

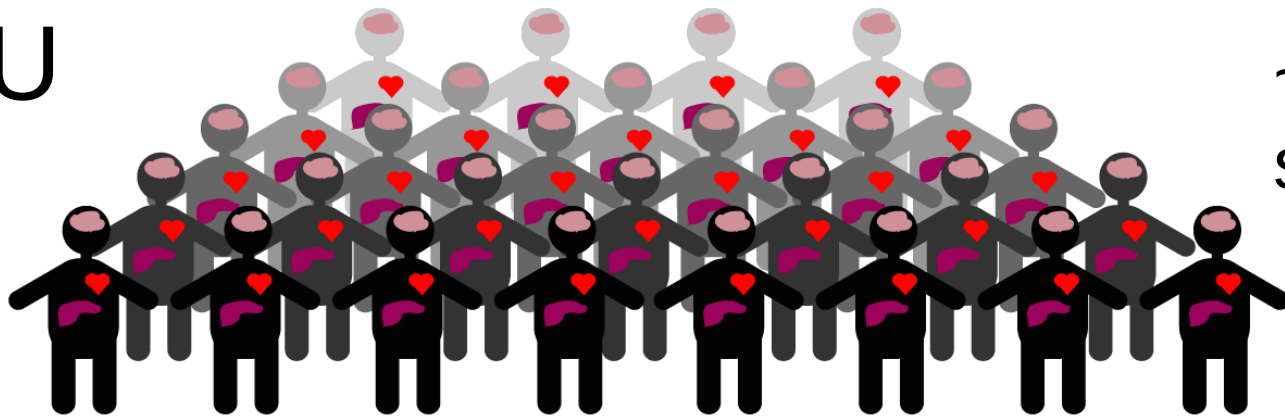
How do we learn what disease biology is driven by environment and GxE?

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:

Problems	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 300c po pm constipation	CBC w/diff 12/12/93 10:30:00 AM
Appendicitis	I	Theophylline Time Release Tab 300mg po q12h	Chem 20 12/13/93 2:00:00 PM
		Maalox Liquid 300c po pm heartburn	CBC 6/6/93 2:00:00 PM
		Metaproterenol Sulfate Aerosol (650mcg/inhalation) q6h	Chem 7 6/6/93 2:00:00 PM
			UA 6/6/93 2:00:00 PM
			CBC 12/15/92 10:30:00 AM
			Chem 7 12/15/92 10:30:00 AM

Visits: Location: Notifications/Alerts:

Visits	Location	Notifications/Alerts
12/12/93 10:30:00 AM	1A	New lab results available.
12/13/93 2:00:00 PM	Gen Medicine	Critical Lab Result: GLUCOSE 480 mg/dL.
6/6/93 2:00:00 PM	Gen Medicine	Order released-requires chart signature.
12/15/92 10:30:00 AM	Gen Medicine	Admitted on Dec 12, 1993@10:30
6/1/92 1:30:00 PM	Cardiology	
9/18/89 10:45:00 AM	1A	
9/17/89 2:30:00 PM	Hematology	
2/27/89 11:00:00 AM	Gen Medicine	

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

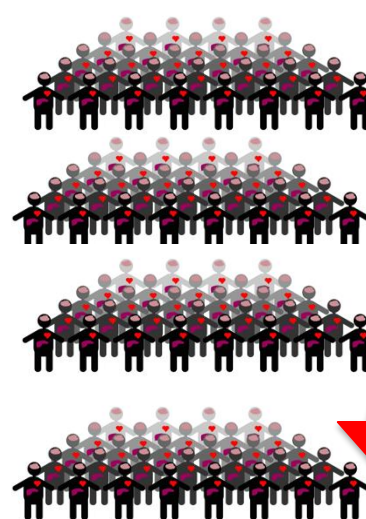
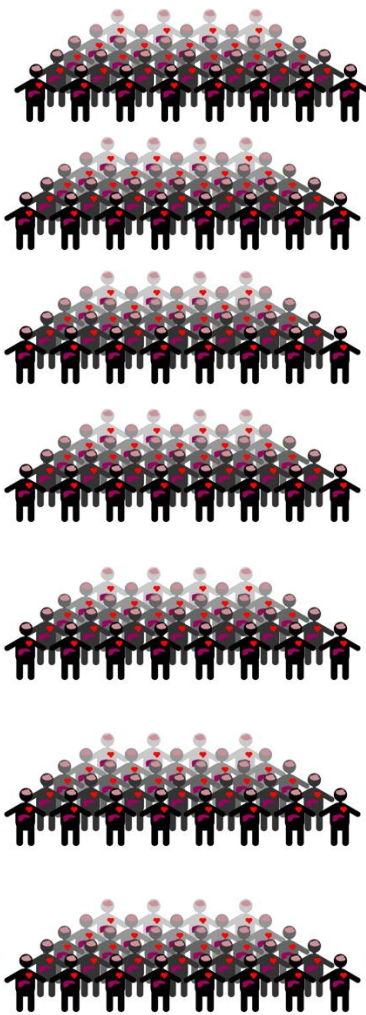
Crisis/Warnings/Directives	Next of Kin	Allergies	Symptoms
Environmental	Jane Doe	Cephalosporin	Thrombocytopenia
		Dairy Products	Diarrhea, Urticaria
		Strawberries	Urticaria

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

-OMICS

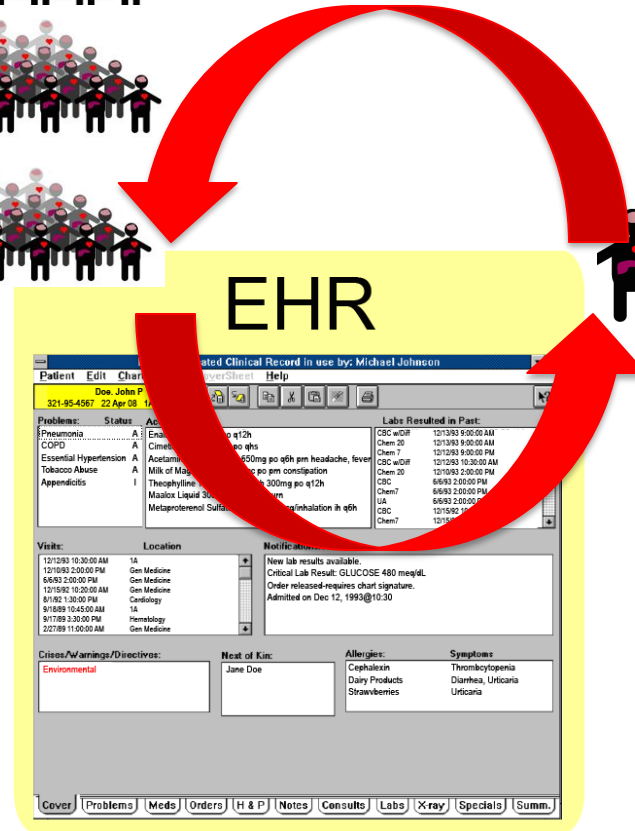
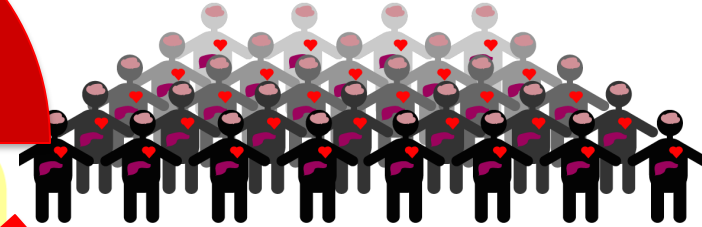
- Genome variation
- Transcriptomes
- Metabolomes

150K
Imputed

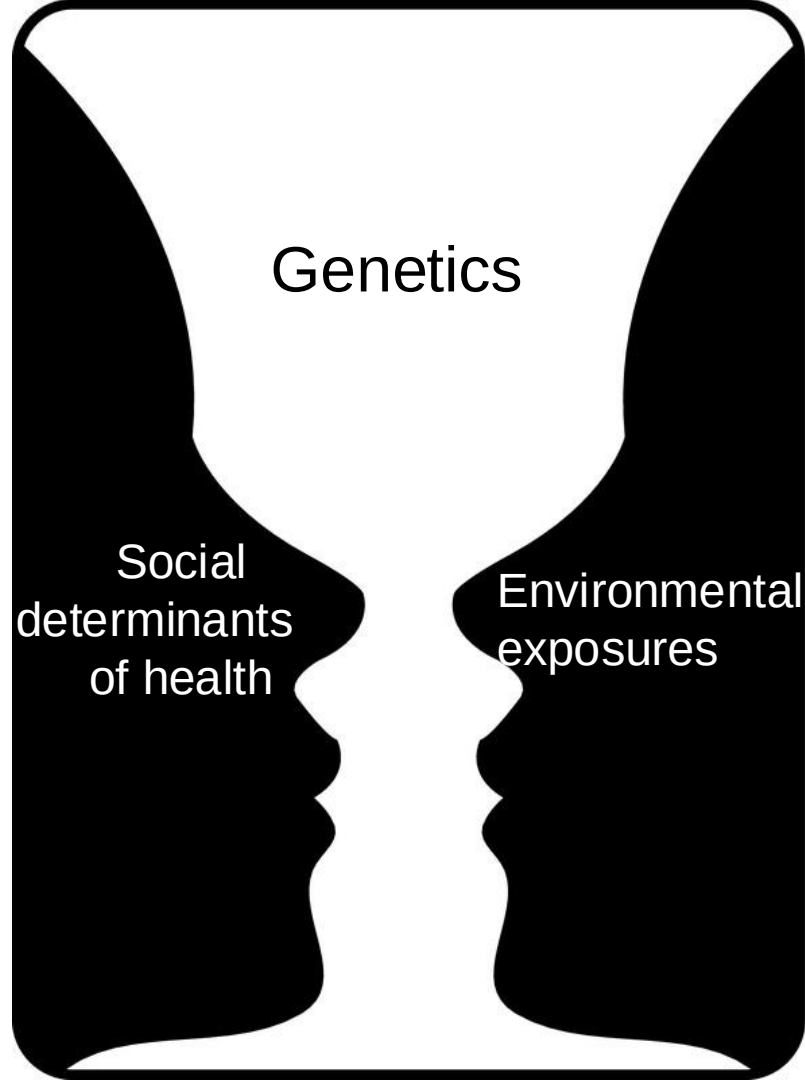


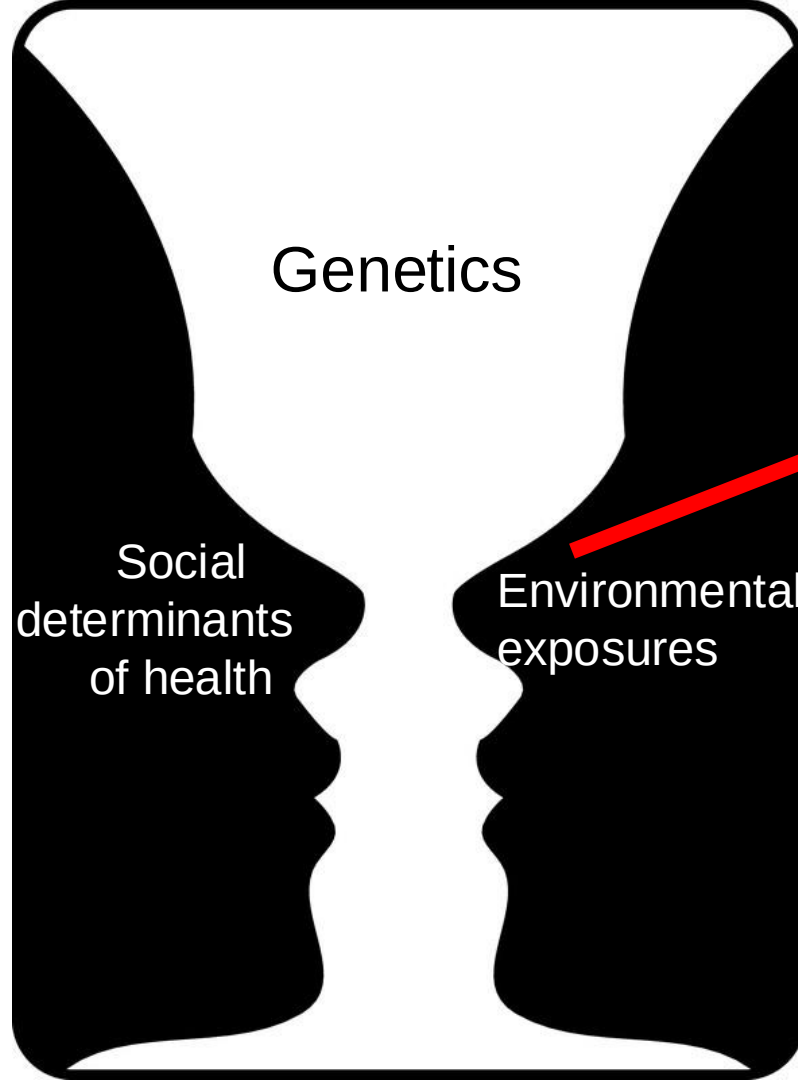
2.8 million with
just EHR data

Substantive new
investments in
social determinants
of health



~330,000 with
EHR phenome
and genome
data





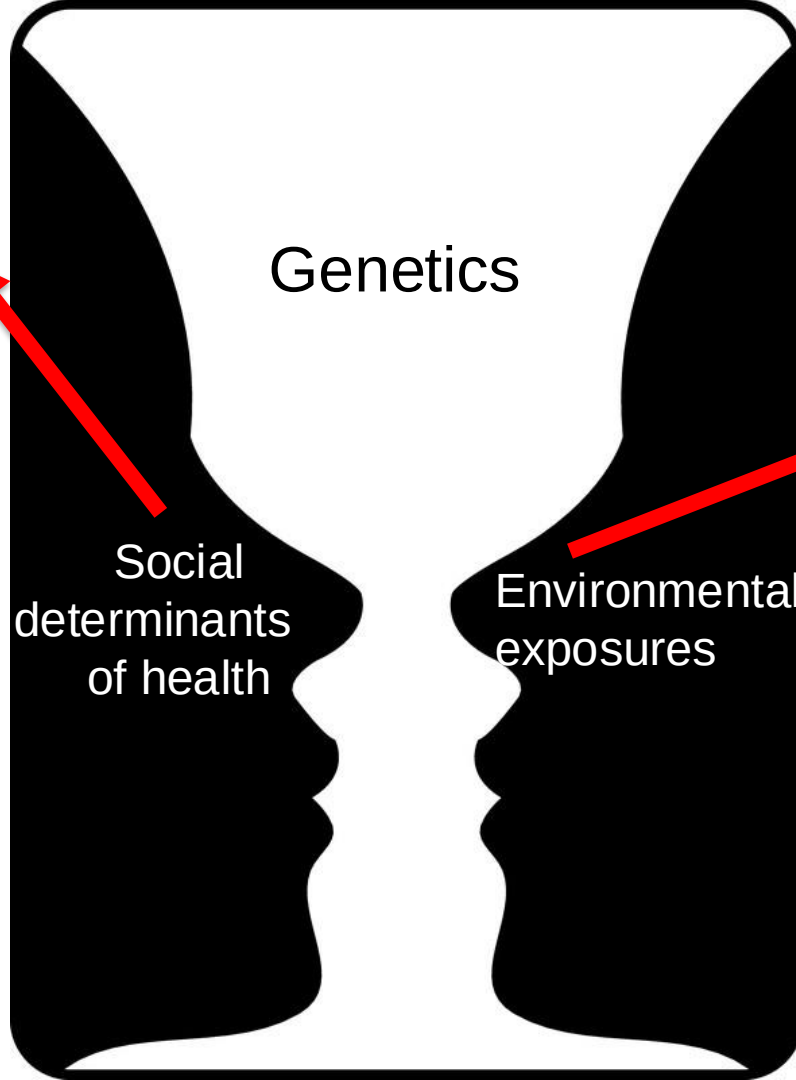
Genetics

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.



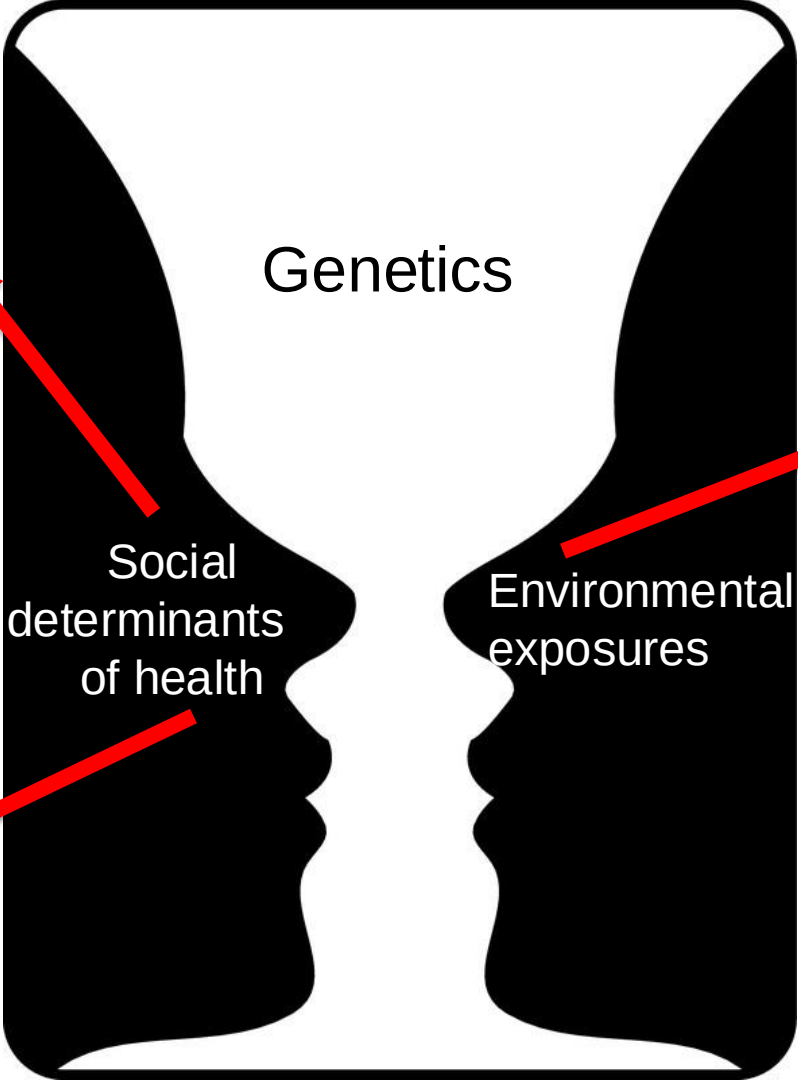
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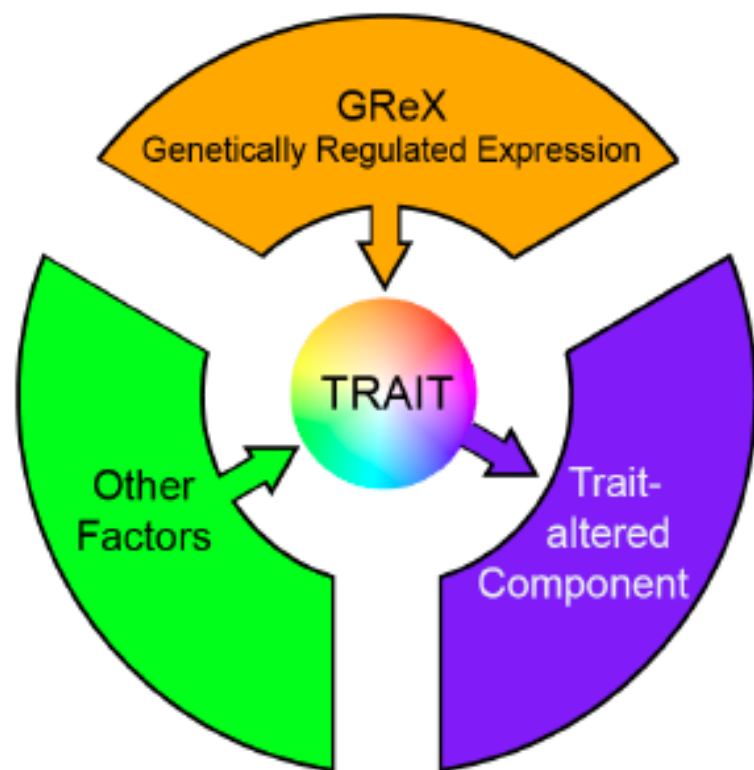
Genetics

The diagram features two black silhouettes of human heads facing each other. The word 'Genetics' is centered in the space between them. On the left profile, the text 'Social determinants of health' is written. On the right profile, the text 'Environmental exposures' is written. Three red arrows originate from external text blocks: one points from the top-left text to the 'Social determinants of health' label, another points from the bottom-left text to the same label, and a third points from the top-right text to the 'Environmental exposures' label.

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

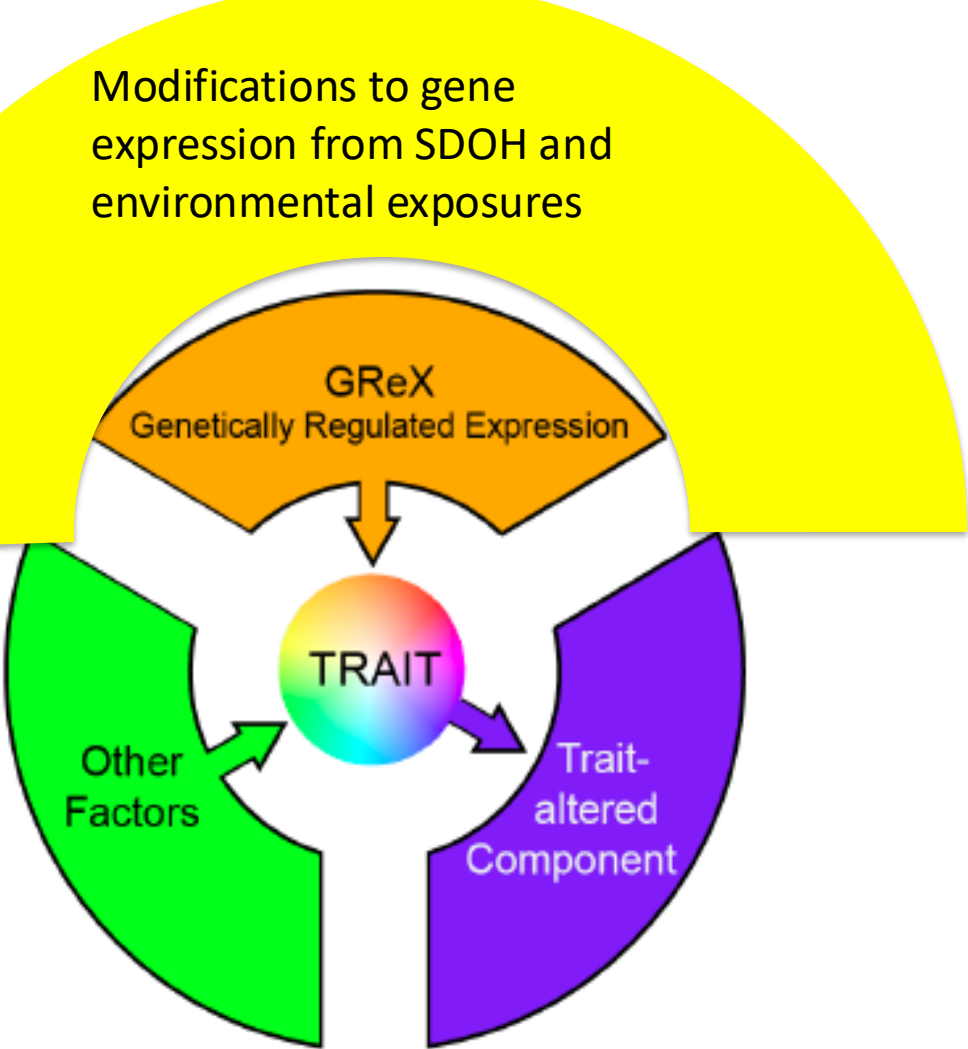
Exposures can damage DNA, RNA, alter methylation, alter chromatin marks or may just damage tissues directly; may be short-acting or long-lived; may be physical, chemical, mixed, ingested, breathed, beamed, ...



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

GReX
Genetically Regulated Expression

TRAIT

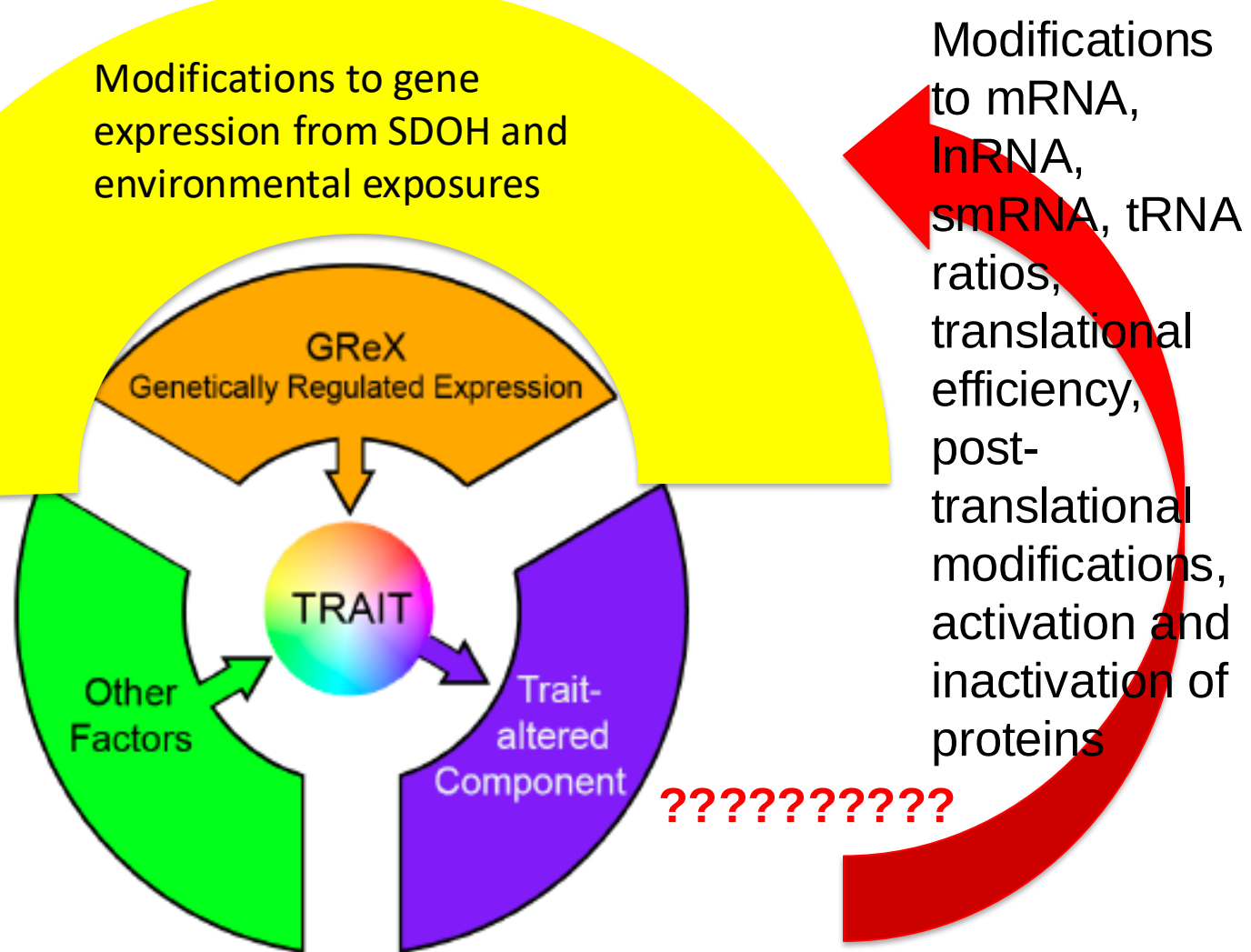
Other Factors

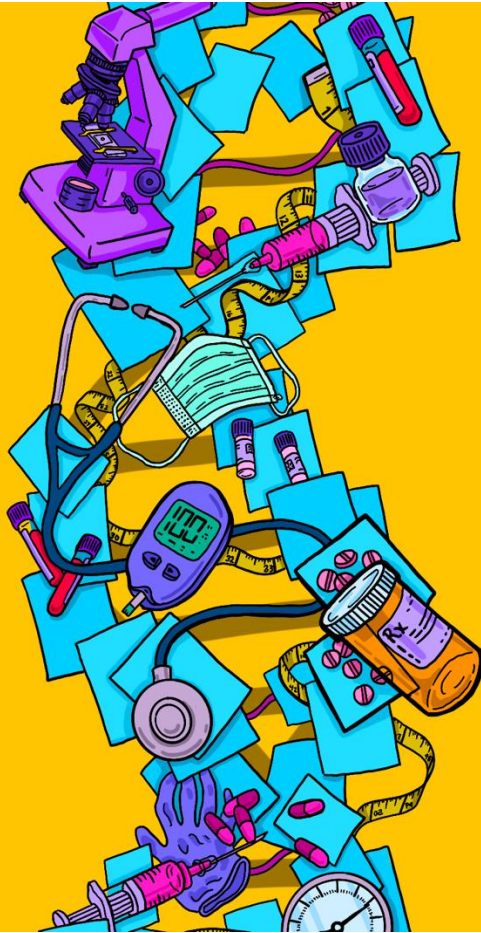
Trait-altered Component

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

??????????





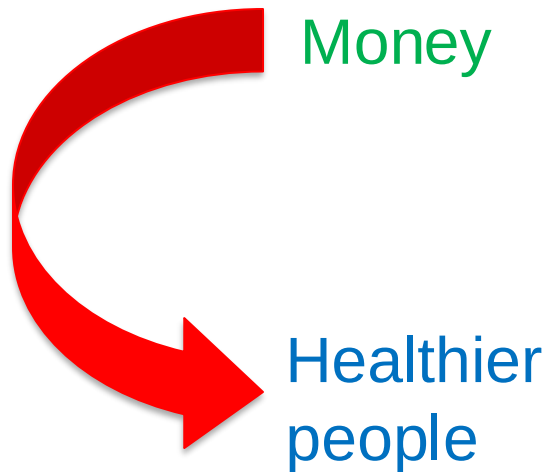
Yes, it's
complicated.
But really,
what should
we do?

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



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



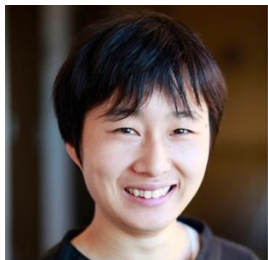
Roy Weiss, MD, PhD
University of Miami

EndoPhenotype Incorporated

PRS (EPIC-PRS)



About Sites and Centers Research Get Involved



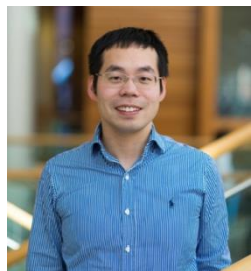
Yun Li, PhD,
UNC



Alex Reiner,
MD, MSC, UW



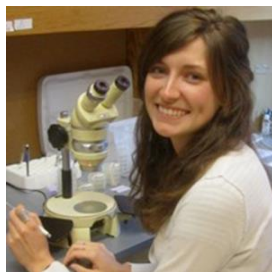
Laura Raffield,
PhD, UNC



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.**