

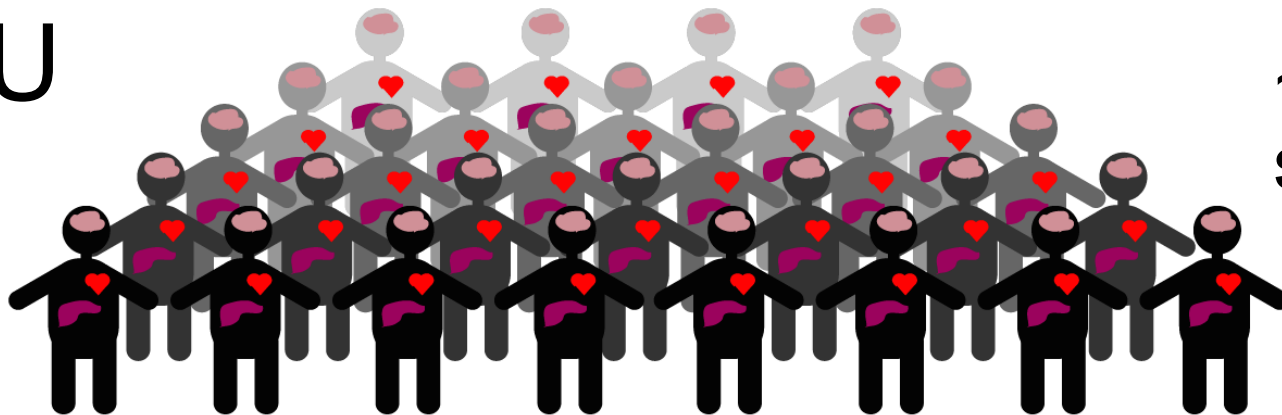
# How do we learn what disease biology is driven by environment and GxE?

Nancy J. Cox, PhD  
Vanderbilt Genetics Institute  
Vanderbilt University Medical Center

# 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

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

## EHR

DHCP Automated Clinical Record in use by: Michael Johnson

Patient Edit Chart Tools CoverSheet Help

Doc: John P  
321-95-4567 22 Apr 08 1A1204-A

Problems: Status: Active Meds: Lab Results in Past:

Problem	Status	Active Meds	Lab Results in Past
Pneumonia	A	Enalapril Tab 10mg po q12h	CBC w/diff 12/13/93 9:00:00 AM
COPD	A	Cimetidine Tab 800mg po qhs	Chem 20 12/13/93 9:00:00 AM
Essential Hypertension	A	Acetaminophen Capsule 650mg po q6h pm headache, fever	Chem 7 12/13/93 9:00:00 PM
Tobacco Abuse	A	Milk of Magnesia Liquid 30cc po pm constipation	CBC w/diff 12/12/93 10:30:00 AM
Appendicitis	I	Theophylline Time Release Tab 300mg po q12h	CBC 12/12/93 2:00:00 PM
		Maalox Liquid 30cc po pm heartburn	CBC 6/6/93 2:00:00 PM
		Metoprolenol Sulfate Aerosol (50mg)inhalation q6h	Chem 27 6/6/93 2:00:00 PM
			UA 6/6/93 2:00:00 PM
			CBC 12/15/92 10:20:00 AM
			Chem 7 12/15/92 10:20:00 AM

Visits: Location: Notifications/Alerts:

Visit	Location	Notifications/Alerts
12/12/93 10:30:00 AM	1A	New lab results available.
12/15/92 2:00:00 PM	Gen Medicine	Critical Lab Result: GLUCOSE 490 mg/dL.
6/6/93 2:00:00 PM	Gen Medicine	Order released-requires chart signature.
12/15/92 10:20:00 AM	Gen Medicine	Admitted on Dec 12, 1993@10:30
6/1/92 1:30:00 PM	Cardiology	
9/18/93 10:45:00 AM	1A	
9/17/93 2:30:00 PM	Hematology	
2/27/93 11:00:00 AM	Gen Medicine	

Crisis/Warnings/Directives: Next of Kin: Allergies: Symptoms:

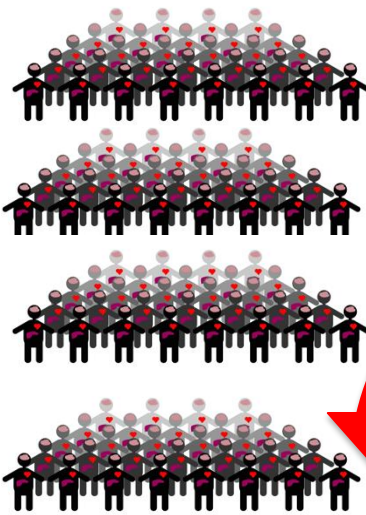
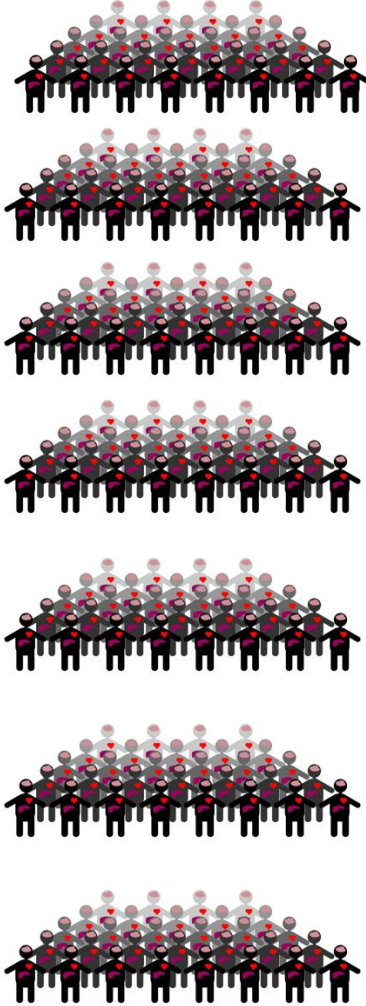
Crisis/Warnings/Directives	Next of Kin	Allergies	Symptoms
Environmental	Jane Doe	Cephalosins Dairy Products Strawberries	Thrombocytopenia Diarrhea, Urticaria Urticaria

Cover Problems Meds Orders H & P Notes Consults Labs Xray Specials Summ.

## -OMICS

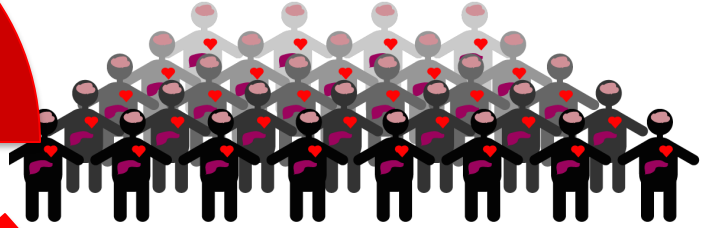
- Genome variation
- **Transcriptomes**
- **Metabolomes**

150K  
**Imputed**



2.8 million with just EHR data

Substantive new investments in social determinants of health



ated Clinical Record in use by: Michael Johnson

Patient Edit Chart Help

Doe, John P  
321-95-4567 22 Apr 08 12:00

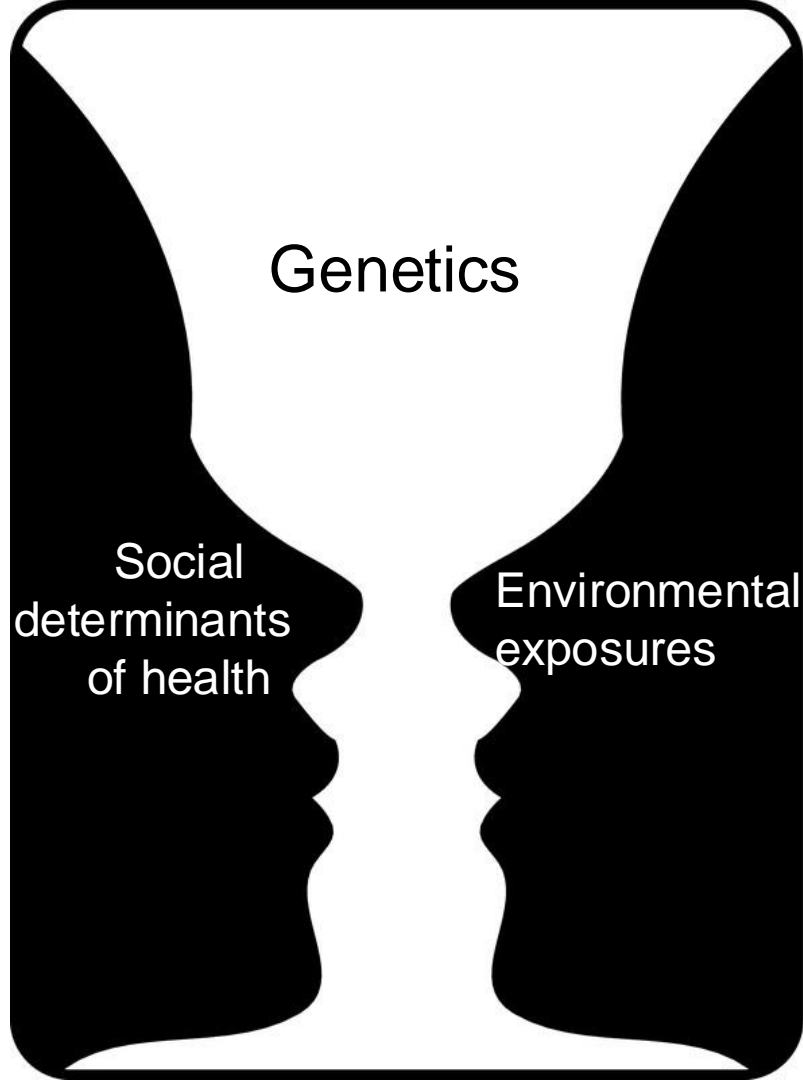
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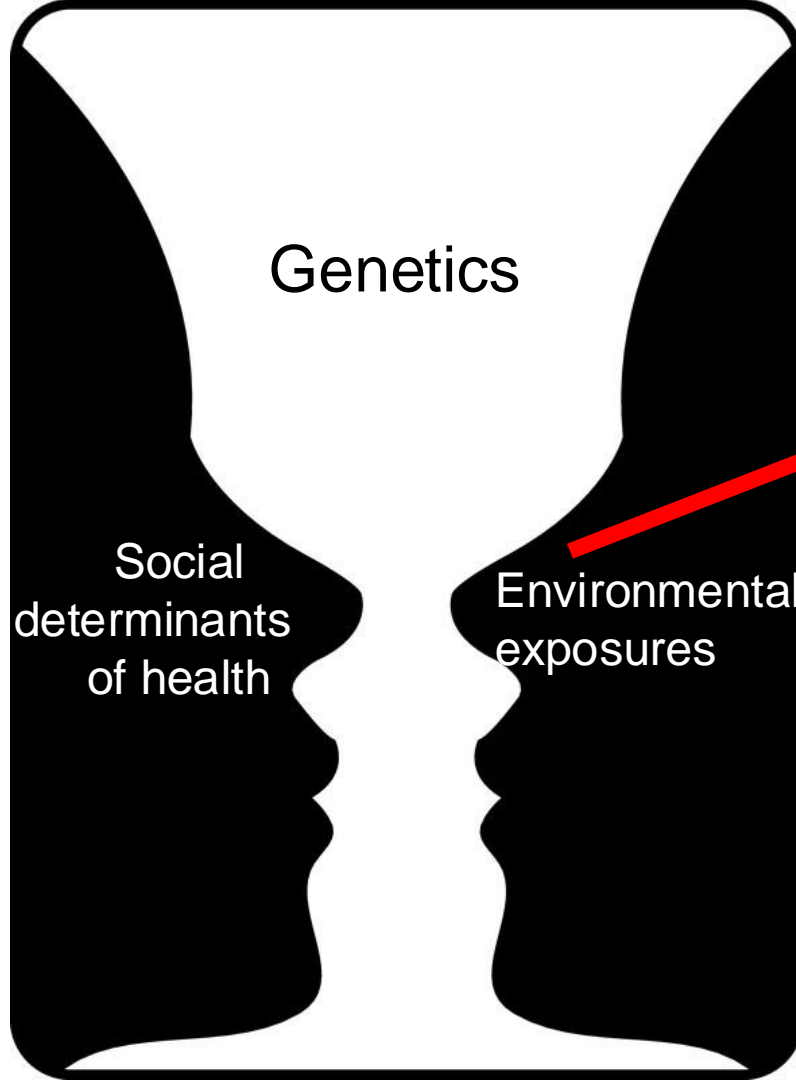
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Critics/Warnings/Directives:	Next of Kin:	Allergies:	Symptoms:
Environmental	Jane Doe	Cephalosporin Dairy Products Strawberries	Thrombocytopenia Diarrhea Urticaria

Cover | Problems | Meds | Orders | H & P | Notes | Consults | Labs | X-ray | Specials | Summ.

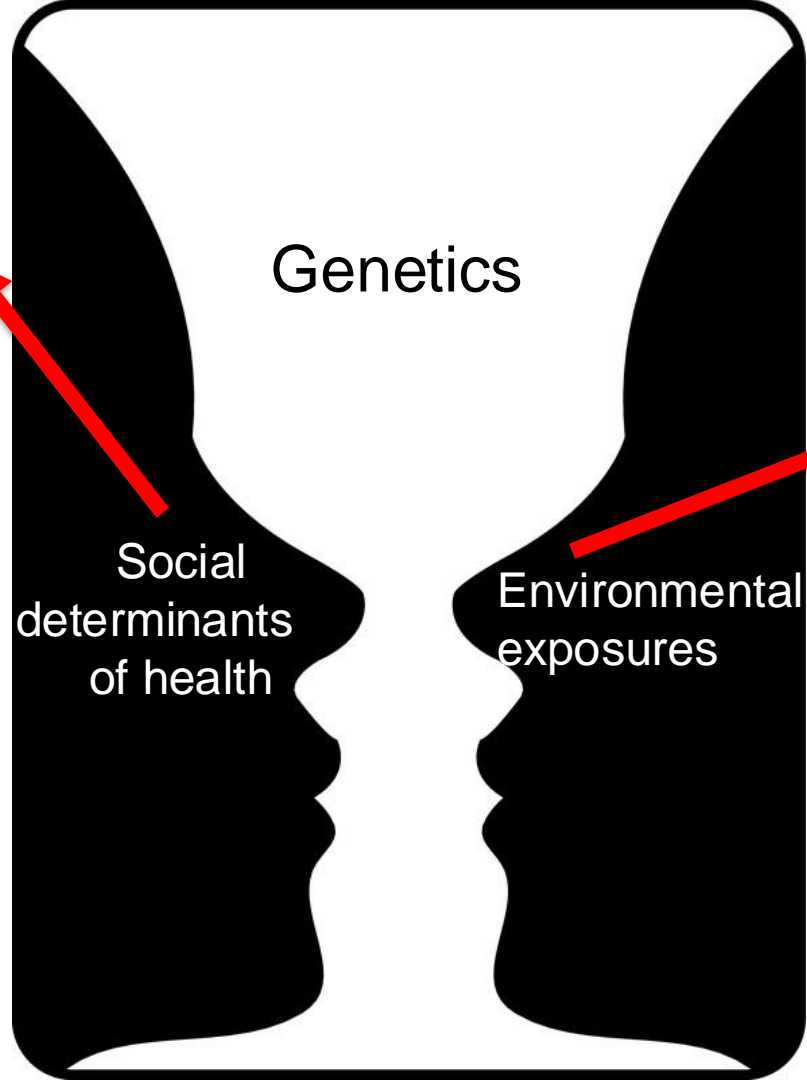
~330,000 with EHR phenome and genome data



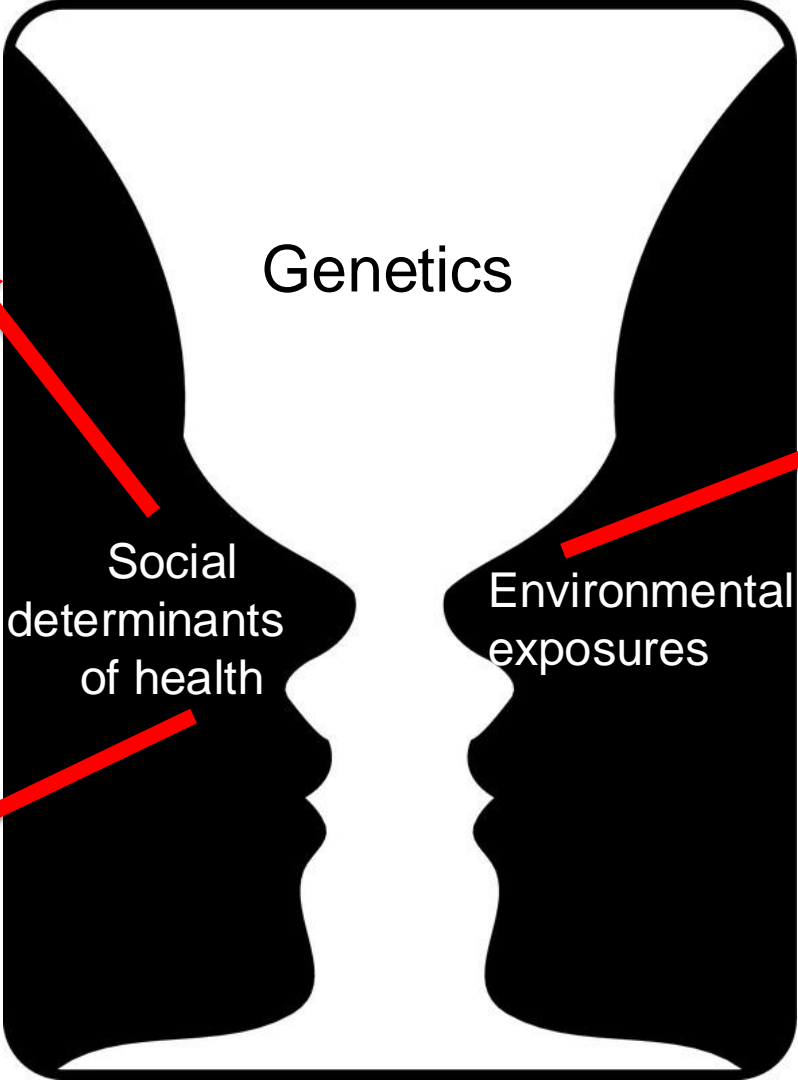


Exposures can damage DNA, RNA, alter methylation, alter chromatin marks or may just damage tissues directly; may be short-acting or long-lived; may be physical, chemical, mixed, ingested, breathed, beamed, ...

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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Genetics

Social  
determinants  
of health

Environmental  
exposures

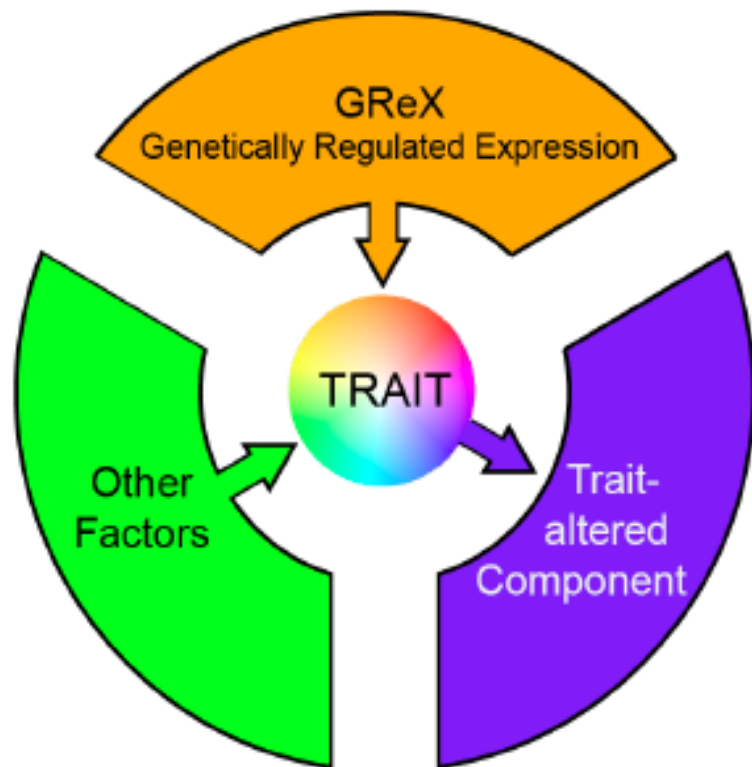
Some SDOH may be so pervasive that they do not need to effect biology at all but still have profound and direct effects on health and outcomes.

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

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, ...

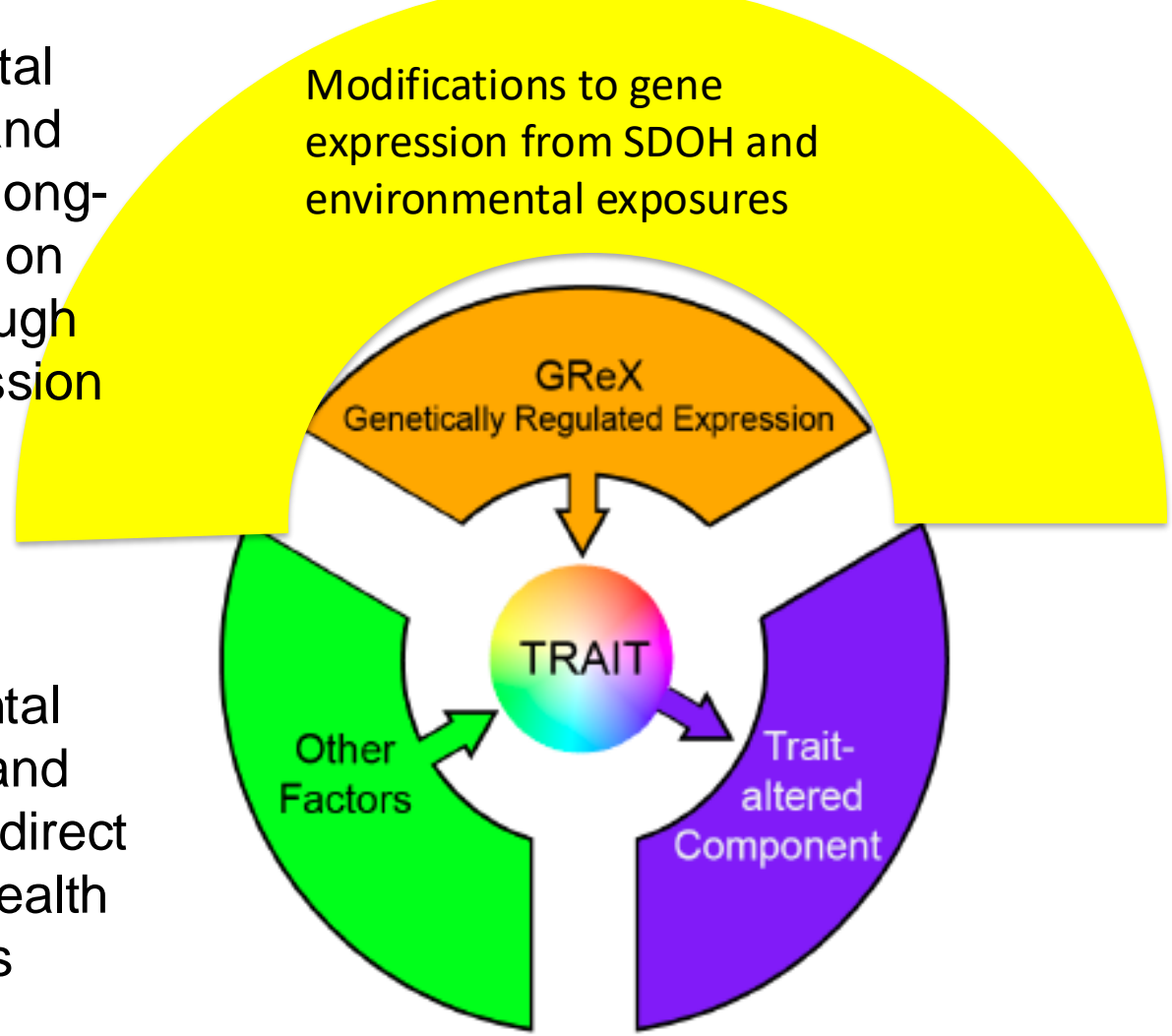






Environmental exposures and SDOH with long-term effects on biology through gene expression

Modifications to gene expression from SDOH and environmental exposures



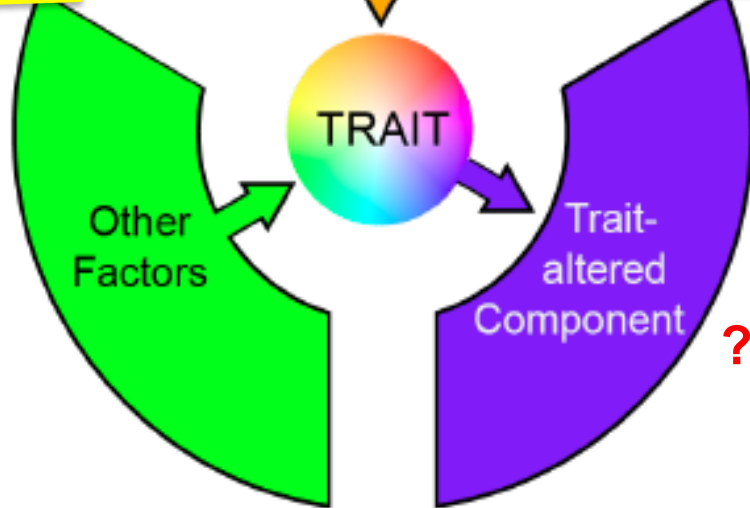
Environmental exposures and SDOH with direct effects on health related traits

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

Modifications to gene expression from SDOH and environmental exposures

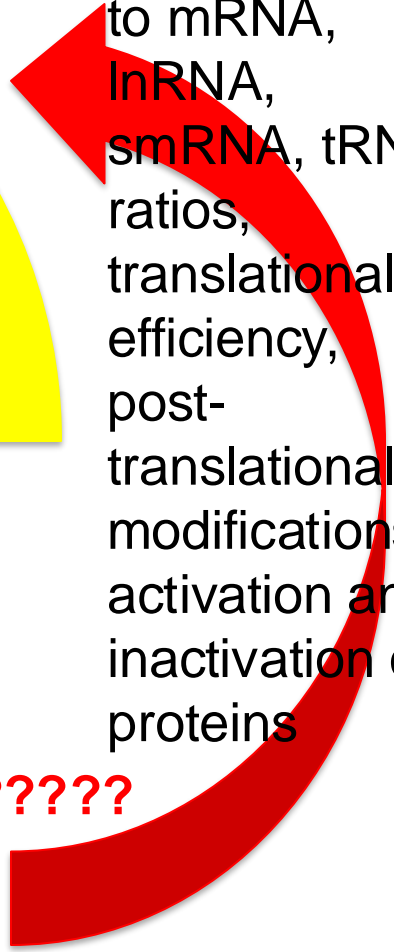


Environmental exposures and SDOH with direct effects on health related traits



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

??????????



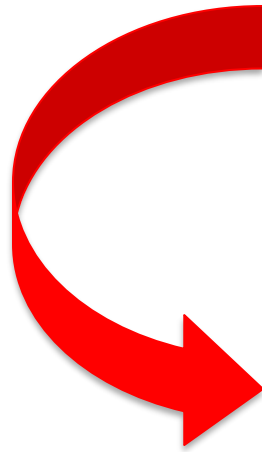


# Inquiring minds want to know...

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

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Money

Healthier  
people

# 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



Consuelo Wilkins, MD, MSCI  
VUMC



Stephania Miller-Hughes, PhD, MS,  
MSCI, Meharry Medical College

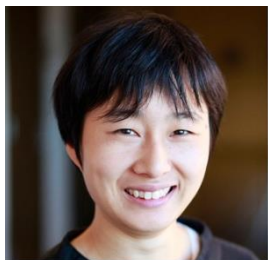


Roy Weiss, MD, PhD  
University of Miami

# EndoPhenotype Incorporated PRS (EPIC-PRS)



About Sites and Centers Research Get Involved



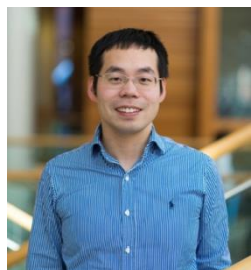
Yun Li, PhD,  
UNC



Alex Reiner,  
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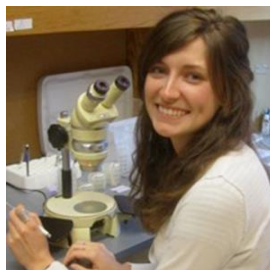
Laura Raffield,  
PhD, UNC



Ran Tao, PhD.



Jibril Hirbo, PhD



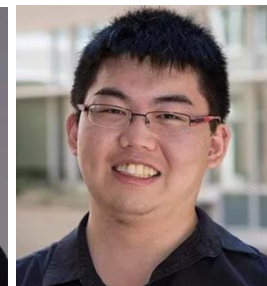
Tyne Miller-Fleming, PhD



Jiawen Du



Quan Sun



Minzi Shared



National Human Genome  
Research Institute



American  
Heart  
Association.



National Institute  
on Minority Health  
and Health Disparities



National Institute  
of Mental Health

**Transforming the understanding  
and treatment of mental illnesses.**