How do we learn what disease biology is driven by environment and GxE?

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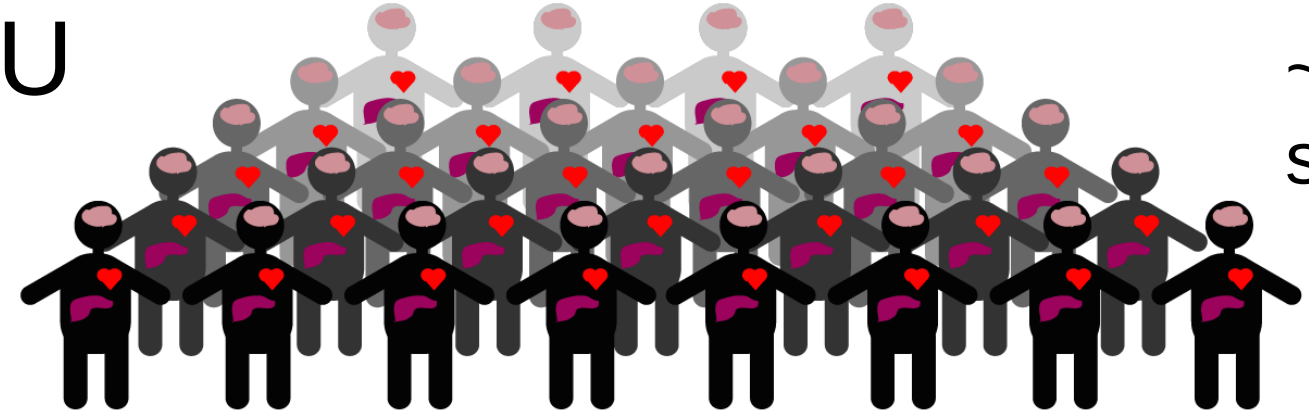
Overview

- We have a host of ways to measure how non-genetic factors can influence the biology of disease through effects on genomes
  - Cheaper interrogation of methylation
  - Multiplexing different kinds of studies on chromatin marks
- But how do we get from those measurements to biology?
  - We need to distinguish long-term effects of exposures being somehow encoded in the genome from direct effects of pervasive exposures

BioVU



~330,000 samples

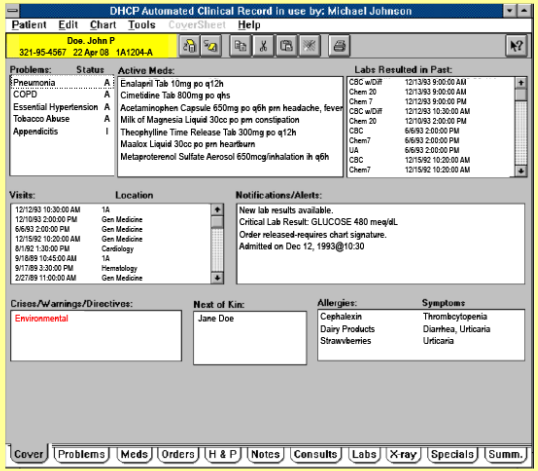
Now ALL samples being whole genome sequenced

150K

Imputed

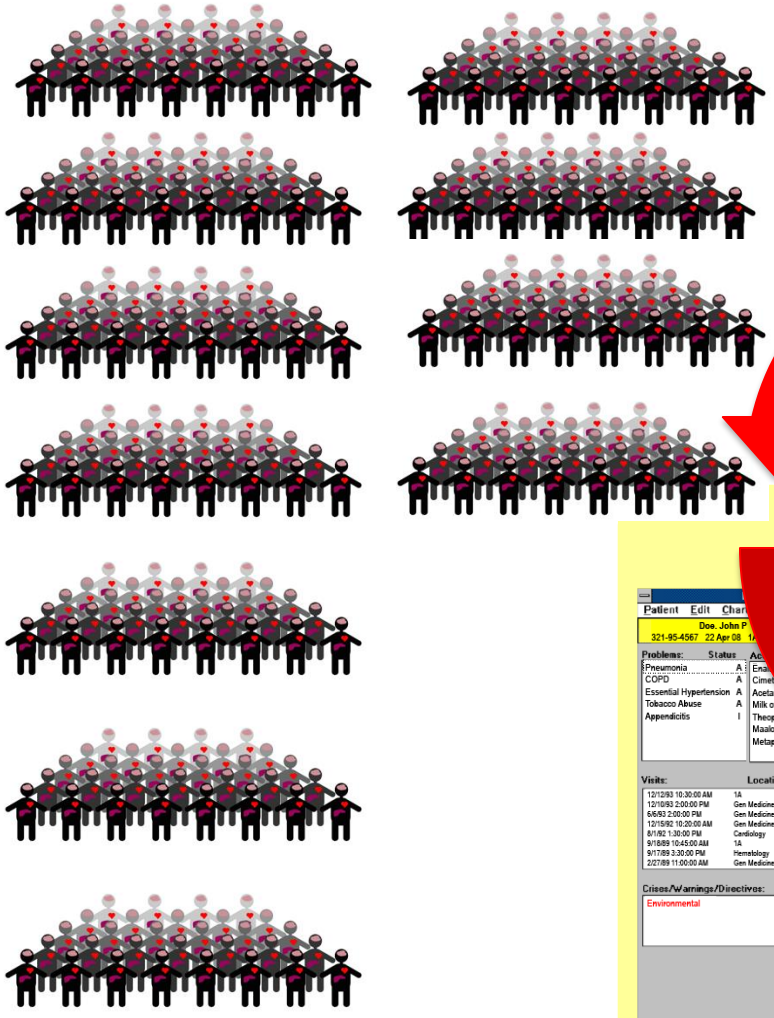
~10-15 yrs (max 30+) of EHR

EHR



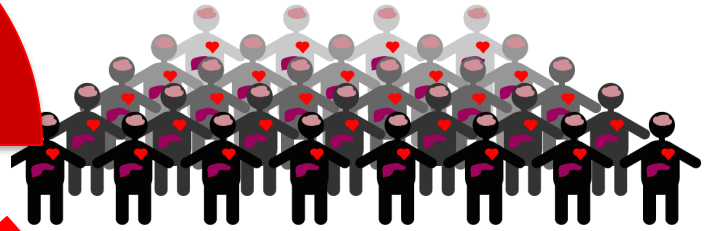
-OMICS

- Genome variation
- Transcriptomes
- Metabolomes

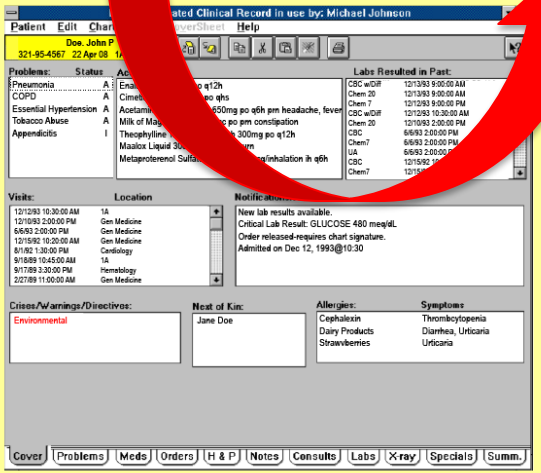


2.8 million with just EHR data

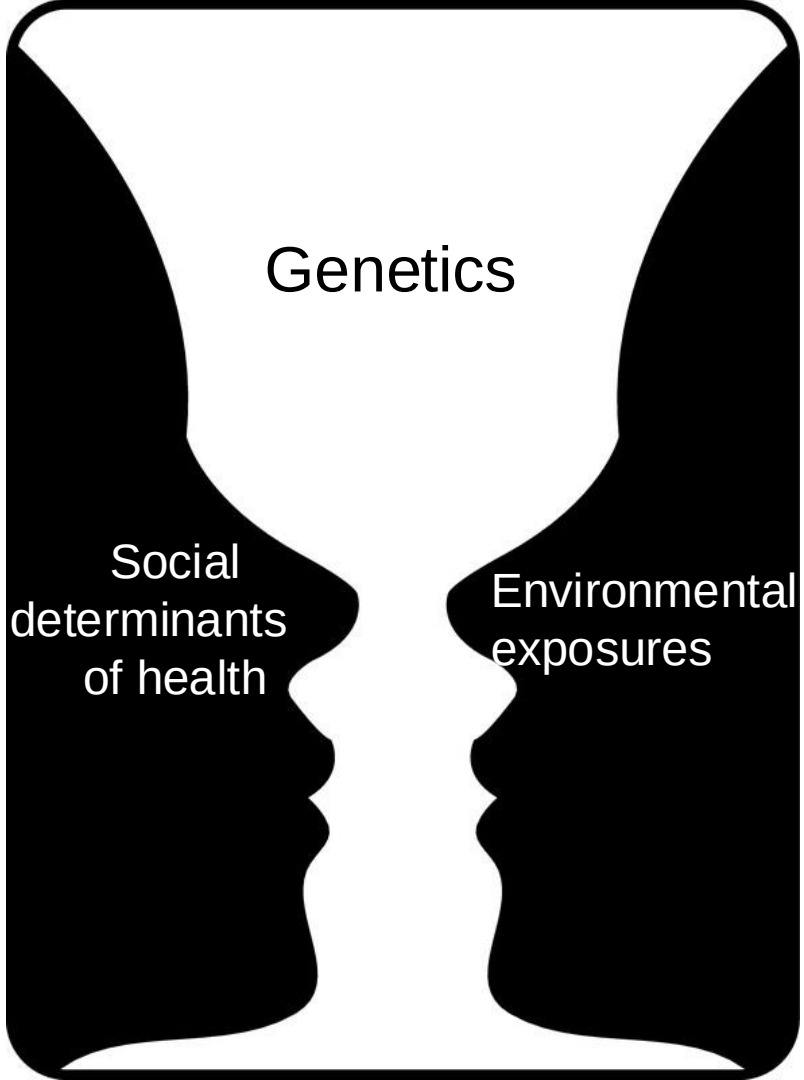
Substantive new investments in social determinants of health

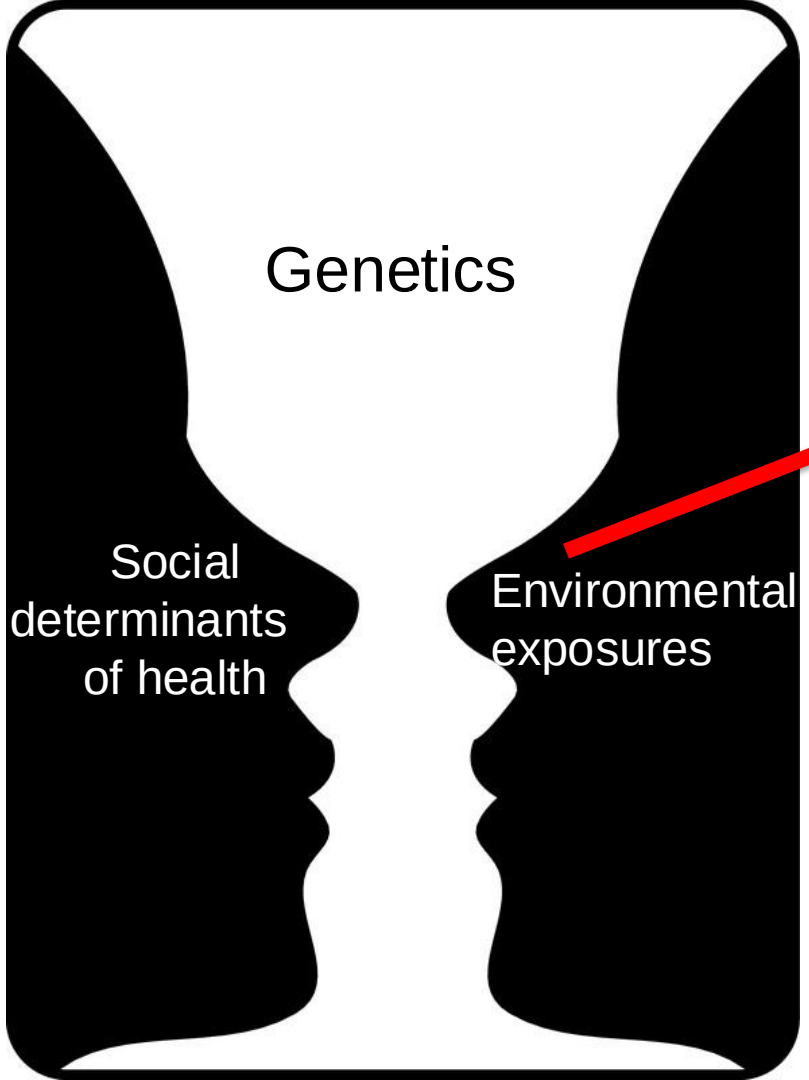


EHR



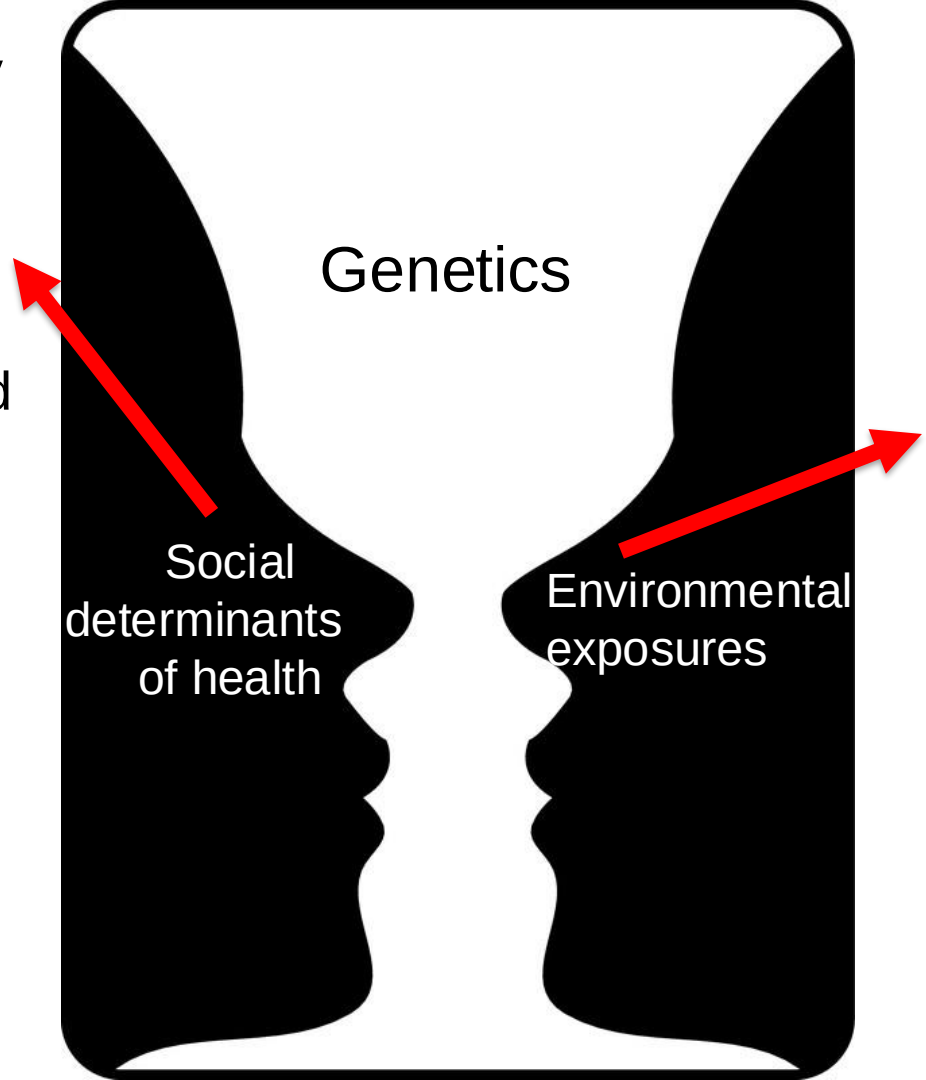
~330,000 with EHR phenome and genome data


Genetics
Social determinants of health
Environmental exposures



Exposures can damage DNA, RNA, alter methylation, alter chromatin marks or may just damage tissues directly; may be short-acting or long-lived; may be physical, chemical, mixed, ingested, breathed, beamed, …

Some SDOH may be so pervasive that they do not need to effect biology at all but still have profound and direct effects on health and outcomes.



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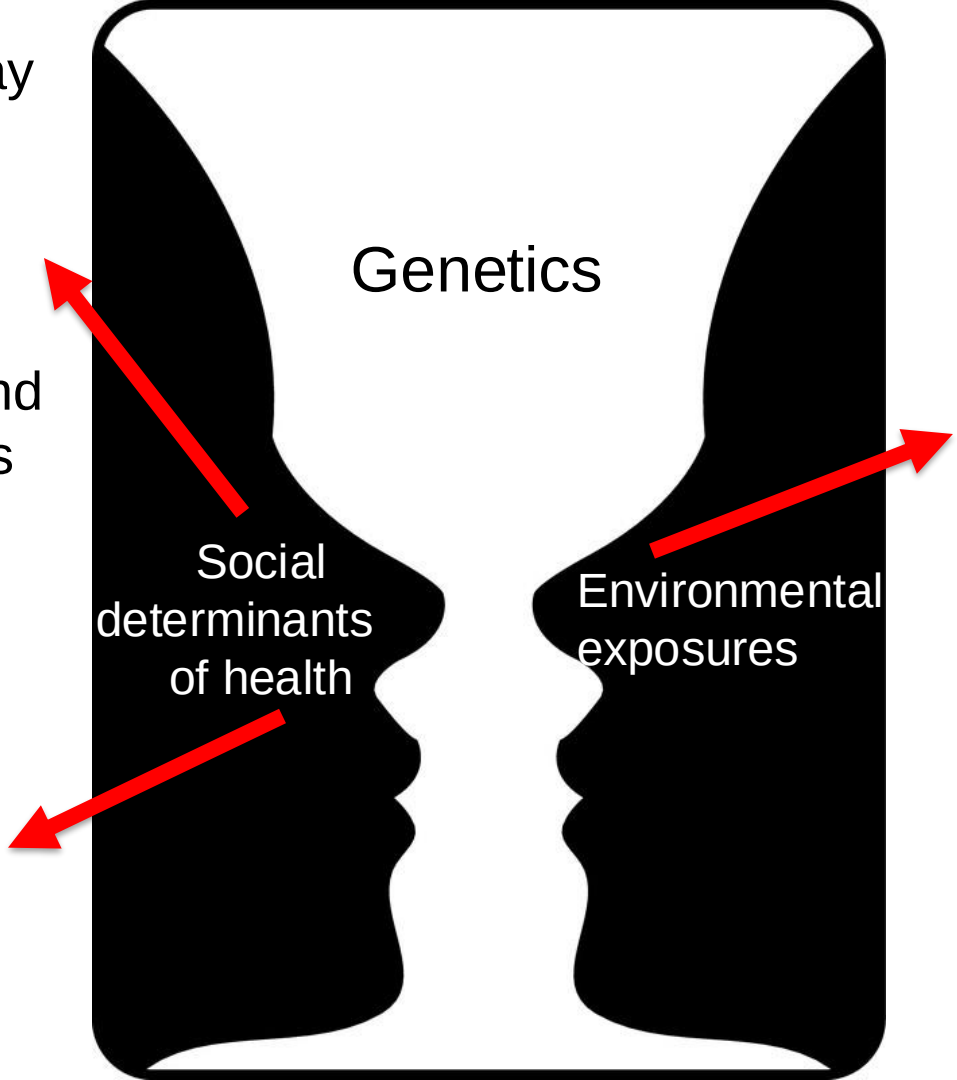
Some SDOH may be so pervasive that they do not need to effect biology at all but still have profound and direct effects on health and outcomes.

SDOH may also damage/effect DNA, RNA, methylation, chromatin, etc



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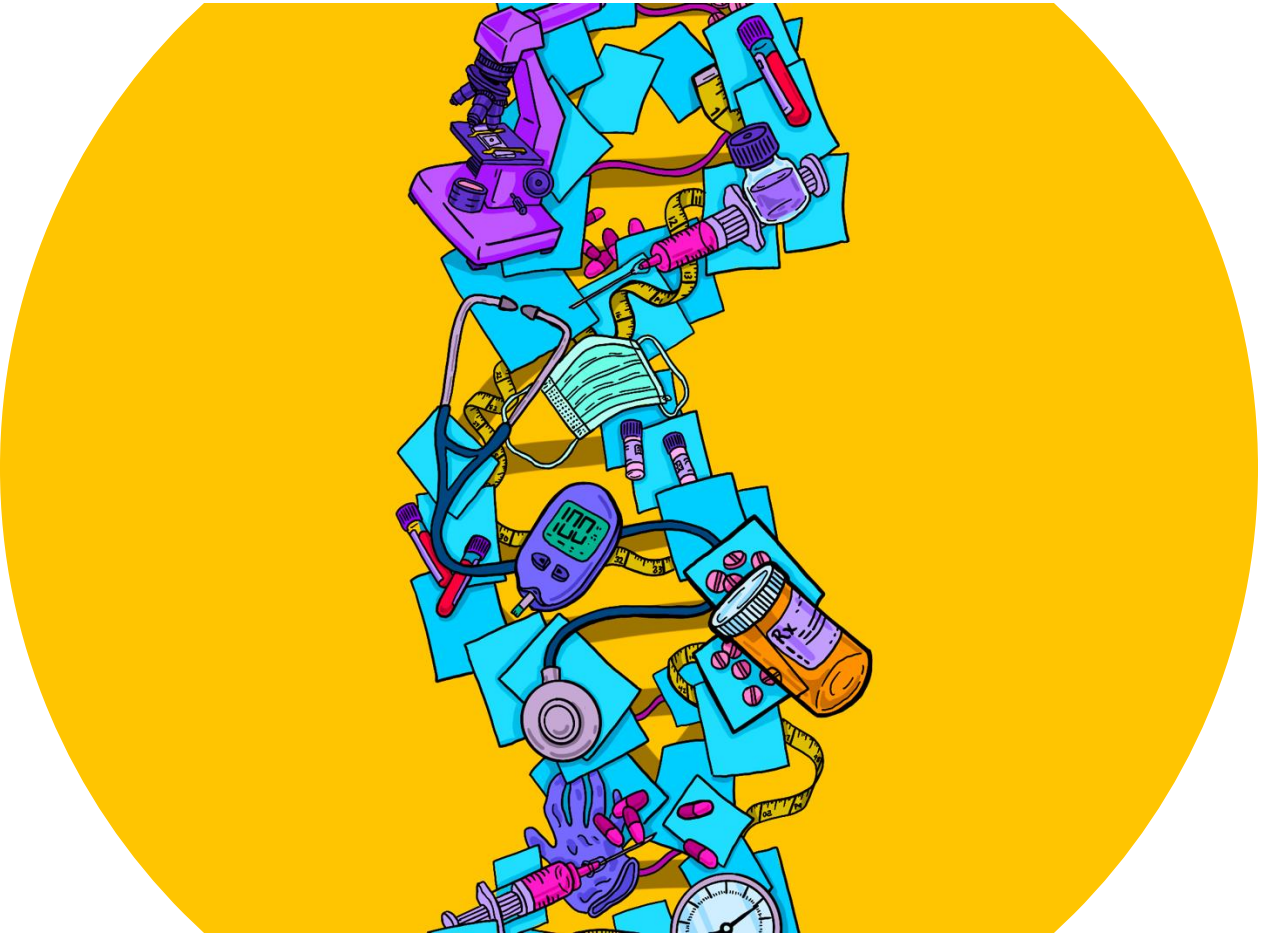
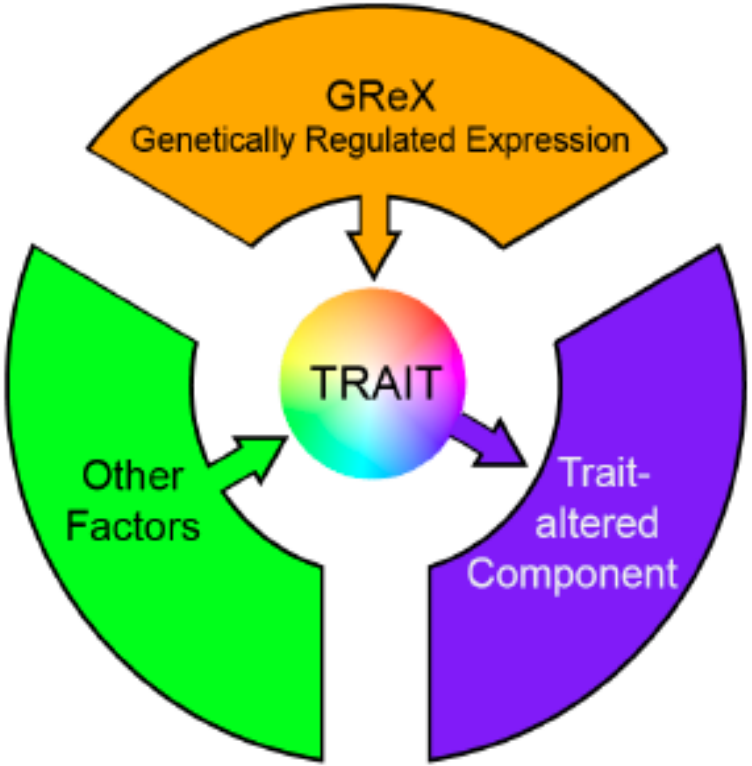
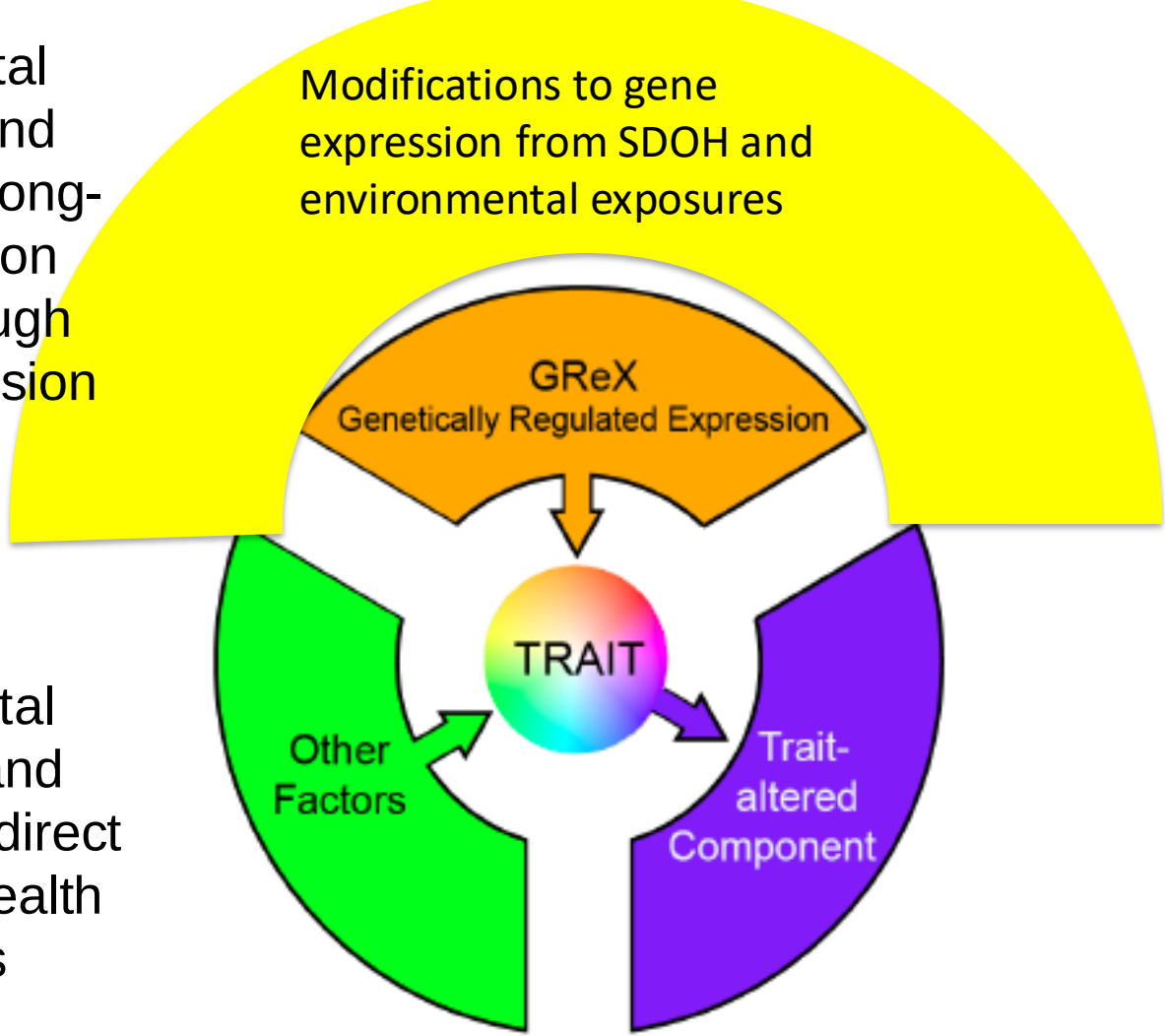


So what should we be doing to learn how E and GxE drive disease biology?

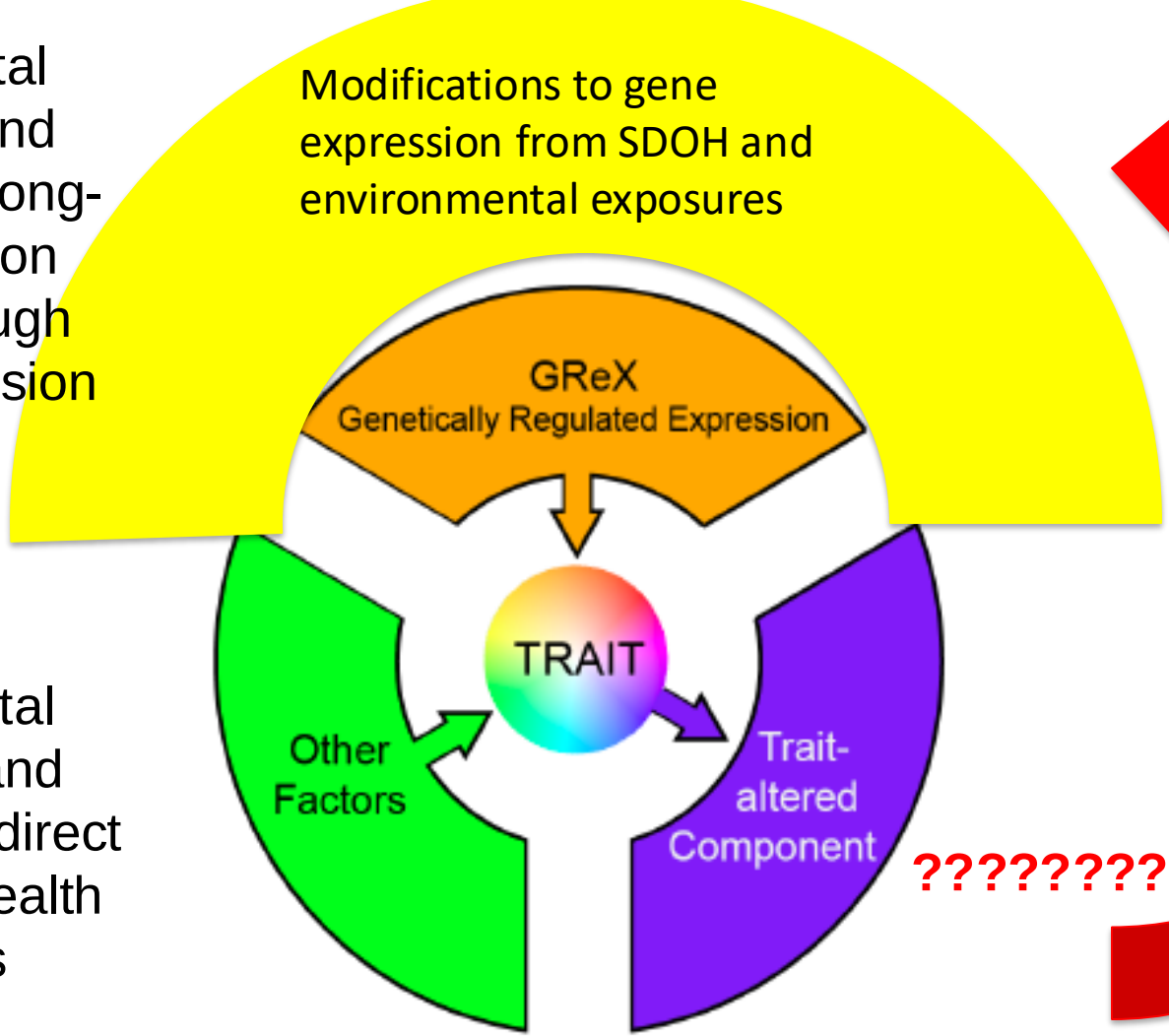

GReX
Genetically Regulated Expression
TRAIT
Other
Factors
Trait-
altered
Component

Environmental exposures and SDOH with long-term effects on biology through gene expression



Environmental exposures and SDOH with direct effects on health related traits

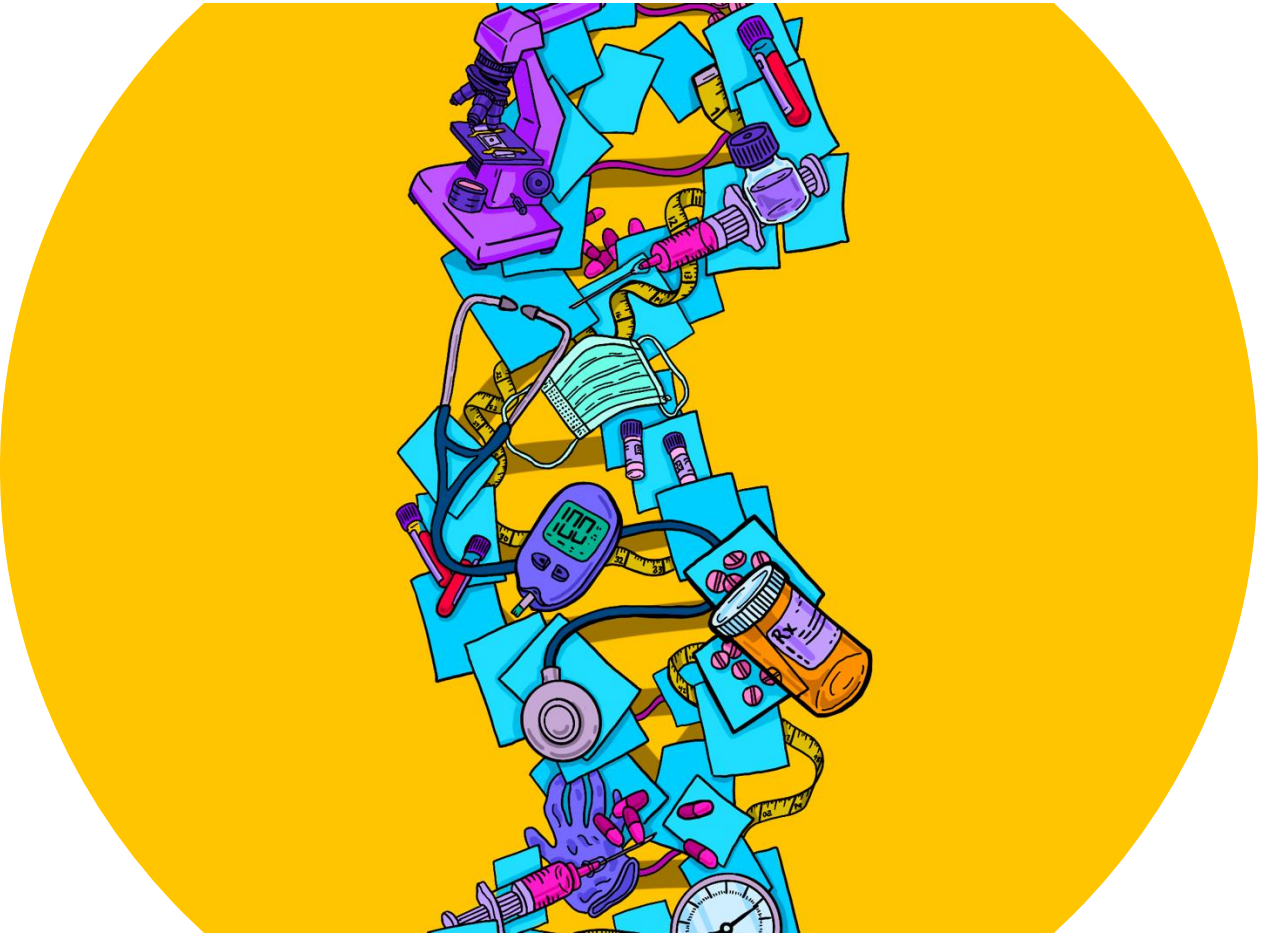
Environmental exposures and SDOH with long-term effects on biology through gene expression



Modifications to mRNA, lnRNA, smRNA, tRNA ratios, translational efficiency, post-translational modifications, activation and inactivation of proteins

??????????

Environmental exposures and SDOH with direct effects on health related traits



Yes, it’s complicated. But really, what should we do?

Inquiring minds want to know…

What proportion of SDOH do not drive biology, but could be directly solved with money for access, better diets, etc?

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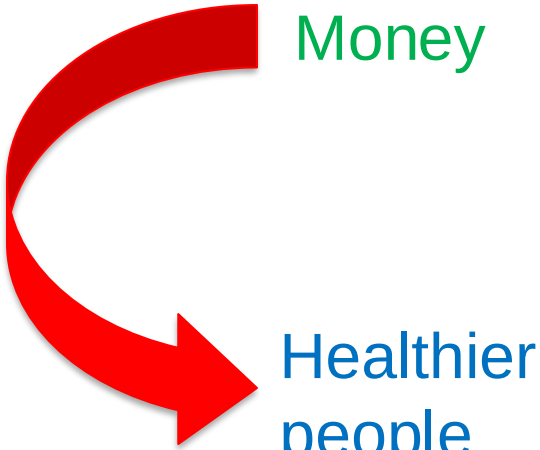

Inquiring minds want to know…

Using the biology we can learn with the tools we have now, does biology driven by E and GxE completely layer onto what biology we know from G? Is it largely orthogonal to G?

Biology is measurable and modifiable even when we can't fully identify all exposures. Developing the tools to measure exposure biology at scale will also allow us to better calibrate interindividual variability in exposures, and more rationally choose appropriate therapies.

Most obvious deep drive traits…

Obesity: Huge G, huge E, almost certainly important GxE, accessible tissue — people want to give it away! Hugely consequential to many diseases as a risk factor. New drugs allow more ability to probe biology.

Inflammatory biology: key driver biology for many diseases, immune cells present in blood and many key biomarkers as well. Known to be affected by stressors of many types. Huge G, important E, likely GxE, high value target for drug development, evolutionary signatures may also help identify targets.

Southeast Collaborative for Innovative and Equitable Solutions to Chronic Disease Disparities

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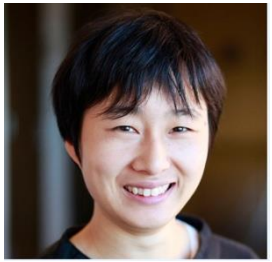
Roy Weiss, MD, PhD
University of Miami

EndoPhenotype Incorporated PRS (EPIC-PRS)



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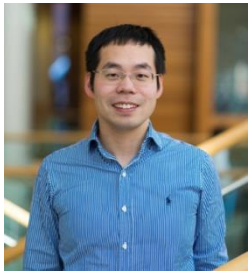

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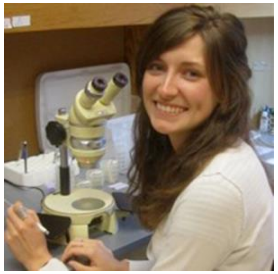

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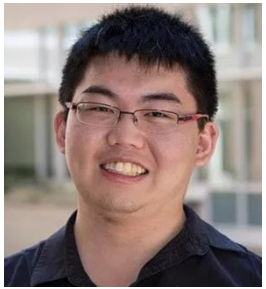
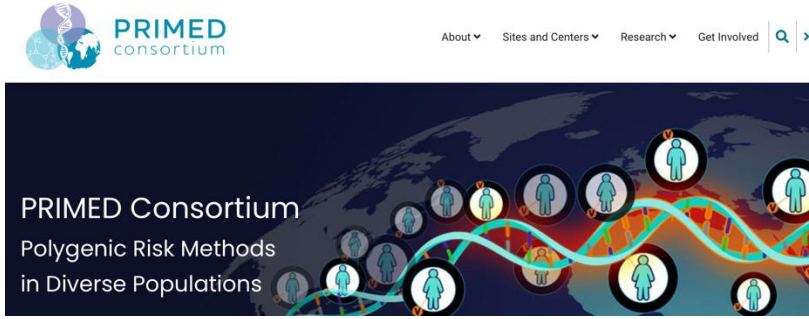


Minzi Shared



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Transforming the understanding and treatment of mental illnesses.