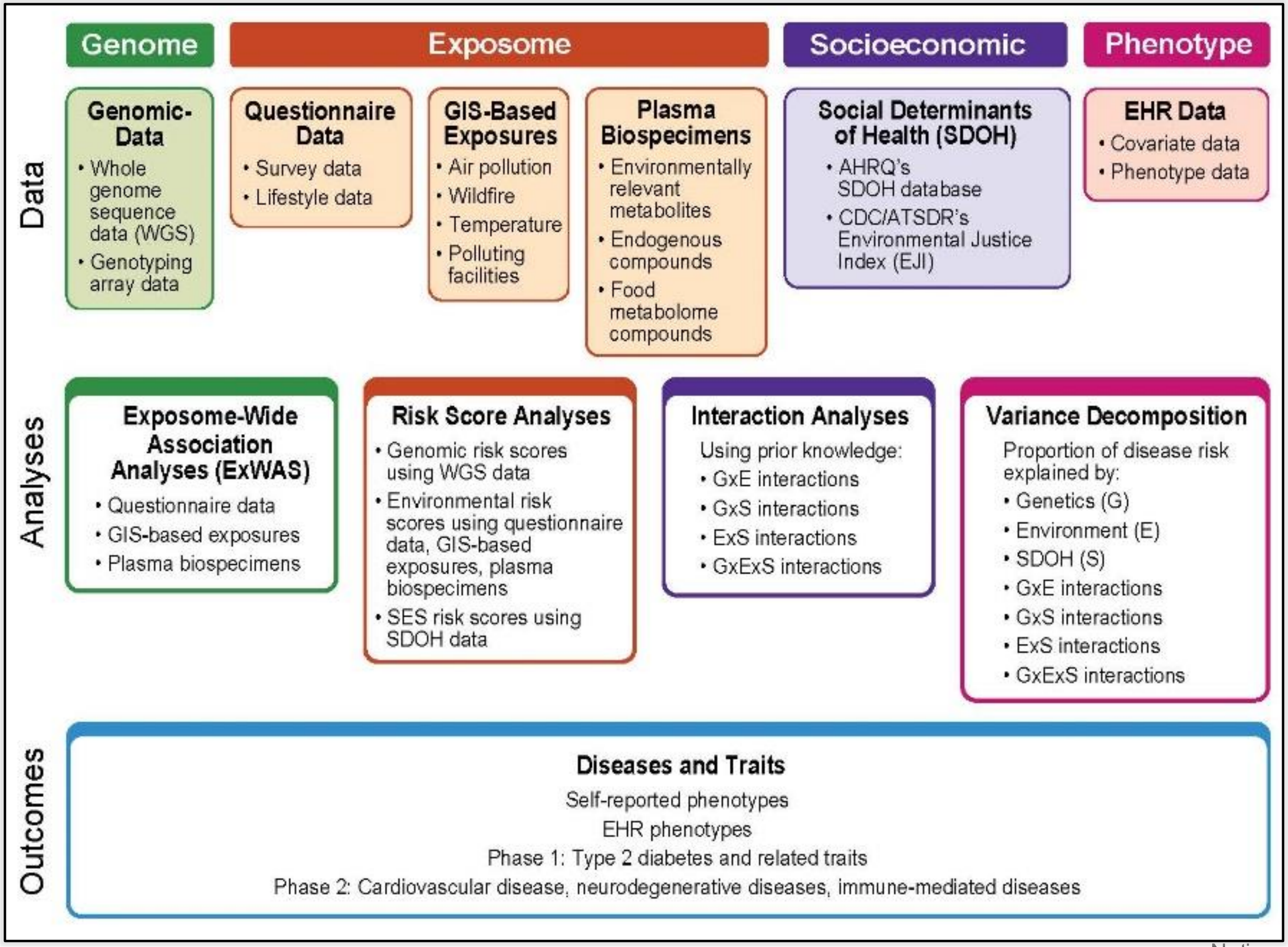
- **Home & Work Environment**
- **Lifestyle & Behaviors**
- **Social & Community Factors**
- **Air & Environmental Pollution**
- **Occupational Exposures**
- **Diet & Chemical Exposures**

Status

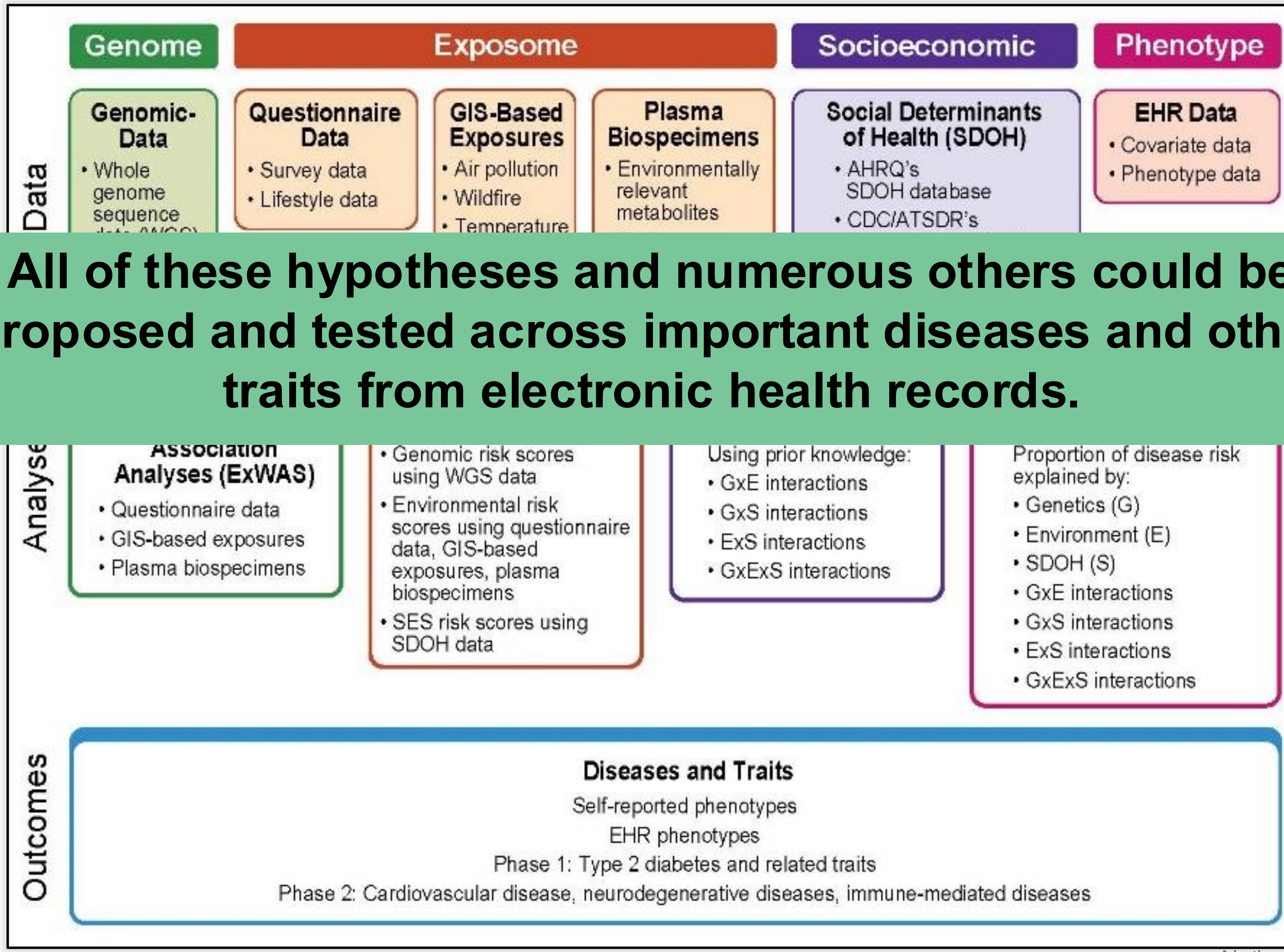
Questionnaires have been approved, translated, and are going through final rounds of burden testing.

Will launch to all All of Us participants in November 2026.

Supports a variety of hypotheses

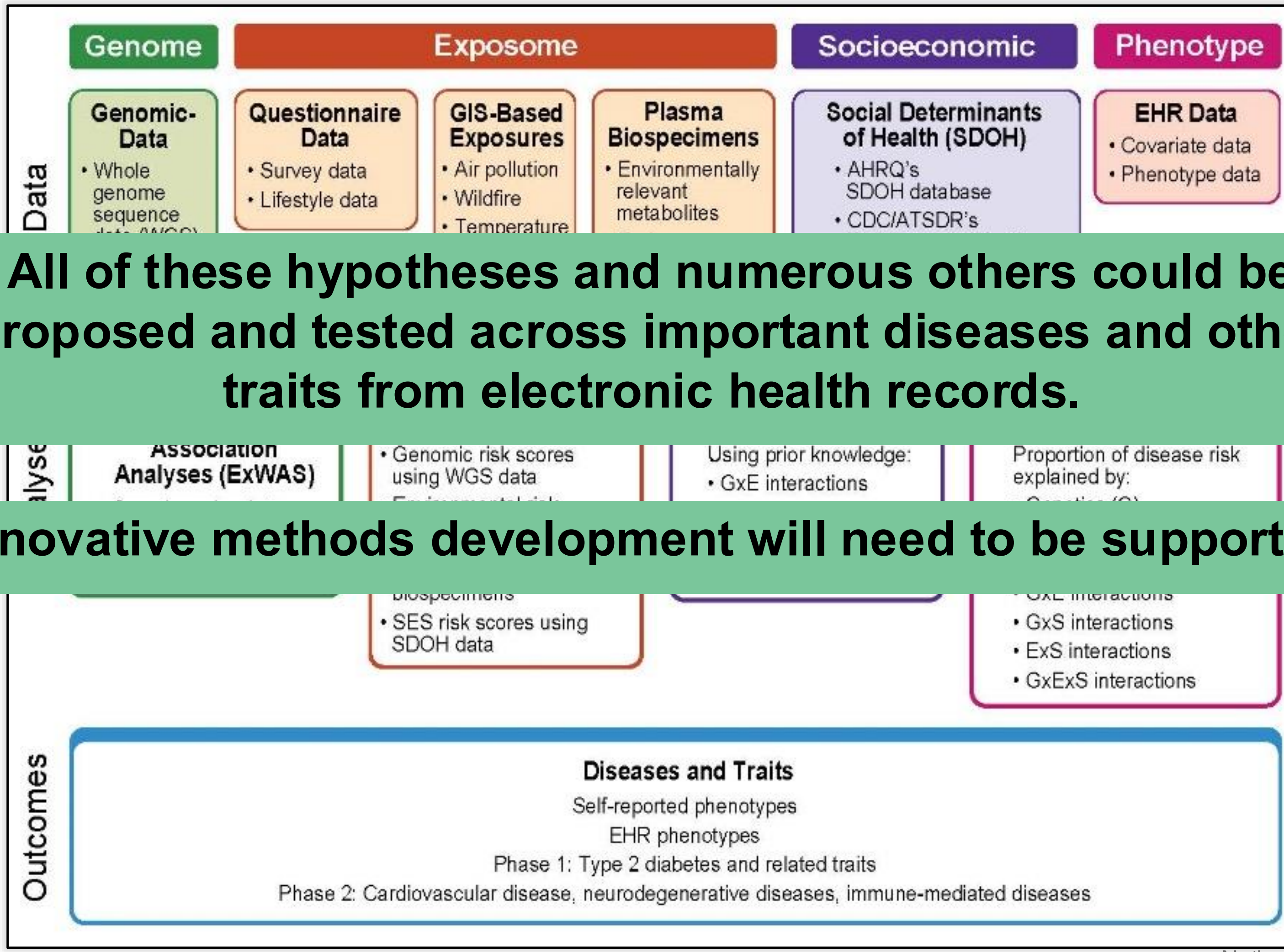


Supports a variety of hypotheses



All of these hypotheses and numerous others could be proposed and tested across important diseases and other traits from electronic health records.

Supports a variety of hypotheses



All of these hypotheses and numerous others could be proposed and tested across important diseases and other traits from electronic health records.

Innovative methods development will need to be supported.

A Whirlwind Tour

ChatGPT

Acknowledgements

- PEGS Leadership
  - Janet Hall (co-PI)
  - David Fargo
  - Charles Schmitt
- GIS Modeling
  - Kyle Messier
  - Melissa Lowe
  - Kristin Eccles
  - Nat McNell
- All of Us
  - Geoff Ginsburg
  - Erica Landis
  - Sheri Schully
  - Josh Denny
- Computational Work
  - Farida Akhtari
  - John House
  - Eunice Lee
  - Xiaron Tong
  - Dillon Lloyd
  - Jasmine Mack
  - Zongli Xu
- Bioinformatics
  - Adam Burkholder
  - Jianying Li
- Collaborators
  - Rick Woychick
  - Ross Simpson
  - John Buse
  - Gordon Smith
  - Les Beiseker
  - Rob Tighe
  - Ken Jacobson
  - Karamarie Fecho
  - …..
- Contract Support
  - S3
  - Sciome

PEGS Participants

Questions?

Alison.motsinger-reif@nih.gov