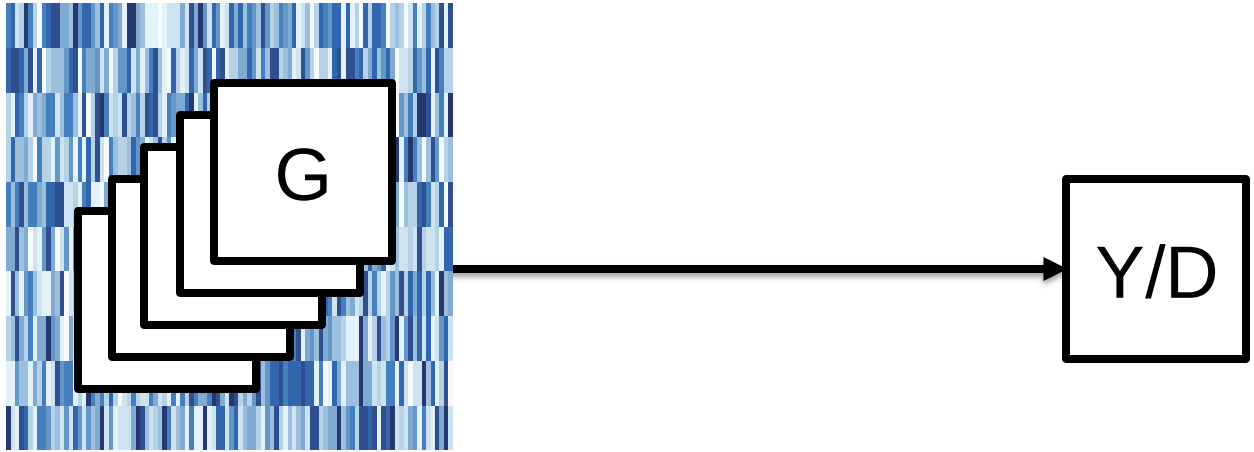
Statistical Approaches to Integrate ‘E’ with Genetics, Functional, and Multi-omic Data

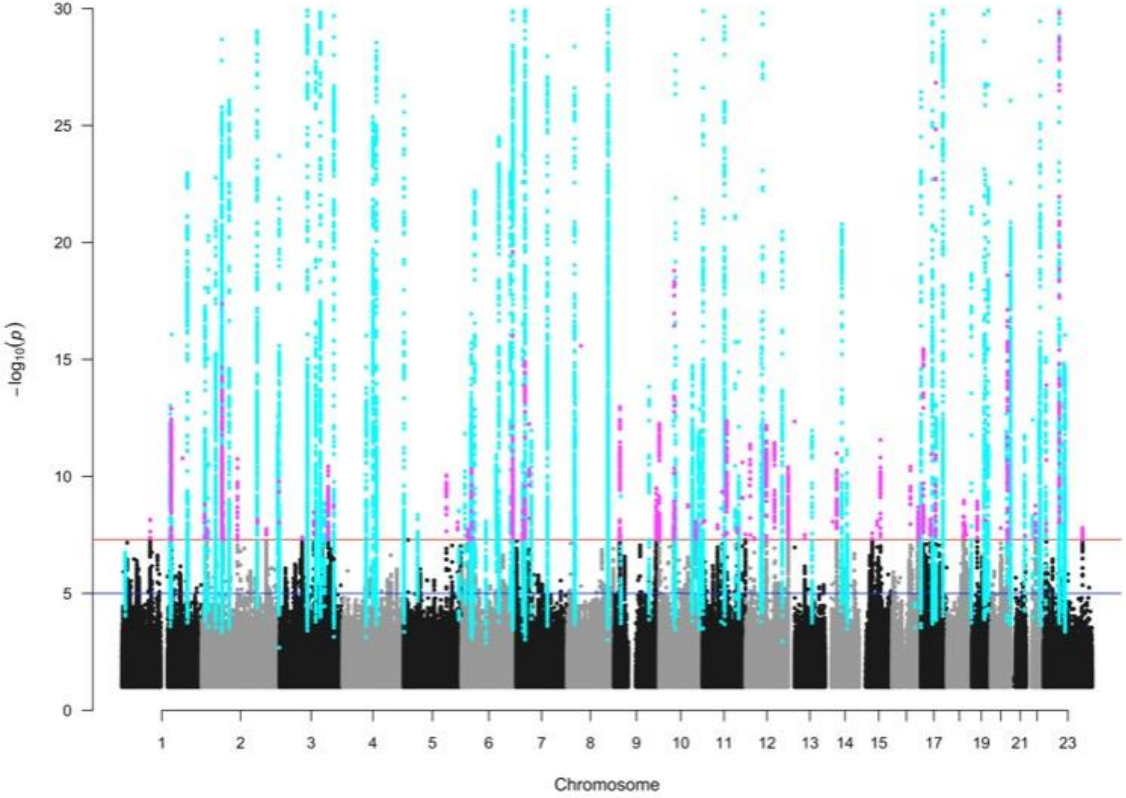
David Conti, PhD
University of Southern California

Genomewide Association Studies

SNPs



GWAS


30
25
20
15
10
5
0
$-\log_{10}(p)$
1
2
3
4
5
6
7
8
9
10
11
12
13
14
15
17
19
21
23
Chromosome

What Are We Missing?

- SNPs with modest marginal effect that might be important in one or more subgroups?

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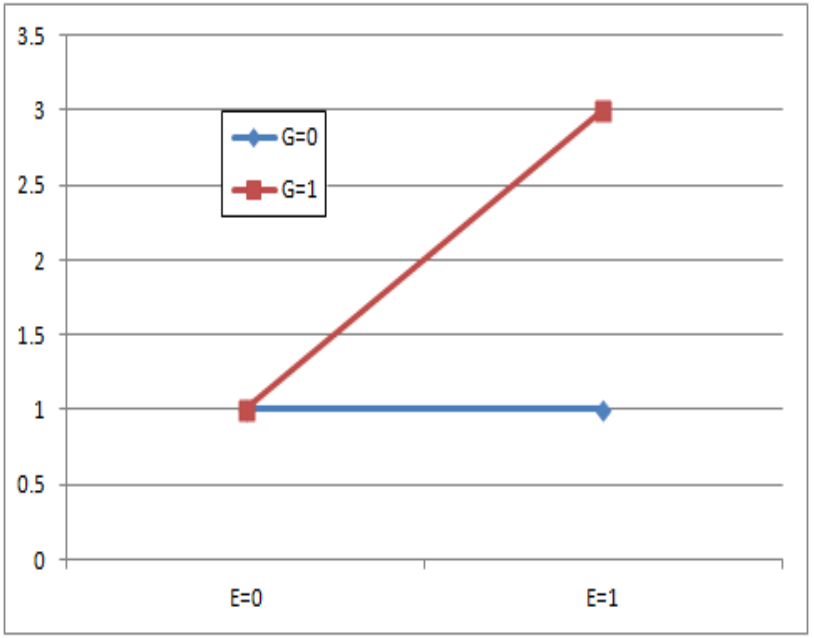

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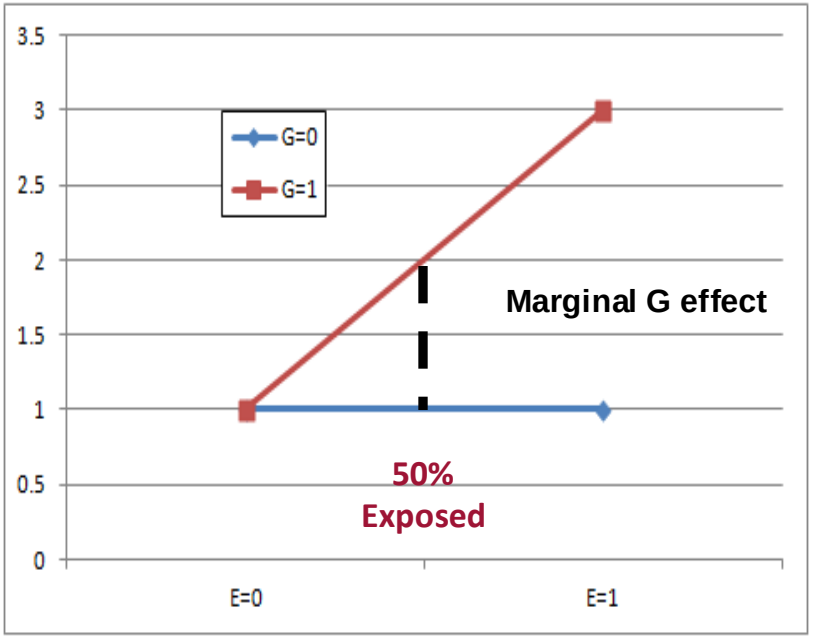
- **Size of the marginal G effect** depends on prevalence of exposure



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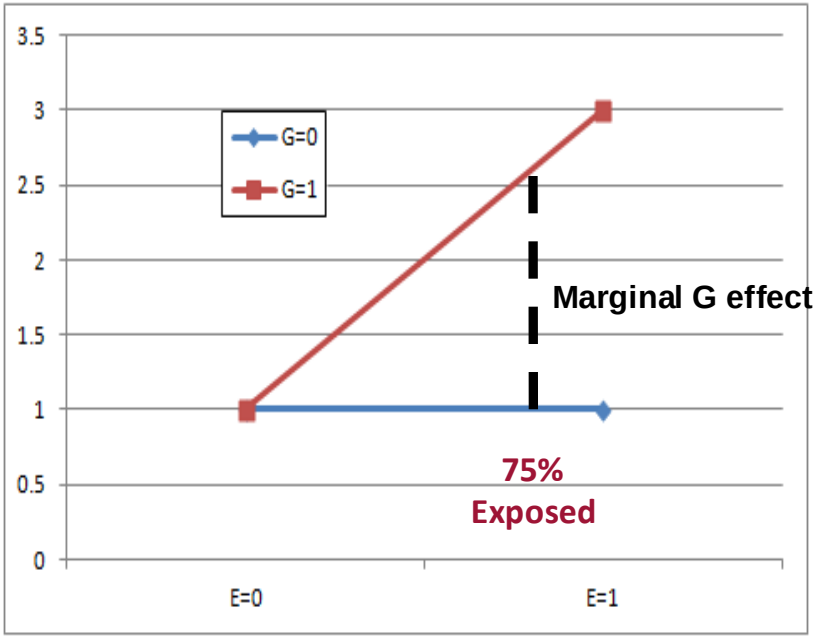

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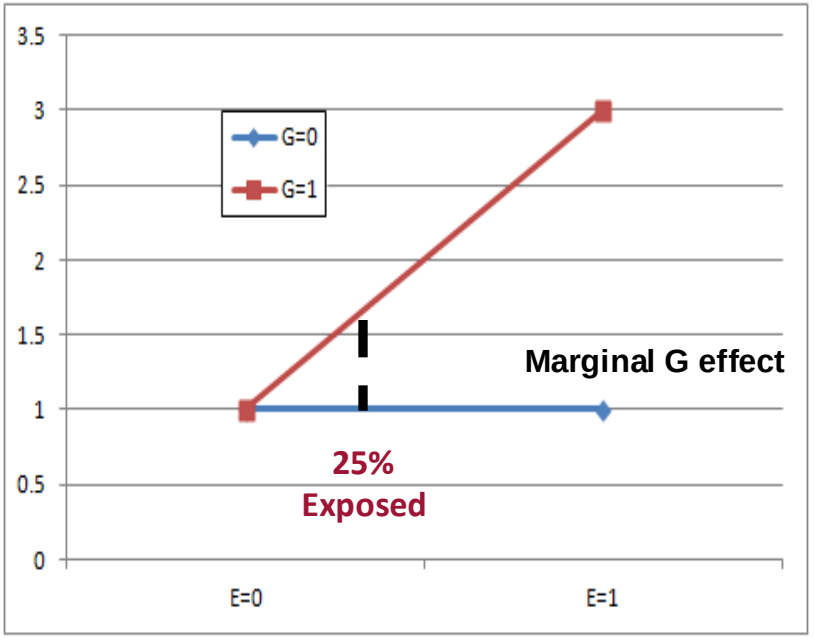
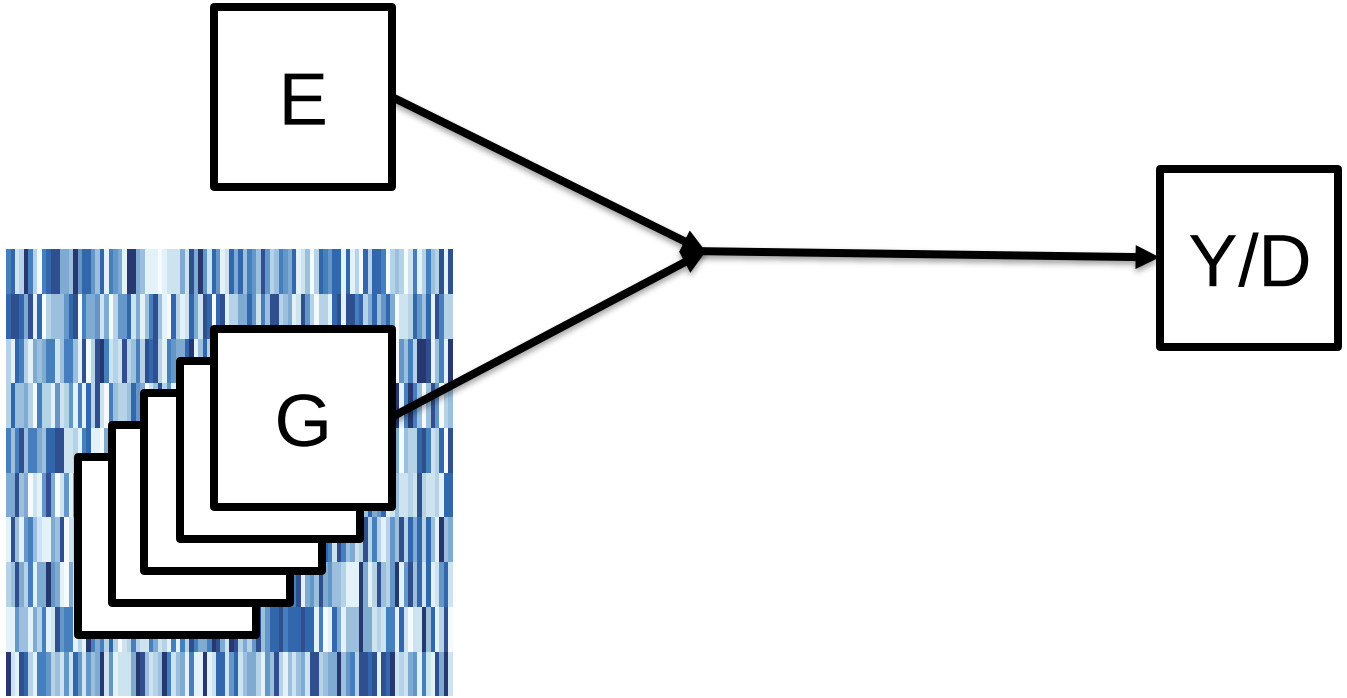


Genomewide Interactions (GWIS)



Improving GWIS Efficiency: The Basic Idea

- For logistic regression of a case control sample:

$$\text{logit}(\Pr D=1|G, E) = \alpha + \beta_G G + \beta_E E + \beta_{GxE} G*E$$

the test of $H_0: \beta_{GxE}=0$ has low power

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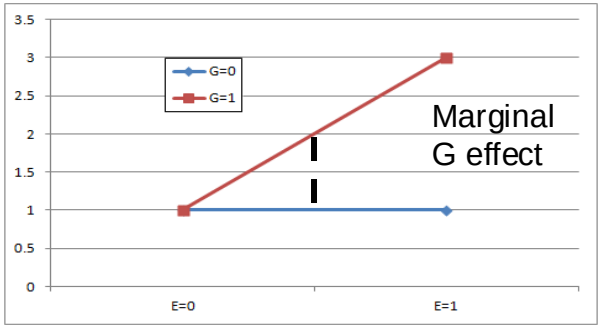
- There is *additional information* in a case-control sample about GxE interaction that is not used in the above test

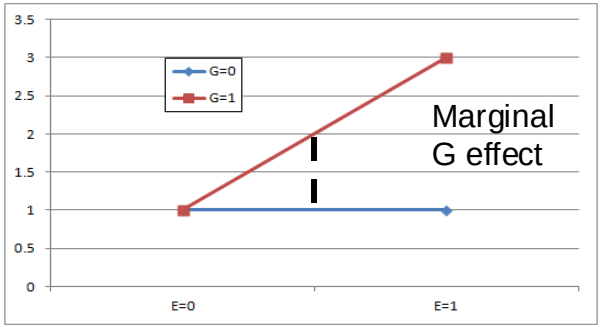
In the Presence of GxE…

- Induced “Marginal”:
  - G to D association →



In the Presence of GxE…

- Induced “Marginal”:
  - G to D association →
  - G to E association
    - ‘case-only’ style association
    - Observed in combined case-control sample if cases are oversampled relative to population prevalence



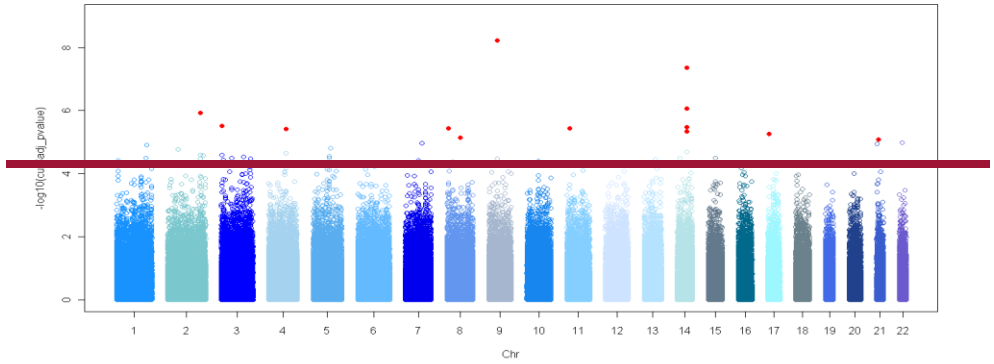
- Can we use this extra info to construct more efficient GW interaction scans?

2-step Approach: **DG**|GxE

- Step 1: Genomewide screen of *M* SNPs using 'marginal-effect' test on all subjects

$$\text{Logit}[\Pr(D=1 \mid G)] = \mu_0 + \mu_1 G$$

  - Test H_o: $\mu_1=0$ for each SNP at α_M level



α_M

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- **Step 2**: For *m* SNPs with Step-1 $p < \alpha_M$, standard GxE analysis:

$$\text{Logit}[\Pr(D=1 \mid G, E)] = \beta_0 + \beta_G G + \beta_E E + \beta_{GxE} GxE$$

  - **Test H_o: β_{GxE}=0** for the m SNPs at α/m level

2-step Approach: **EG**|GxE

- Step 1: Genomewide screen of *M* SNPs using 'E vs. G' test on all subjects

$$\text{Logit}[\Pr(E=1 \mid G)] = \gamma_0 + \gamma_1 G$$

  - Test H_o: $\gamma_1=0$ for each SNP at α_M level

2-step Approach: **EDGE**

- Step 1: Genomewide screen of *M* SNPs using both 'D vs. G' *and* 'E vs. G' information
  - T_{EG} based on **E vs G** *(Murcray et al.)*
  - T_{DG} based on **D vs G** *(Kooperberg & LeBlanc)*

  → Screening Test: $T_{EgDg} = T_{EG} + T_{DG}$ (2-df test)

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$$\text{Logit}[\Pr(D=1 \mid G,E)] = \beta_0 + \beta_G G + \beta_E E + \beta_{GxE} GxE$$

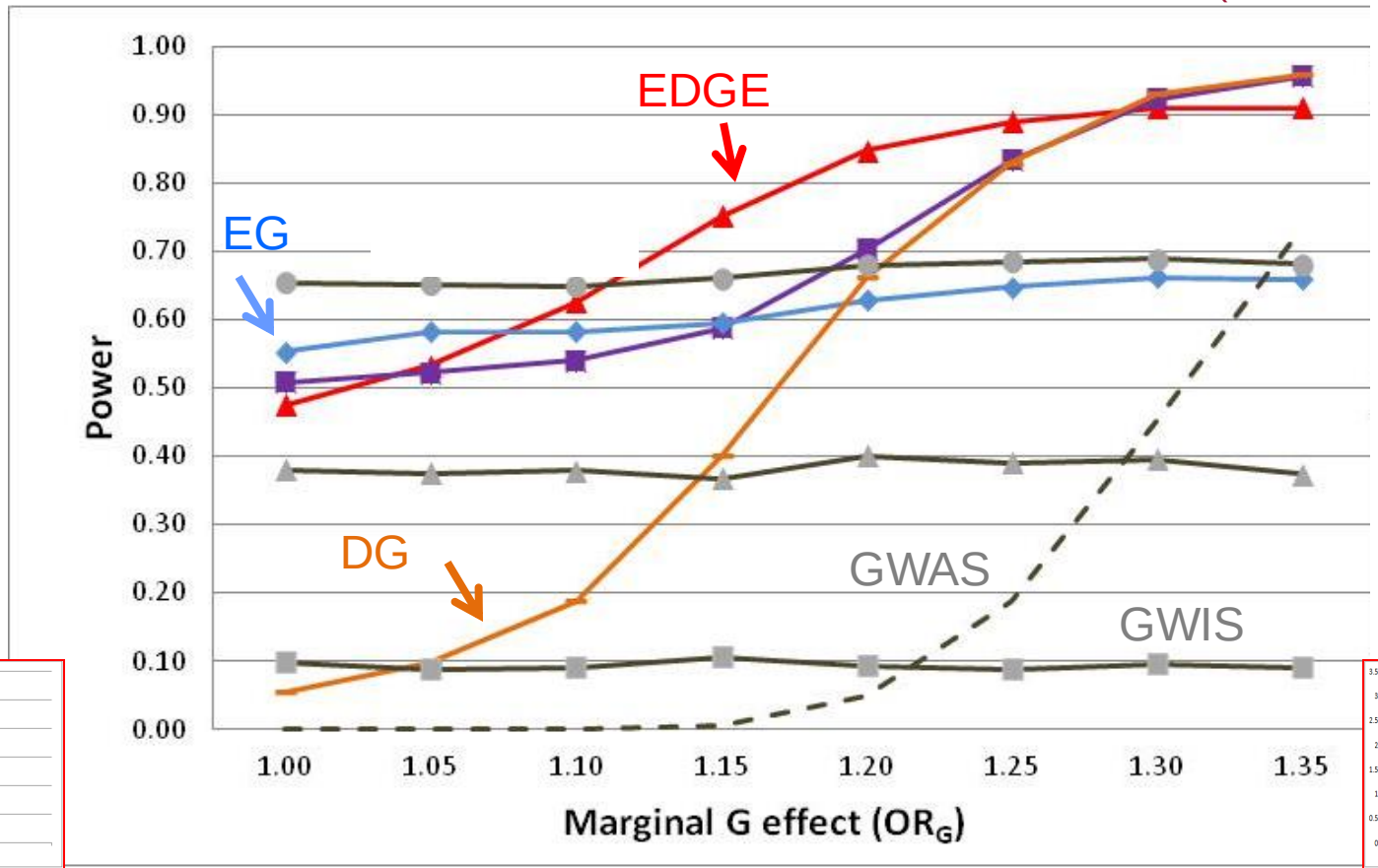
  – Test H_o: $\beta_{GxE}=0$ for the m SNPs at α/m level

2-step "Subset" Testing

Genomewide Power to Detect

OR_{GxE}=1.5 (N=3,500 cases, 3,500 controls)

(Gauderman et al., 2013)

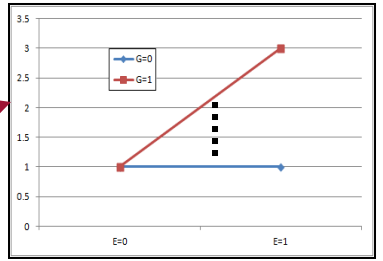


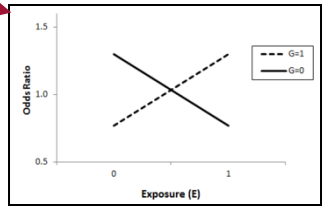
Another way to combine information: The "2-df" joint test

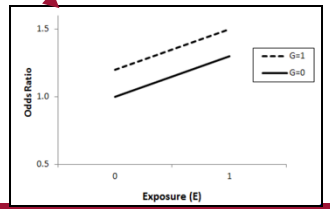
$$\text{Logit}(\Pr D=1|G, E) = a + \beta_G G + \beta_E E + \beta_{GxE} G*E$$

H_0: $\beta_G = \beta_{GxE} = 0$ (Joint 2-df test of G, GxE;)

- Can identify loci with …
  - A GxE effect and induced marginal G effect
  - A GxE effect but no G effect
  - A G effect but no GxE effect







Kraft et al., 2007

The “3-df” Joint Test

$$\text{Logit}[\Pr(G=1 \mid D, E, \mathbf{C})] = \beta_0 + \beta_D D + \beta_E E + \beta_{D\times E}\, D\times E + \beta_{\mathbf{C}}\mathbf{C}$$

$$H_0: \beta_D = \beta_E = \beta_{D\times E} = 0$$

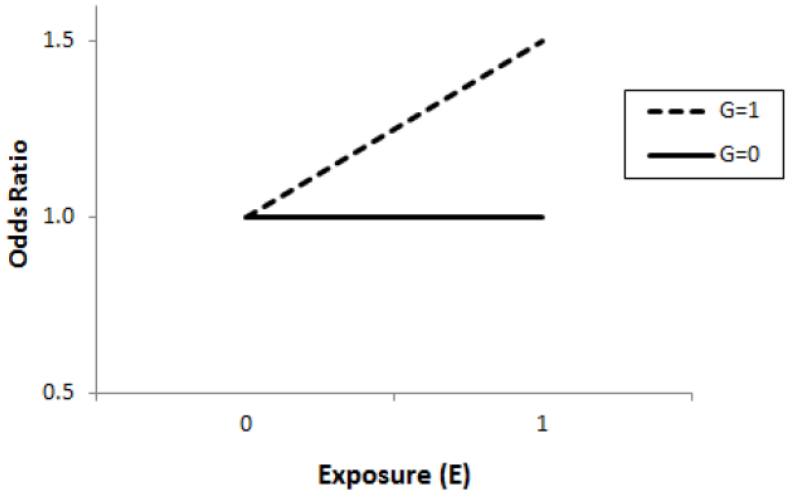
What is it testing?

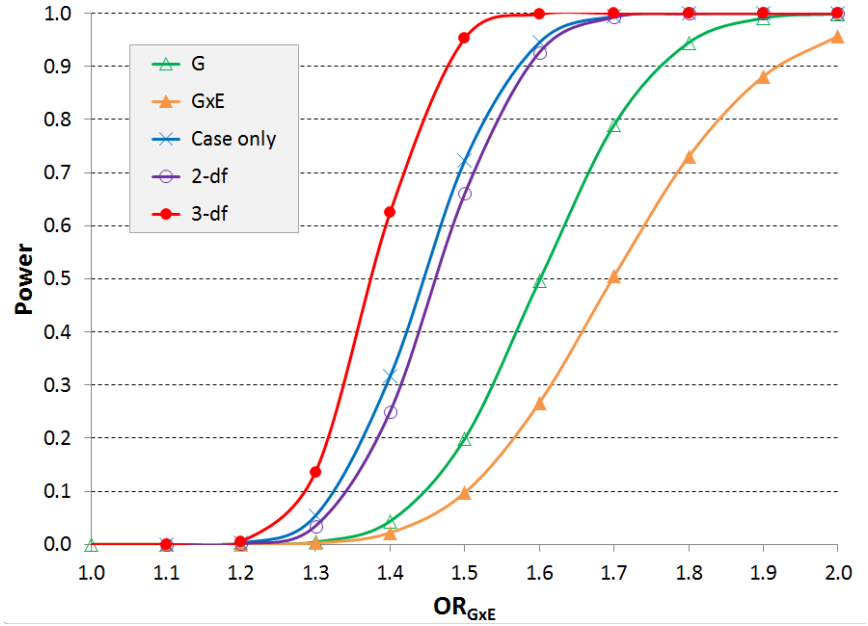
- Marginal G vs. D association (standard GWAS)
- Marginal G vs. E association (“case-only” style G x E)
- G x E interaction (standard GWIS)

- Potentially powerful for discovery

The “3-df” Joint Test: Power

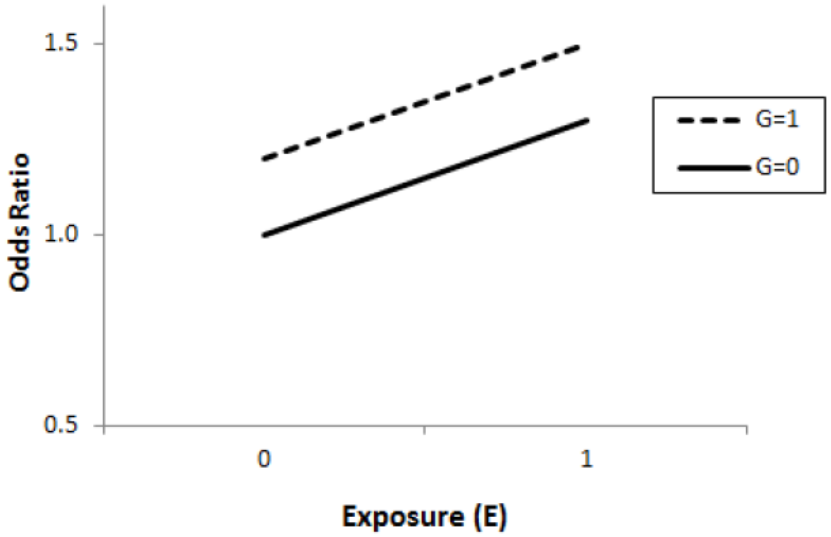
Pure GxE

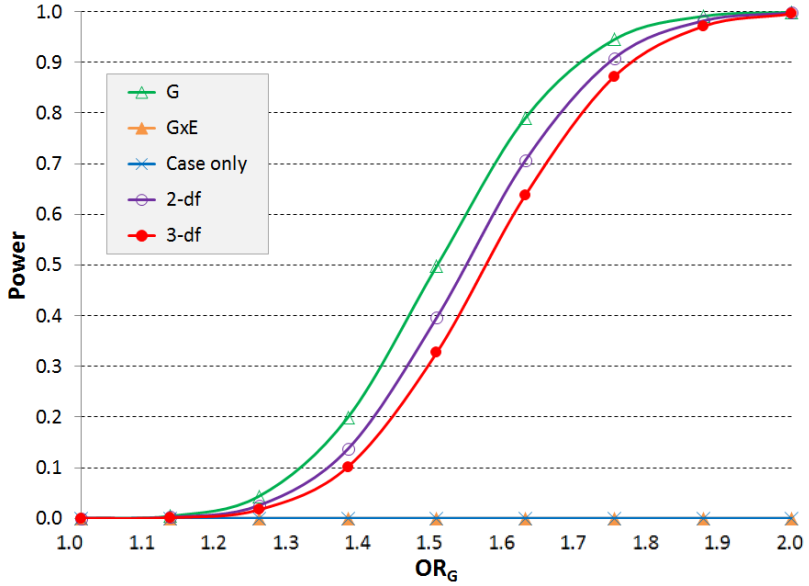




The “3-df” Joint Test: No Free Lunch

No GxE





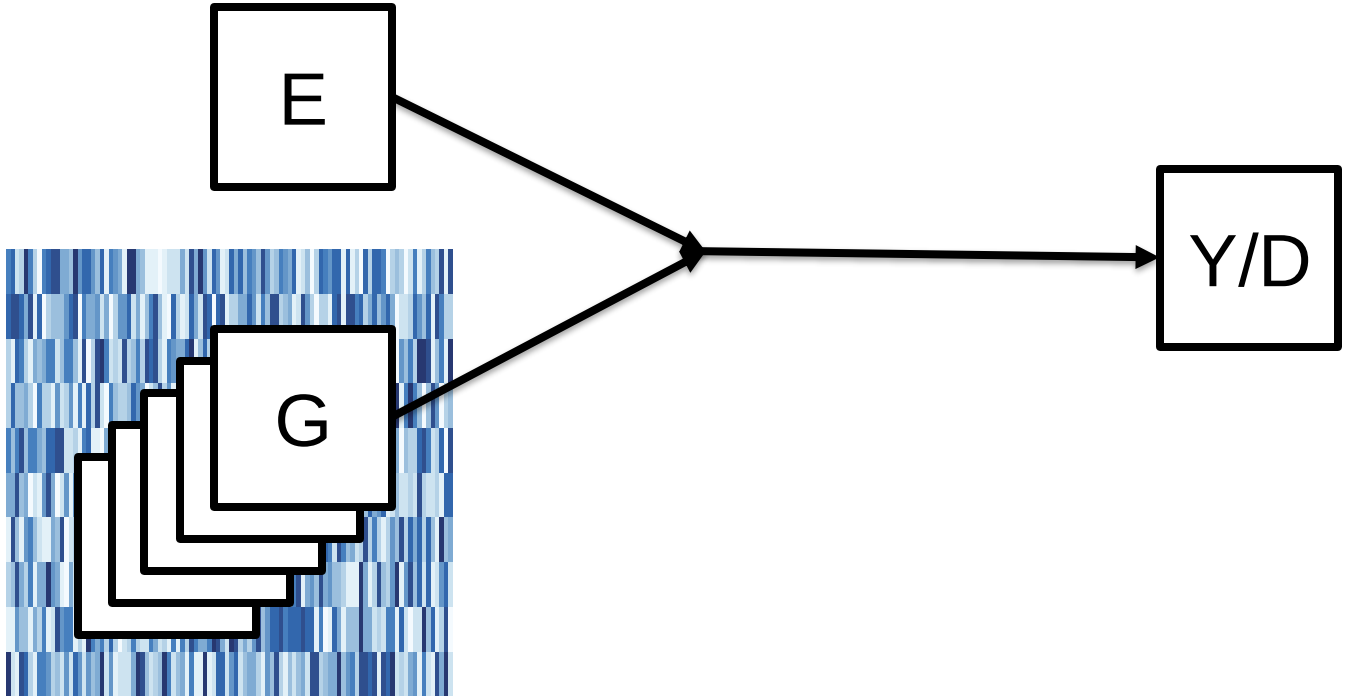
GWIS Discoveries Using Efficient Methods

Authors	Exposure	GxE discovery Method(s)
Jordahl et al.	Alcohol	**2-step**
Aglago et al.	BMI	**2-step, 3df**
Diez-Obrero et al.	Calcium	**2-step**
Dimou et al.	Diabetes	2df, **3df**
Bouras et al.	Folate	1df
Papadimitriou et al.	Fruit, Veggie, Fiber	**3df**
Stern et al.	Red meat	**2-step, 3df**
Tian et al.	HRT	**2-step**, 2df
Drew et al.	NSAIDS/aspirin	1df, **2-step, 3df**
Peoples et al	Physical Activity	1df, **2-step**
Carreras-Torres et al.	Smoking	1df, **3df**

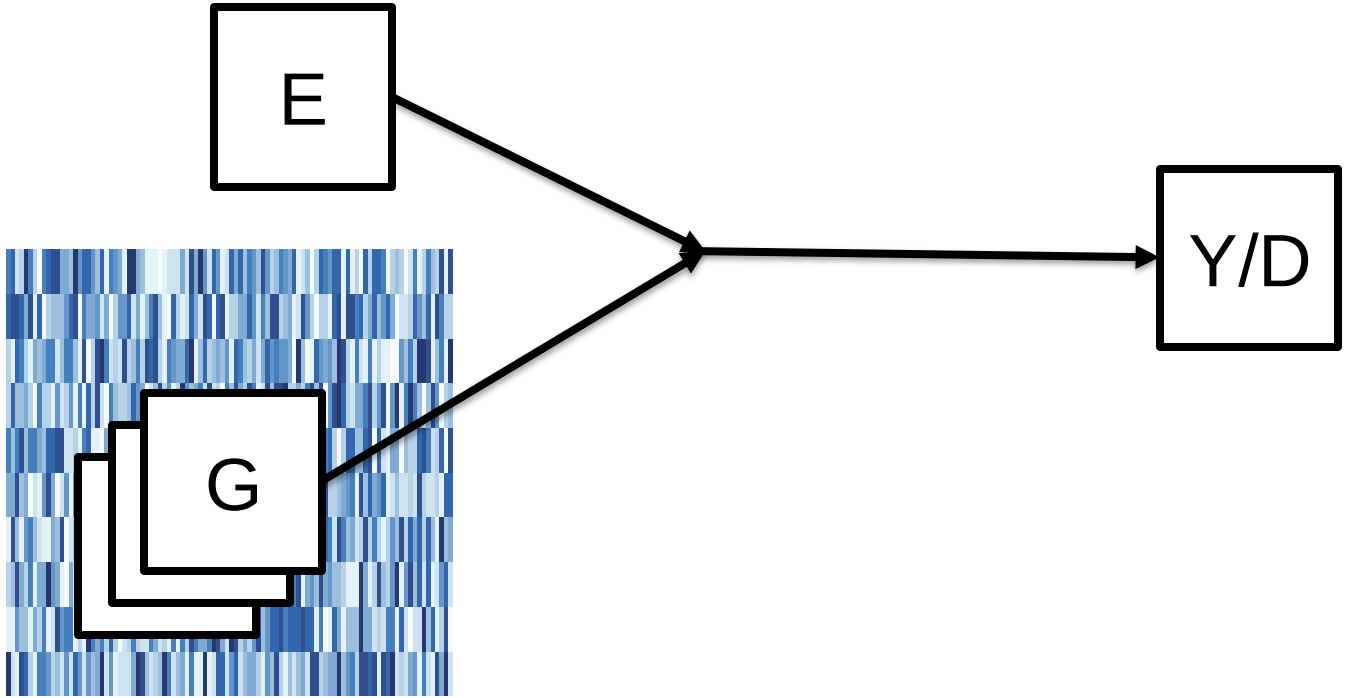
G x  → CRC

All analyses used GxEScanR

Many Single-Marker Interactions



Many Single-Marker Interactions



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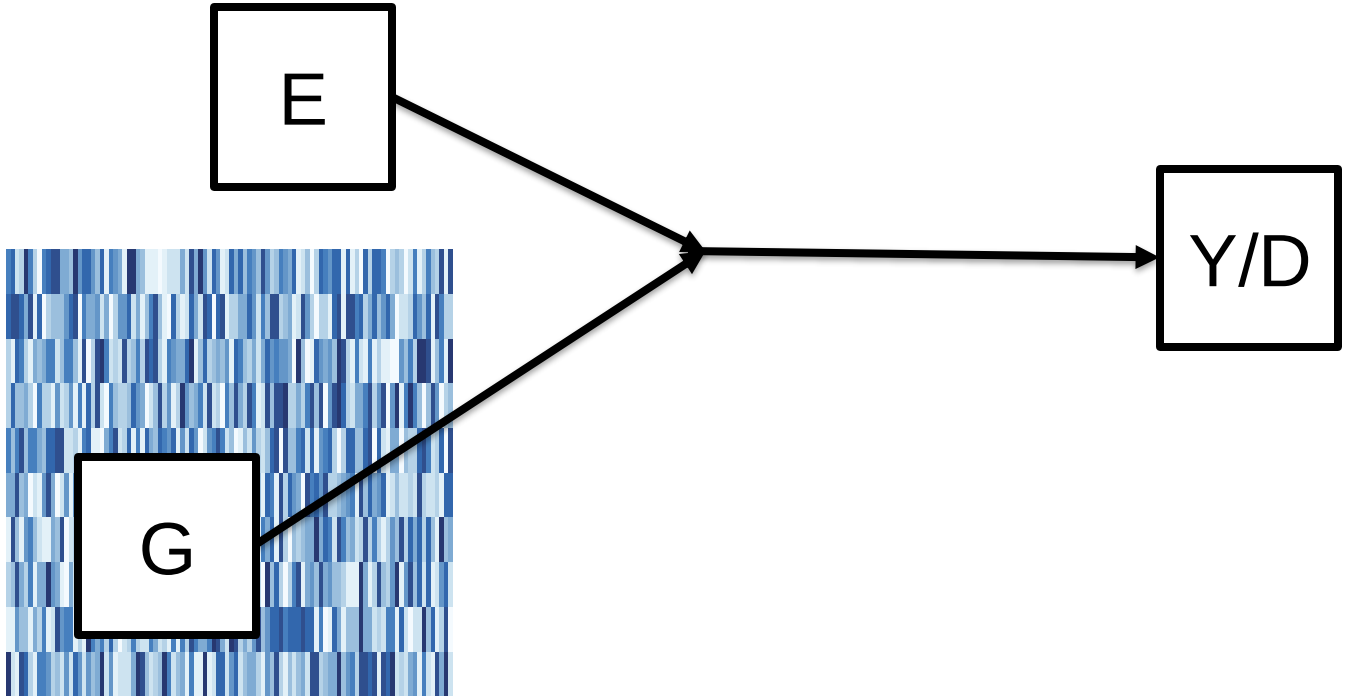
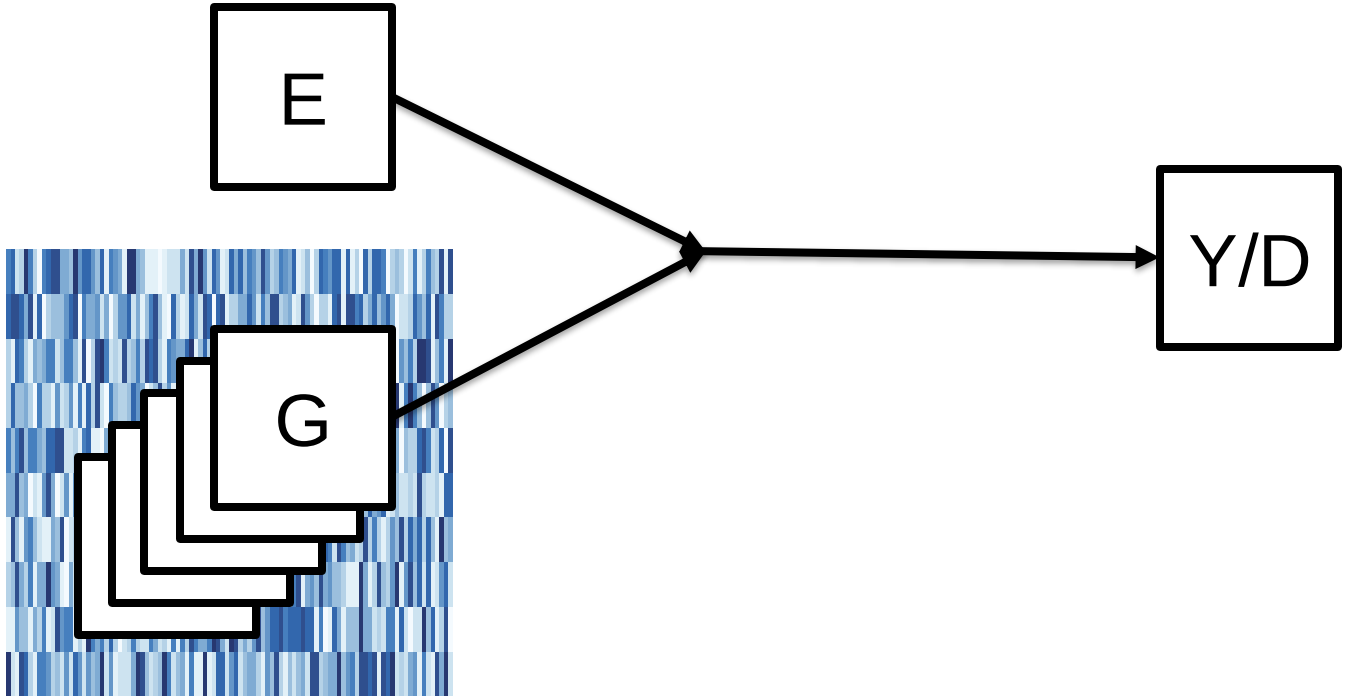


High Dimensional Interactions



Single-marker analysis vs. joint analysis

single-marker:
one-SNP-at-a-time

$$Y \sim \beta_0 + \beta_E E + \beta_{G_j} G_j + \beta_{G_j \times E} G_j \times E, \text{ for each j} = 1, .., p$$

joint:
all p SNPs together

$$Y \sim \beta_0 + \beta_E E + \sum_{j=1}^{p} \beta_{G_j} G_j + \sum_{j=1}^{p} \beta_{G_j \times E} G_j \times E$$

- Polygenic traits
  - Nature of the signal is multi-marker/polygenic for complex traits
- Joint analysis considers the impact other markers on the outcome
  - A weak effect may be more apparent when other causal effects are already accounted for
  - A false signal may be weakened by inclusion in the model of a stronger signal from a true causal association

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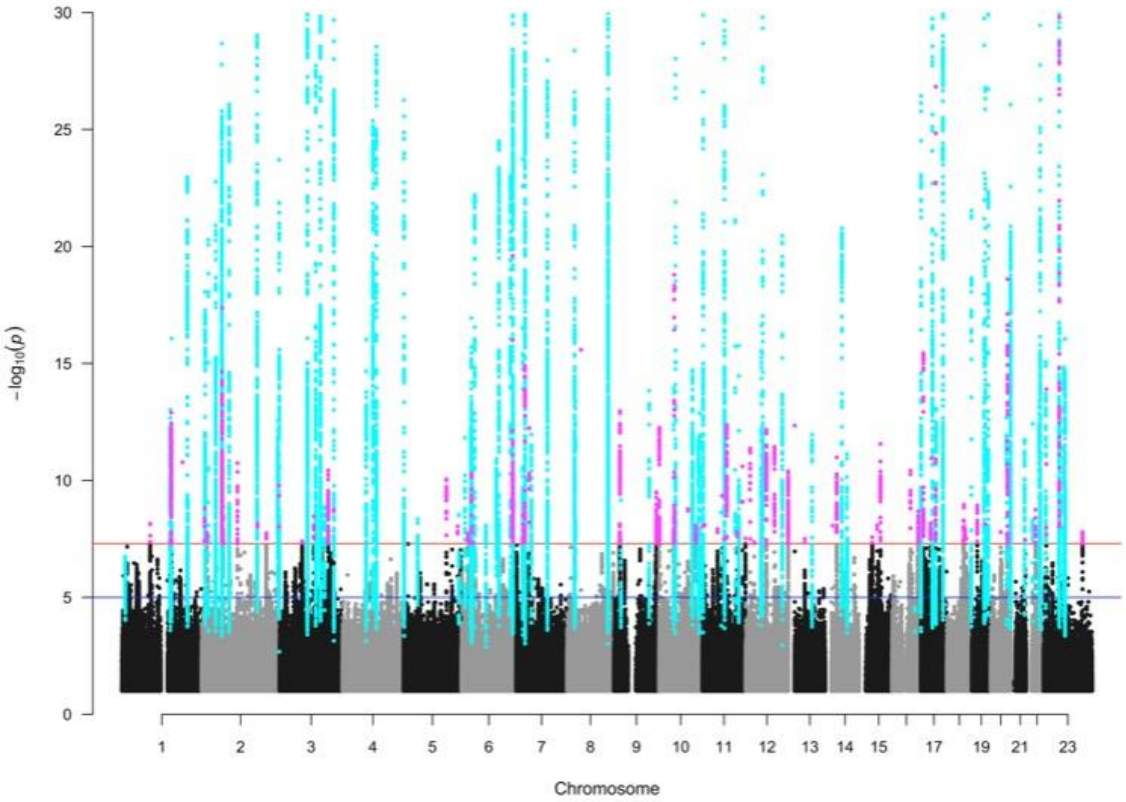
- gesso [G(by)E(la)sso] model

subject to
$$\begin{cases} (1)\ \sum_{j=1}^{p} (|\beta_{G_j}| + |\beta_{G_j \times E}|) \leq t \\ (2)\ |\beta_{G_j \times E}| \leq |\beta_{G_j}| \end{cases}$$

Hierarchical Constraints

$\beta_{G \times E} \neq 0 \Rightarrow \beta_G \neq 0$ or
$\beta_G = 0 \Rightarrow \beta_{G \times E} = 0$

GWAS and Polygenic Risk



Polygenic Risk Score (PRS):

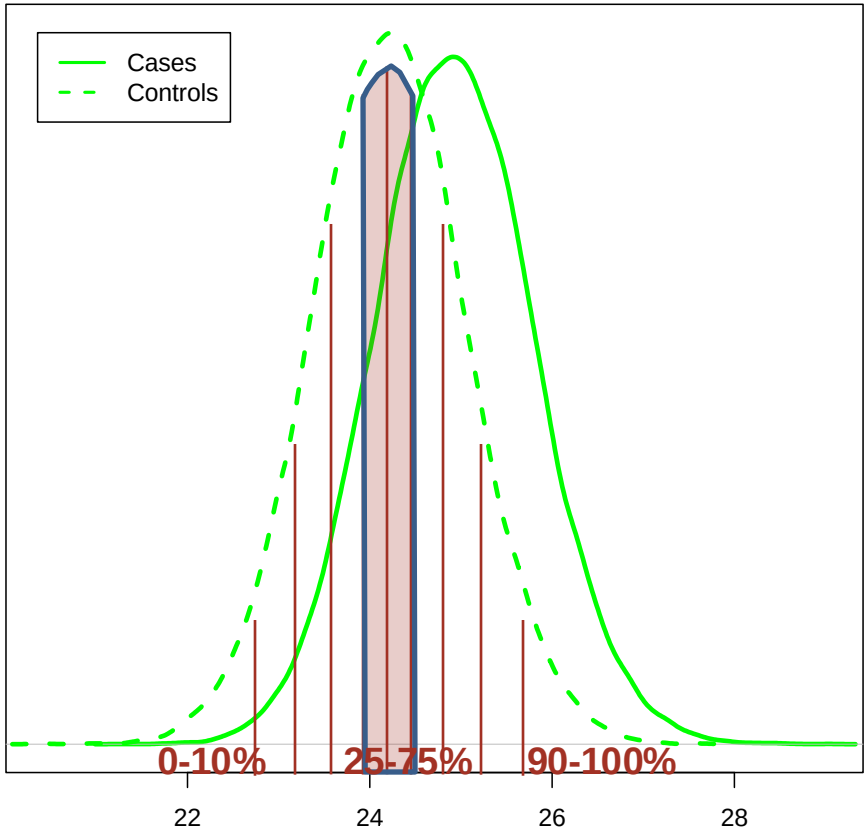
Weighted sum of # risk alleles carried by each participant

Count of risk alleles for variant *m* for individual *i*

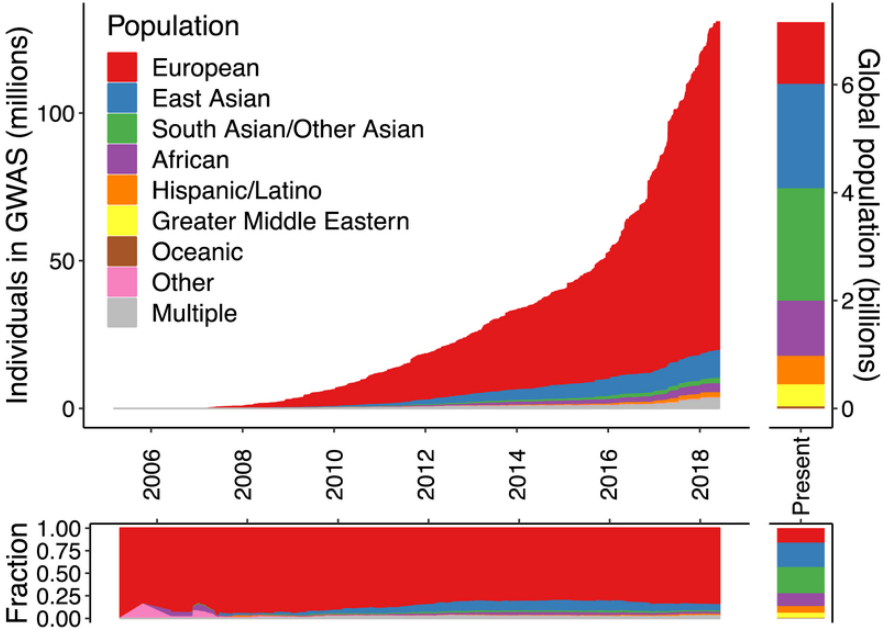
What SNPs?

$$PRS_i = \sum_{m=1}^{M} w_m G_{im}$$

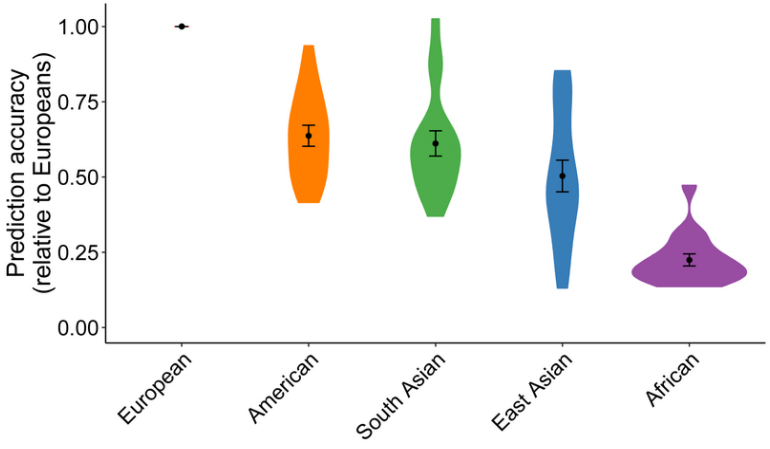
What weight?



Lack of Diversity Could Impact Health Disparities



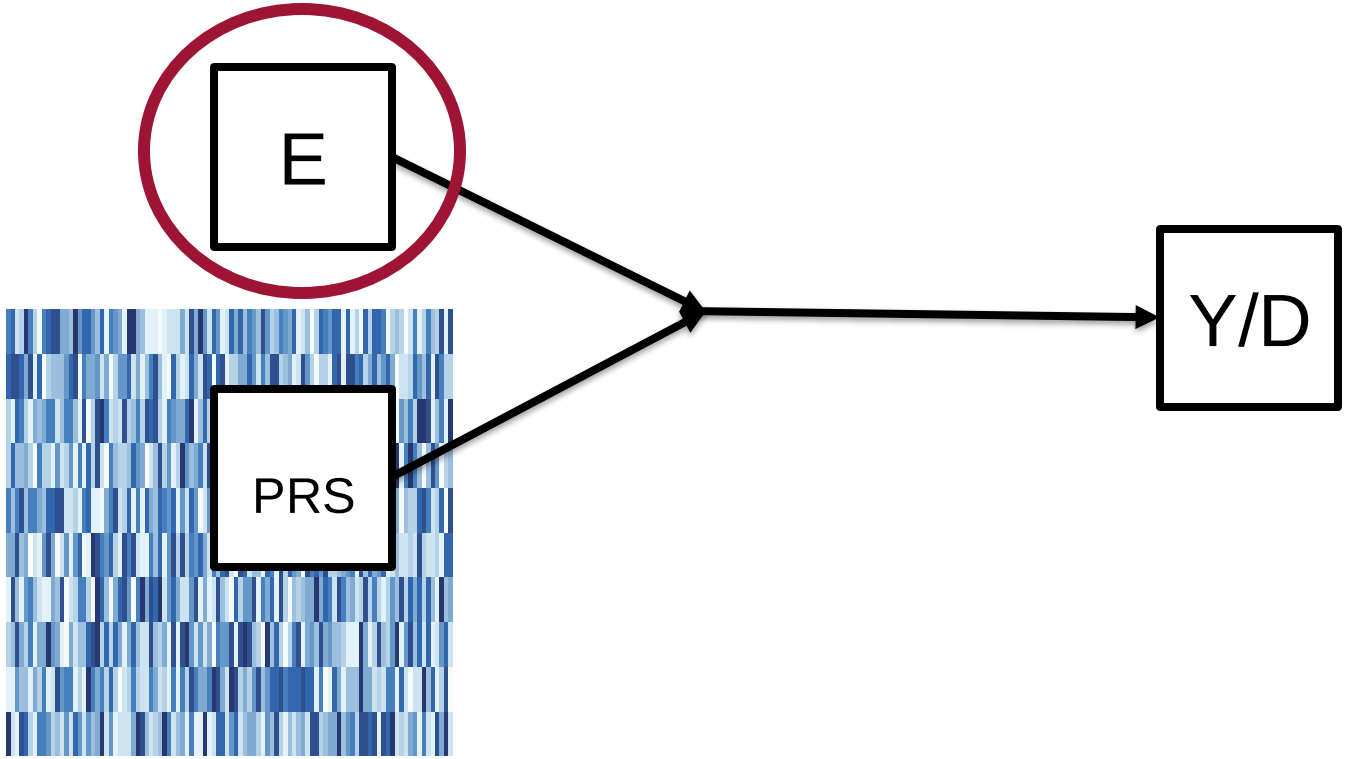
Ancestry of GWAS participants over time relative to the global population



Polygenic prediction accuracy relative to European ancestry individuals across 17 quantitative traits

Martin et al., *Nature Genetics* 2019

Polygenic Risk Score and E Interactions



PRS Across Populations in Prostate Cancer

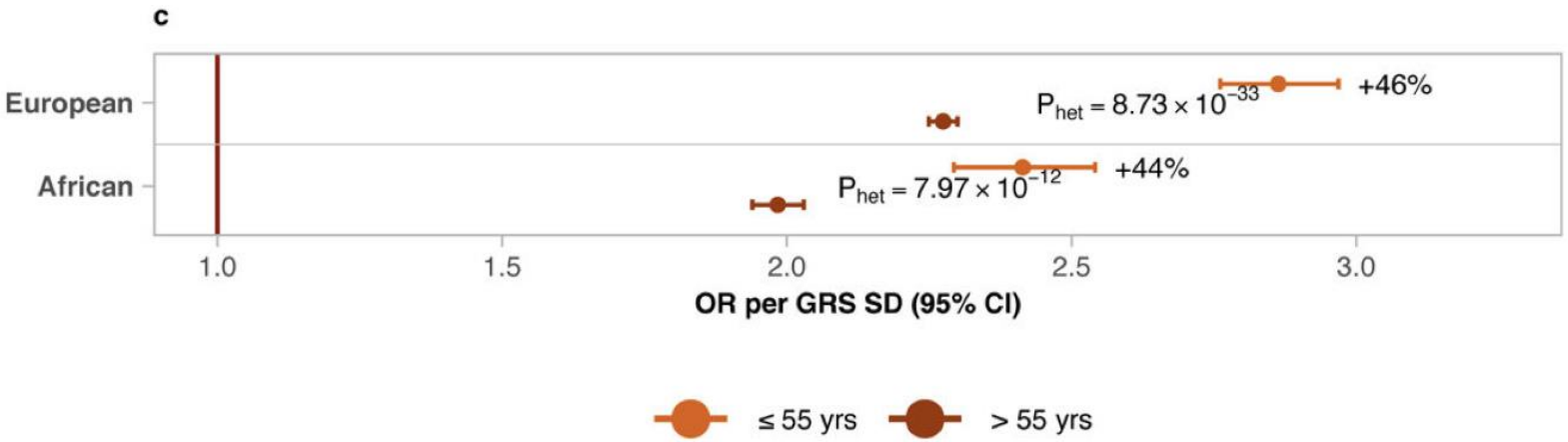
- 156,319 prostate cancer cases
- 788,443 controls

- European, African, Asian and Hispanic men
- A 57% increase in the number of non-European cases from previous GWAS.

Population	1 SD OR
European	2.32 [95%CI: 2.30-2.35]
African	2.04 [95%CI: 2.00-2.08]
Asian	2.15 [95%CI: 1.99-2.32]
Hispanics	2.12 [95%CI: 2.03-2.23]

Wang et al. Nat. Gen. 2023

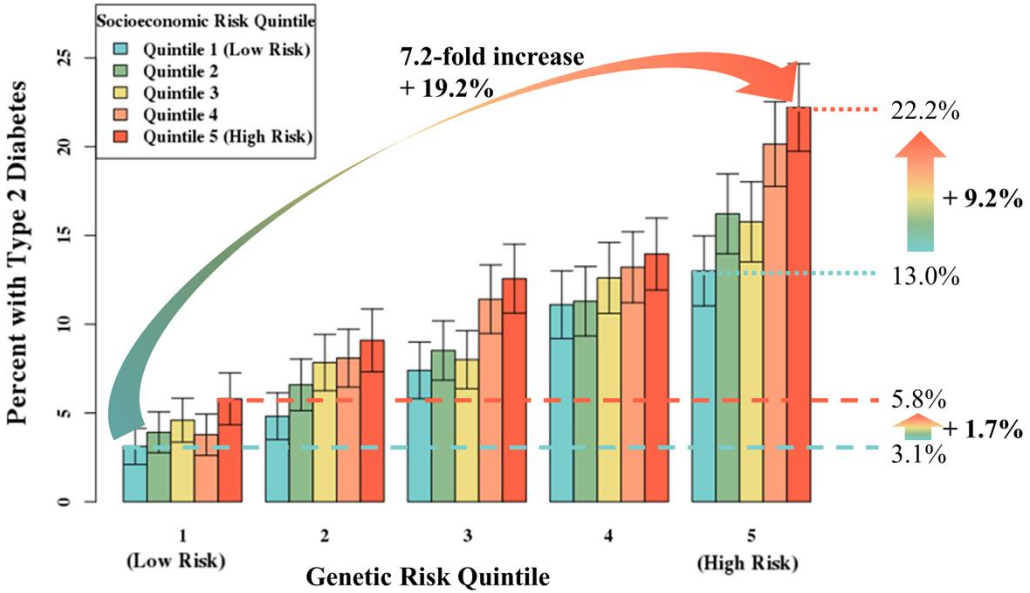
PRS x Age in Prostate Cancer



Wang et al. Nat. Gen. 2023

PRS x SDoH

What is the combined effect of genetic and socioeconomic risk on the prevalence of type 2 diabetes (T2D) and obesity?

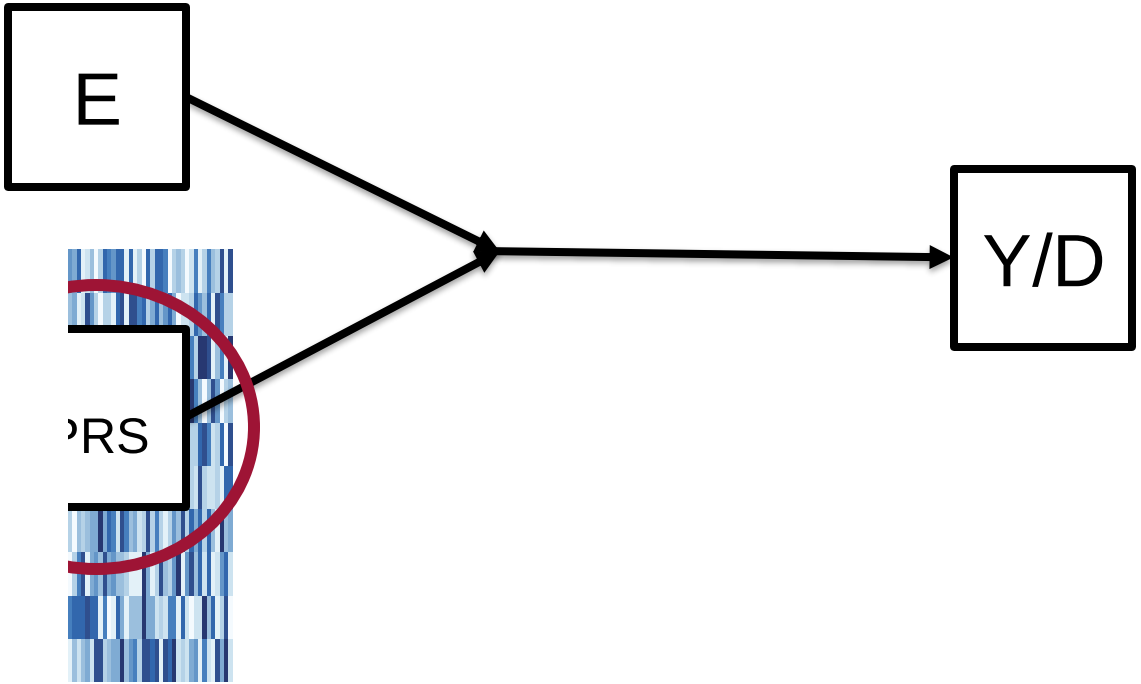


Combined high genetic and socioeconomic risk, compared to combined low risk, was associated with a 7-fold and 3-fold increase, respectively, in T2D and obesity prevalence.

Increasing socioeconomic risk is associated with a greater absolute increase in T2D and obesity prevalence among those at high genetic risk compared to those at low genetic risk.

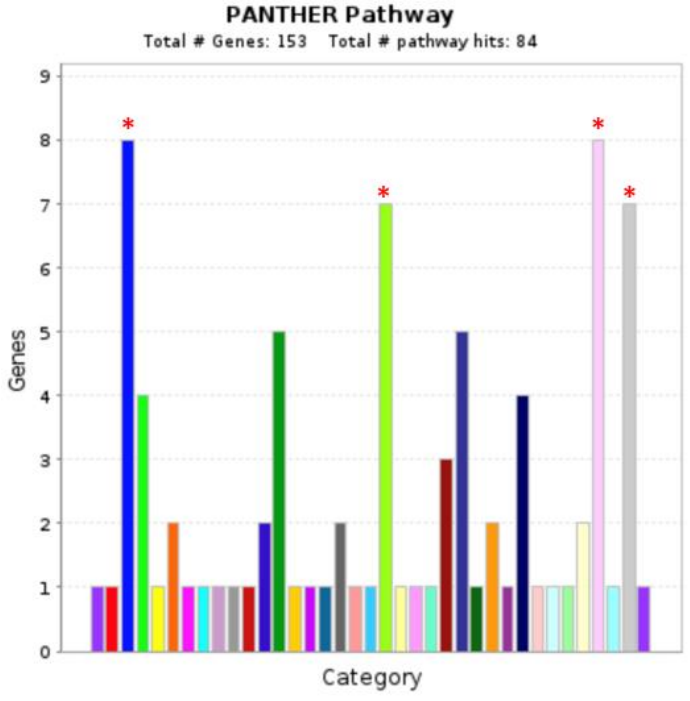
Cromer et al. Diabetes Care 2023

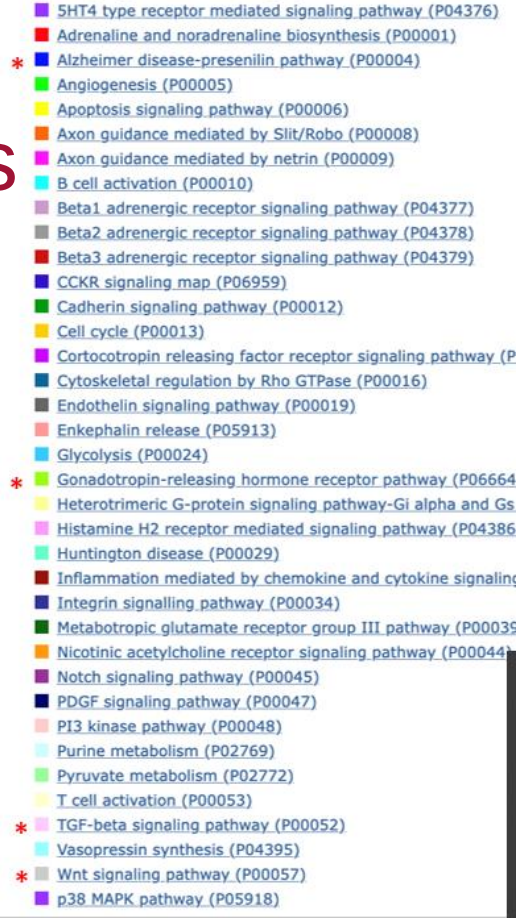
Polygenic Risk Score and E Interactions



Colorectal Cancer PRS: Incorporating Functional Annotations

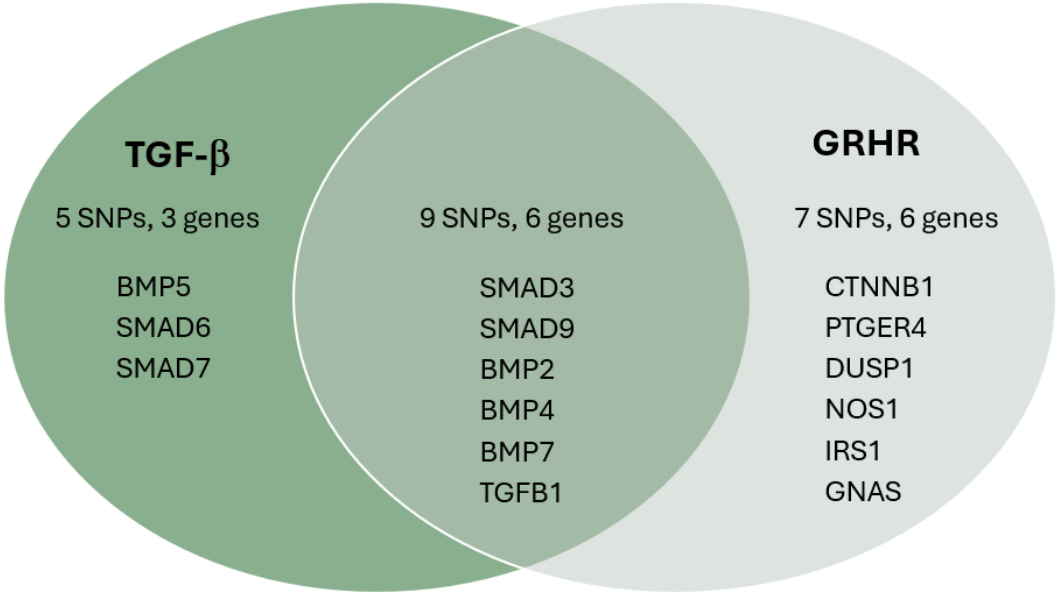
- ANNOQ (Liu et al., 2022) used to annotate GWAS SNPs to genes (153/205 SNPs annotated)
- PANTHER (Mi et al., 2017) used for pathway analysis of those genes





Gauderman et al. in preparation

SNPs In Multiple Pathways



Gauderman et al. in preparation

PRS* x NSAIDs

Table S2: Analysis of PGS Catalog derived polygenic risk score x NSAIDS interaction for Colorectal Cancer

	PRS		E (NSAIDS use)		PRS x E		
PRS Type	OR[a]	(95% CI)	OR	(95% CI)	OR	(95% CI)	p-value[b]
PRS: All SNPs*	1.59	(1.56, 1.61)	0.77	(0.74, 0.79)	0.98	(0.95, 1.01)	0.240
Pathways[&]							
pPRS: TGF-β	1.18	(1.16, 1.20)	0.76	(0.74, 0.79)	**0.96**	**(0.93, 0.99)**	**0.017**
pPRS: Gonadotropin-receptor	1.17	(1.15, 1.18)	0.76	(0.74, 0.79)	**0.96**	**(0.94, 1.00)**	**0.021**
pPRS: Cadherin-signaling	1.10	(1.08, 1.11)	0.76	(0.74, 0.79)	1.00	(0.97, 1.03)	0.840
pPRS: Alzheimer's presenillin	1.08	(1.07, 1.10)	0.76	(0.74, 0.79)	0.99	(0.96, 1.02)	0.640
PRS Other[#]	1.51	(1.48, 1.53)	0.77	(0.74, 0.79)	0.998	(0.97, 1.03)	0.900

* PRS formed based on 204 GWAS significant SNPS with weights extracted from the PGS Catalog

& pPRS based on subsets of the 204 SNPs within the indicated pathway

PRS based on the subset of 174 of the 204 SNPs that are not within any of the indicated pathways

a Odds ratios (OR) are scaled to a 1 s.d. increase for the indicated PRS and compare users to non-users for NSAIDS

b p-value tests the null hypothesis of no PRS x E interaction. For PRS and E main effects, all $p<10^{-10}$.

Gauderman et al. in preparation

PRS* x NSAIDs

Table S3: Analysis of PGS catalog-derived pPRS x NSAIDS for SNPs in the TGF-β and GRHR pathways

	PRS		E (NSAIDS use)		PRS x E		
PRS Type	OR[a]	(95% CI)	OR	(95% CI)	OR	(95% CI)	p-value[b]
Pathways[&]							
TGF-Beta (14 SNPs)	1.18	(1.16, 1.20)	0.76	(0.74, 0.79)	**0.96**	**(0.93, 0.99)**	**0.017**
Gonadotropin-receptor (16 SNPs)	1.17	(1.15, 1.18)	0.76	(0.74, 0.79)	**0.96**	**(0.94, 1.00)**	**0.021**
TGF-Beta or Gonadotropin (21 SNPs)	1.21	(1.19, 1.23)	0.76	(0.74, 0.79)	**0.95**	**(0.92, 0.98)**	**0.0009**
TGF-Beta Unique (5 SNPs)	1.12	(1.10, 1.14)	0.76	(0.74, 0.79)	**0.96**	**(0.93, 1.00)**	**0.019**
Gonadotropin Unique (7 SNPs)	1.10	(1.08, 1.11)	0.76	(0.74, 0.79)	**0.96**	**(0.93, 0.99)**	**0.010**
TGF-GNR shared (9 SNPs)	1.13	(1.11, 1.15)	0.76	(0.74, 0.79)	0.99	(0.96, 1.02)	0.351

* PRS formed based on 204 GWAS significant SNPS with weights extracted from the PGS Catalog

& pPRS based on subsets of the 204 SNPs within the indicated pathway

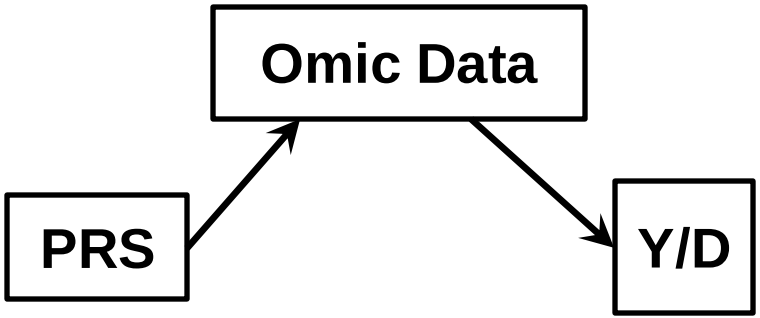
\# PRS based on the subset of 174 of the 204 SNPs that are not within any of the indicated pathways

a Odds ratios (OR) are scaled to a 1 s.d. increase for the indicated PRS and compare users to non-users for NSAIDS

b p-value tests the null hypothesis of no PRS x E interaction. For PRS and E main effects, all $p<10^{-10}$.

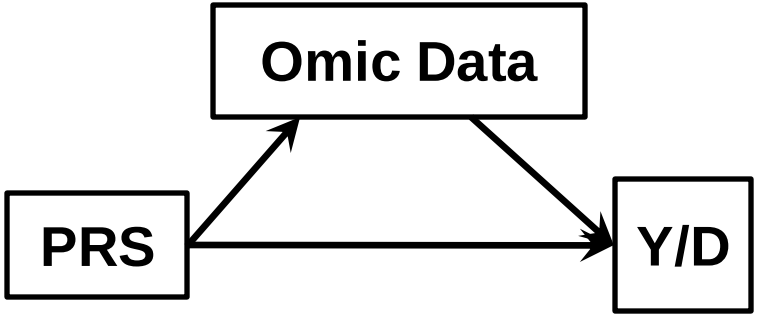
Gauderman et al. in preparation

Omic Data



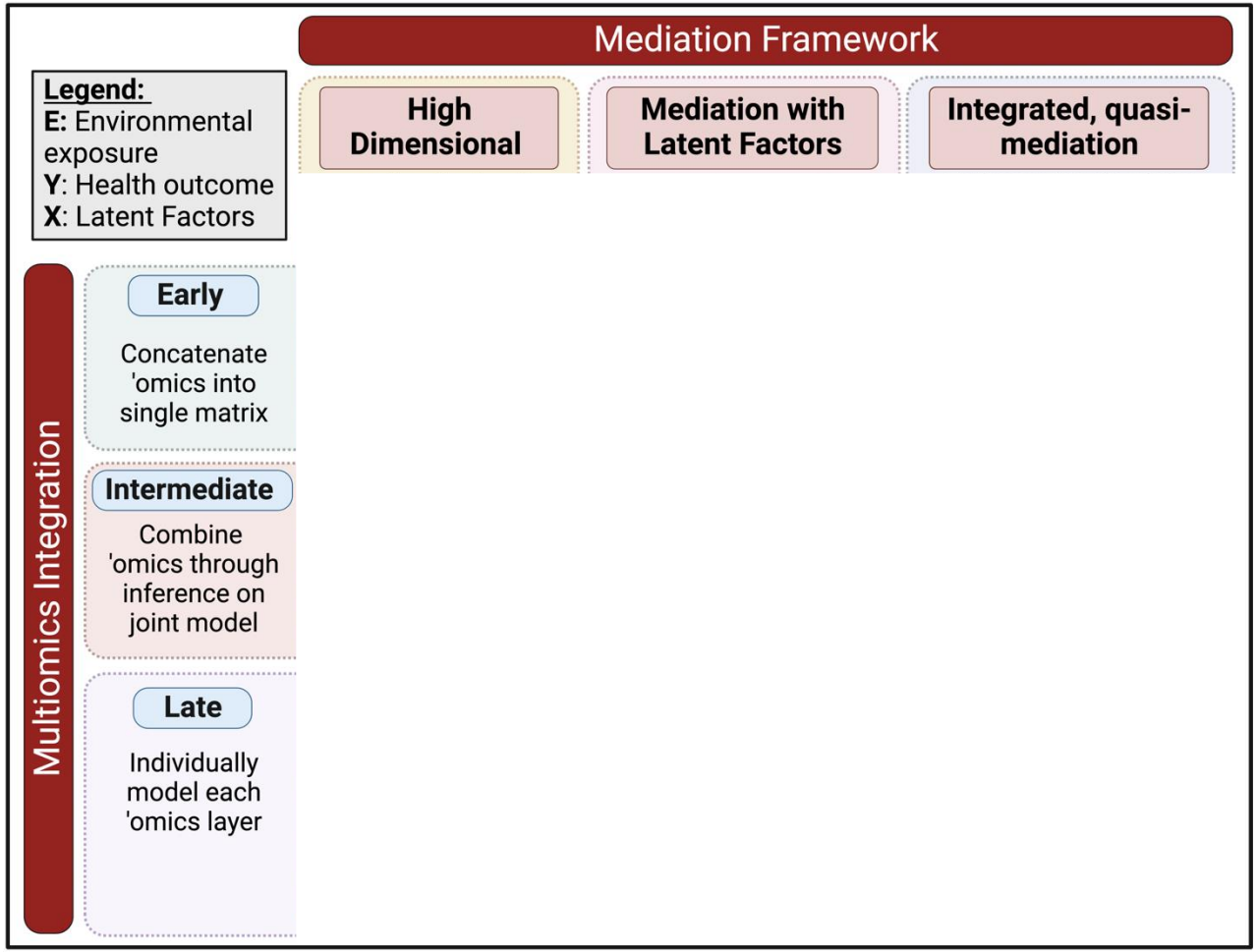
Can we clarify the impact of each SNP within a PRS with ***measured*** omic data that captures the underlying biology?

Omic Mediation



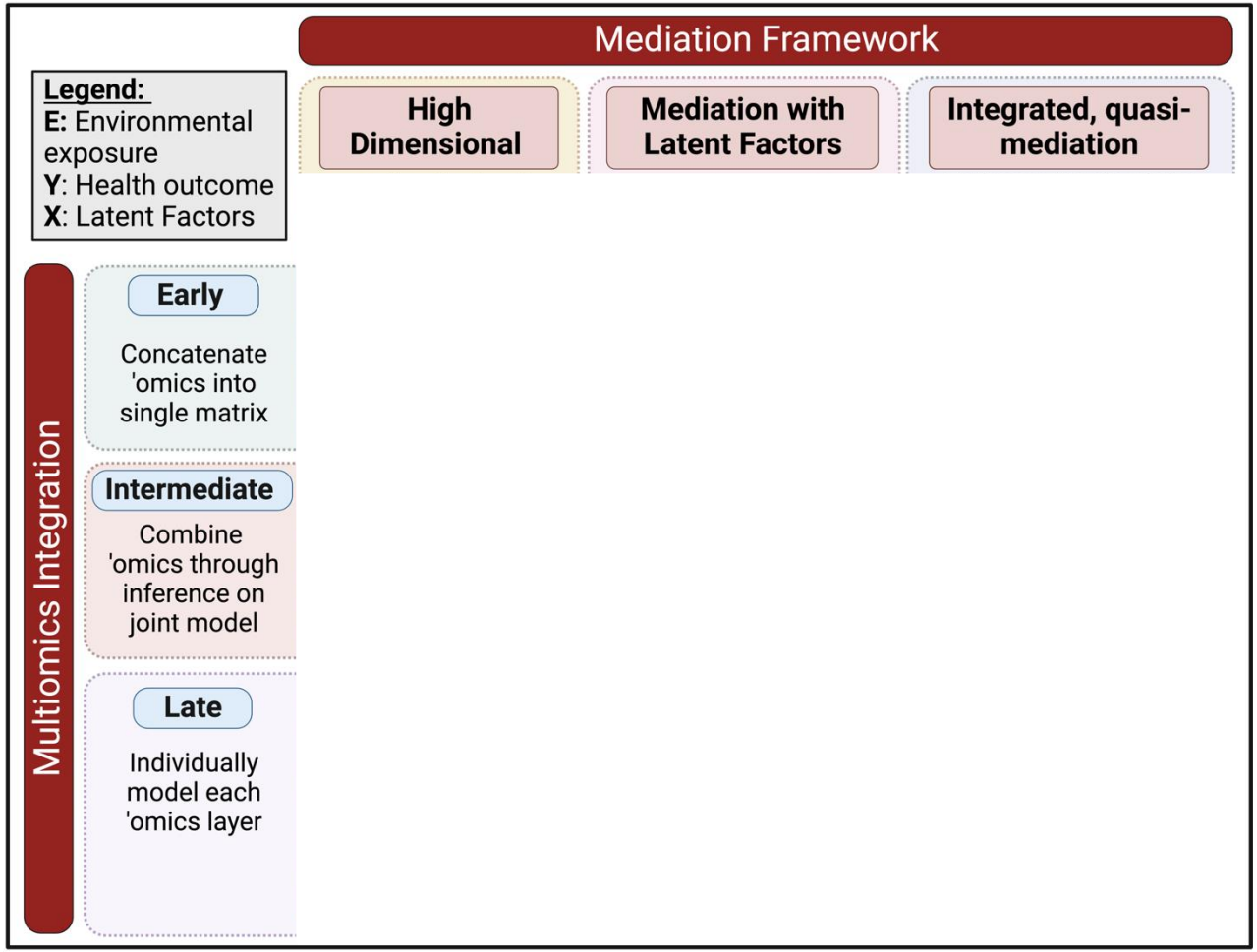
Can we clarify the impact of each SNP within a PRS with ***measured*** omic data that captures the underlying biology?

Multiomic Mediation Framework For Precision Environmental Health



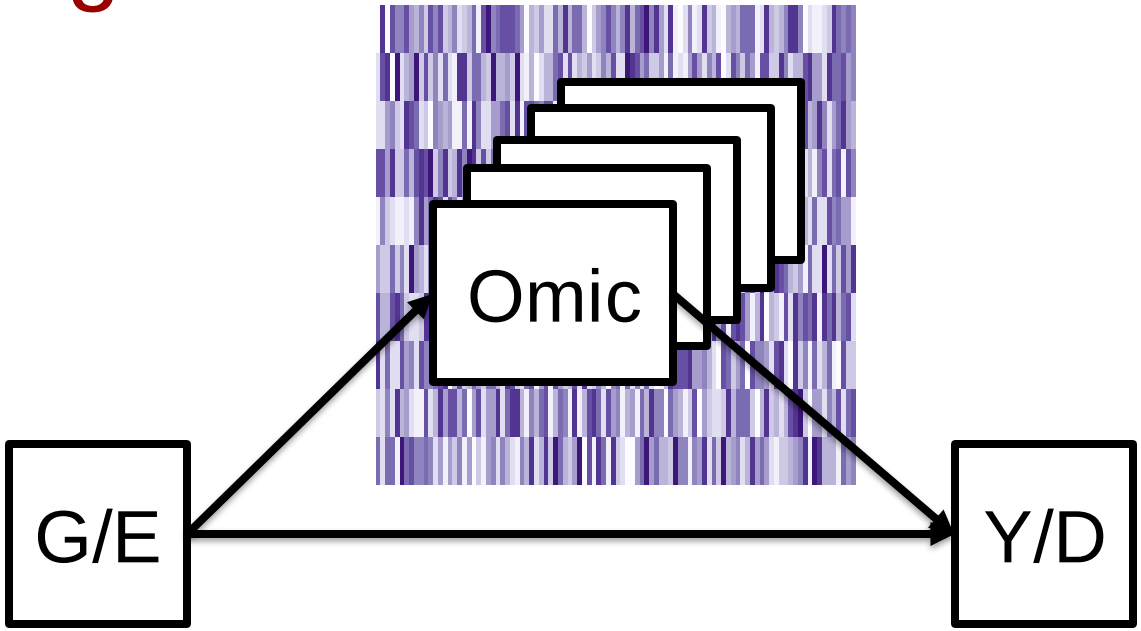
Goodrich et al. *Environ Int.* 2024

Multiomic Mediation Framework For Precision Environmental Health



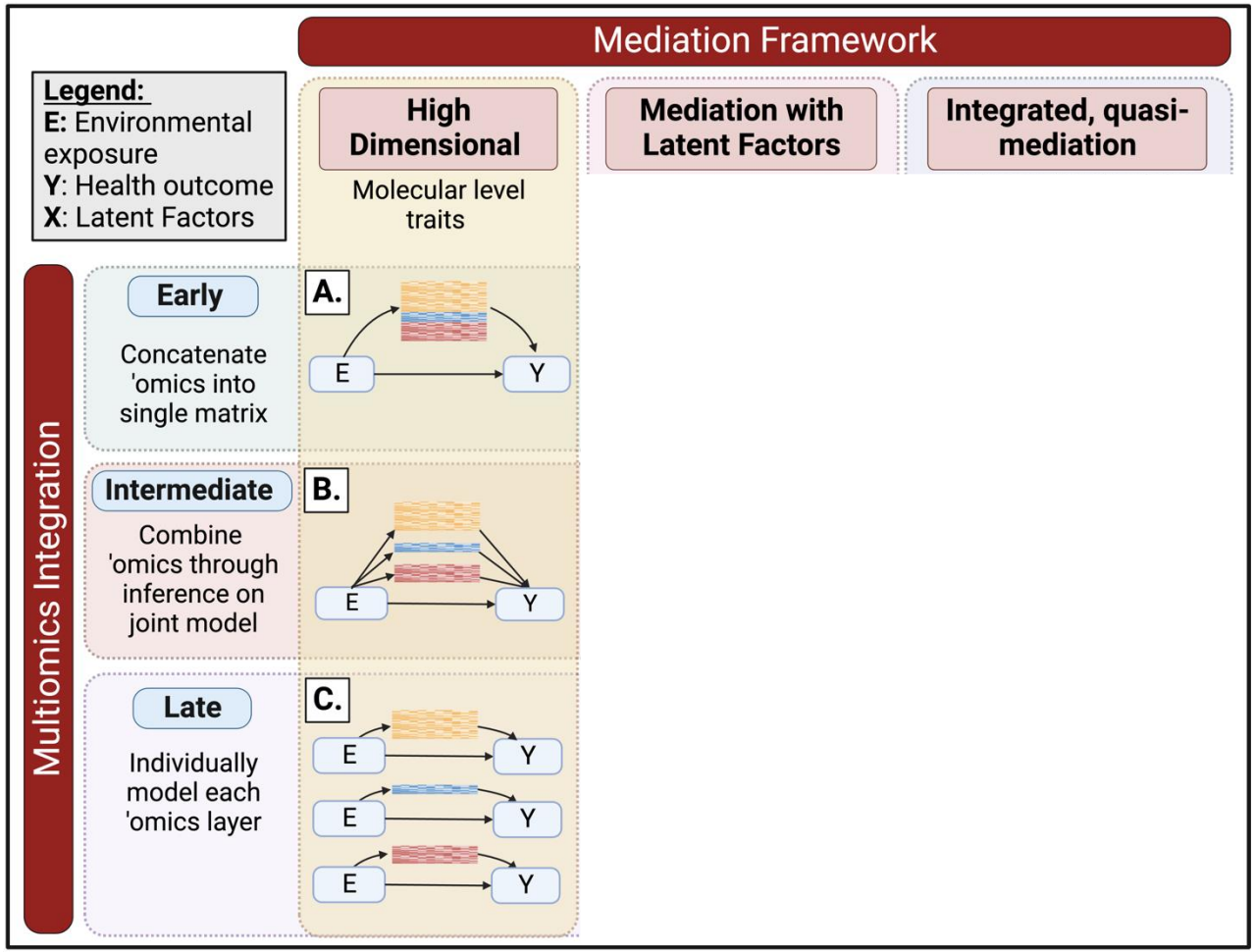
Goodrich et al. *Environ Int.* 2024

High Dimensional Mediation



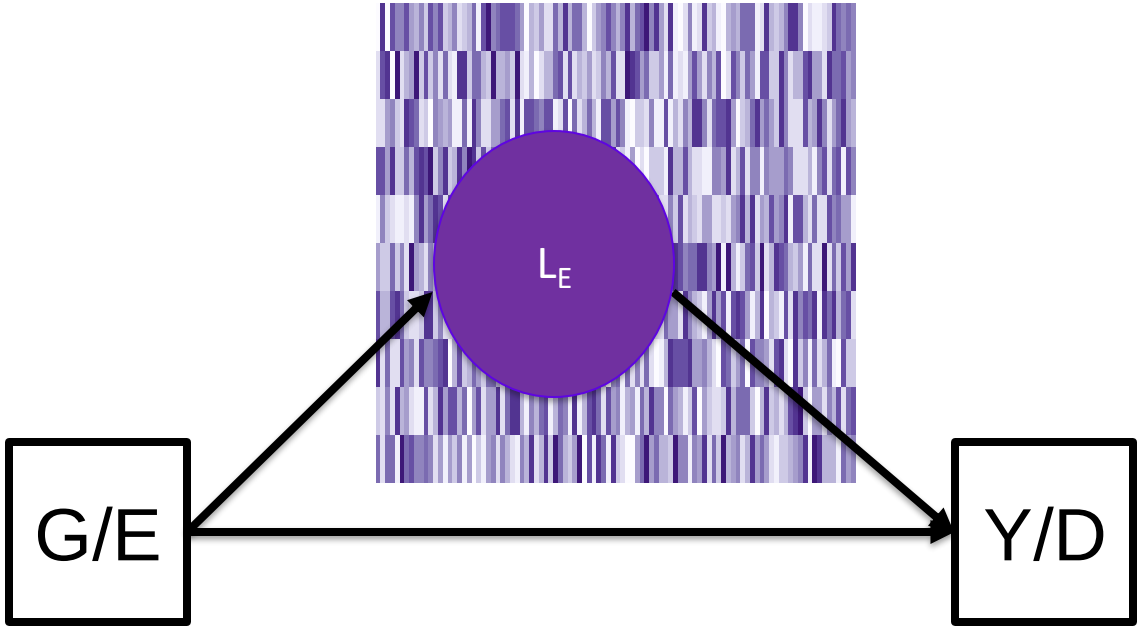
Perera et al. 2022; Song et al. 2020, Zhang et al. 2016

Multiomic Mediation Framework For Precision Environmental Health



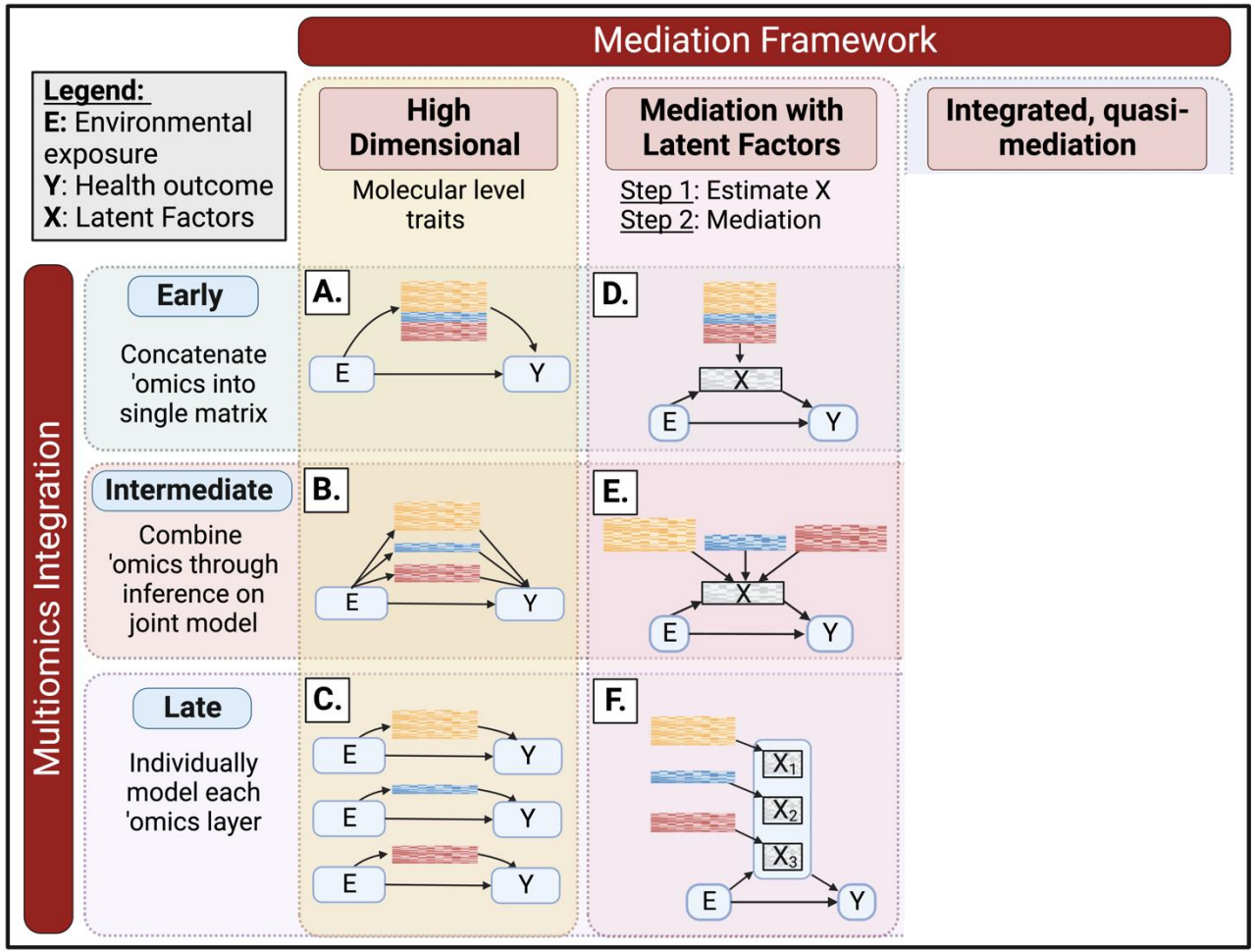
Goodrich et al. *Environ Int.* 2024

Latent Mediation



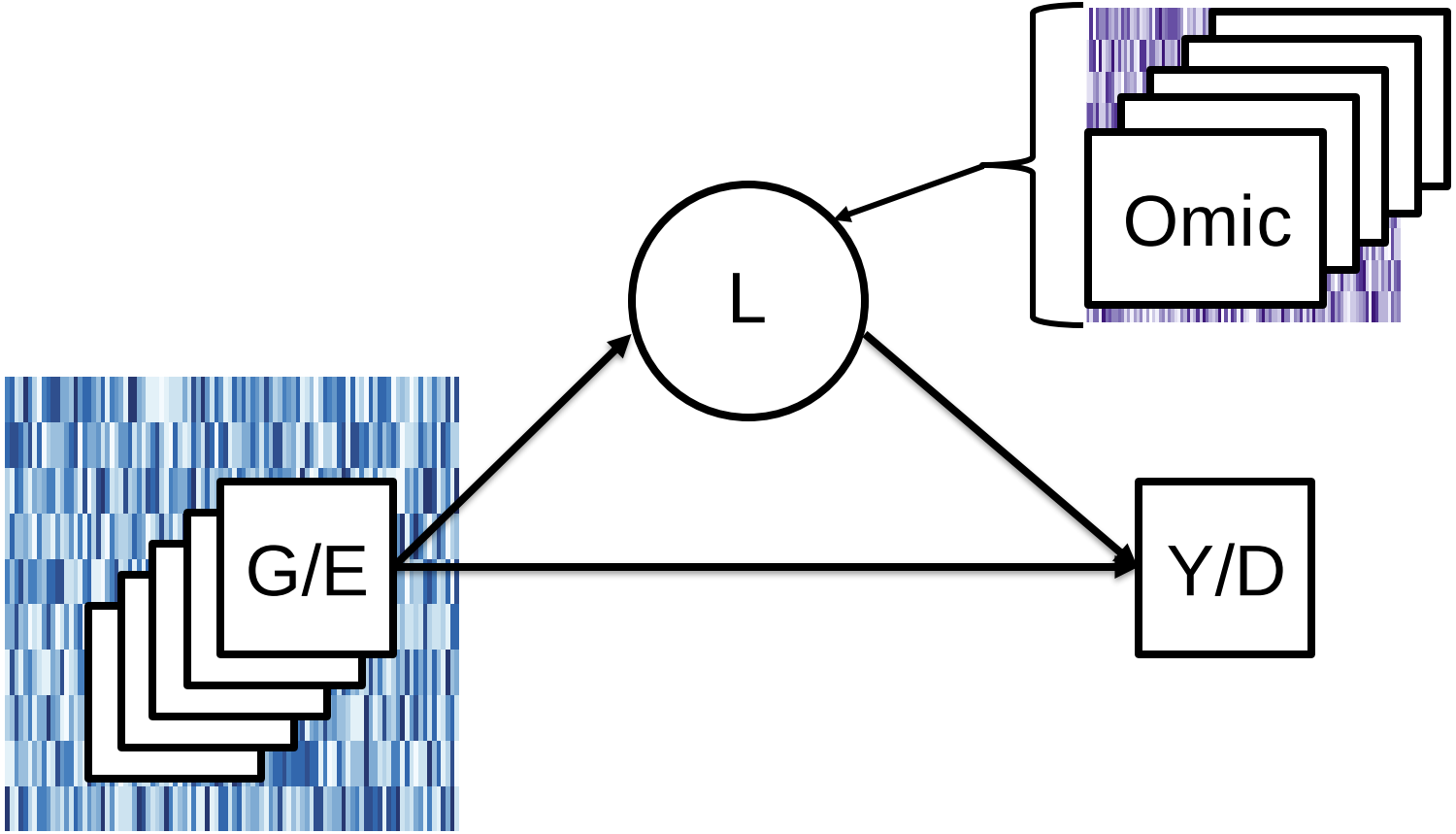
O'Connell et al. 2016; Lock et al. 2013 ; Derkach et al. 2019; Albert et al. 2016

Multiomic Mediation Framework For Precision Environmental Health



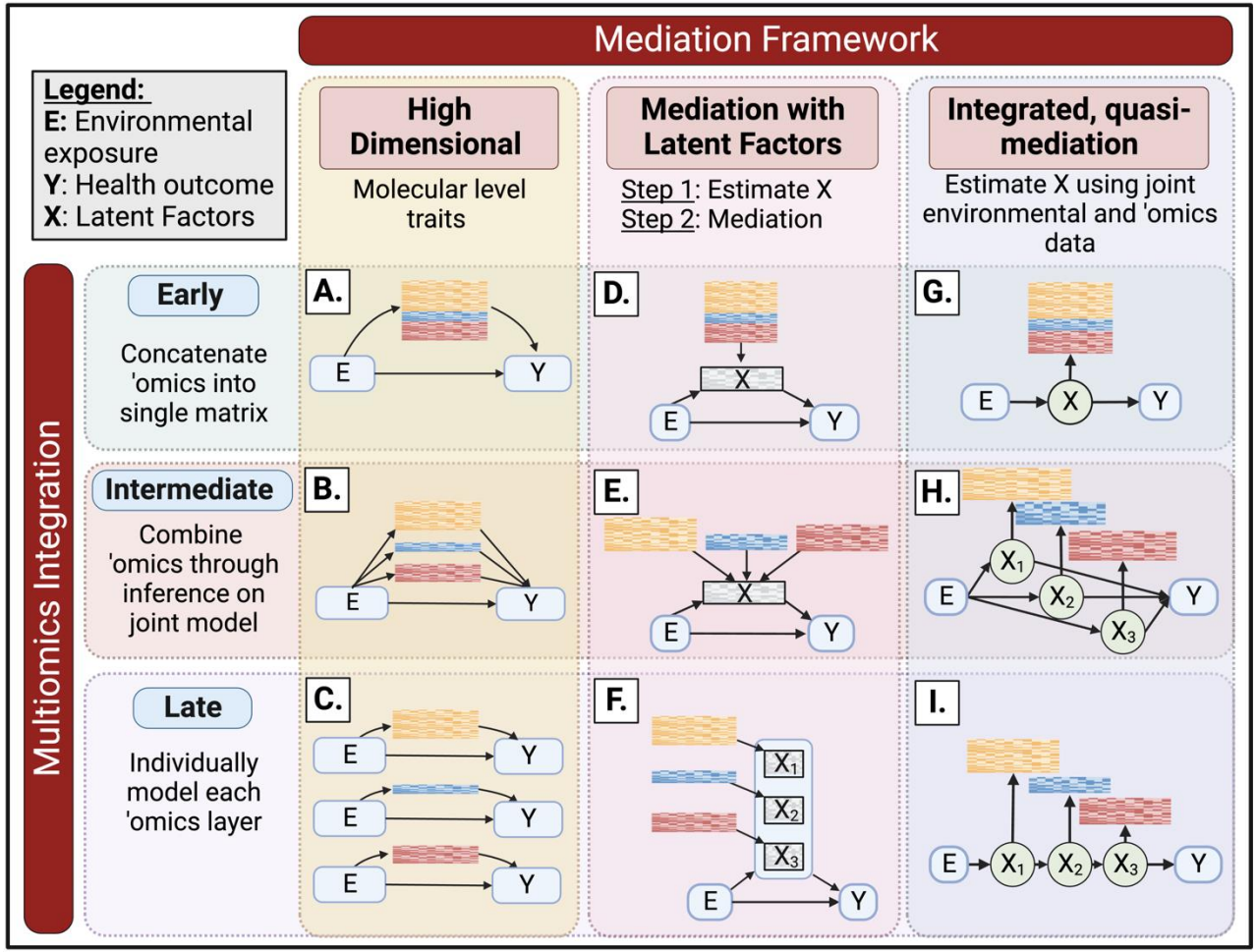
Goodrich et al. *Environ Int.* 2024

Estimate Latent Variables



Peng et al. 2020; Zhao et al. 2024; Zhao et al. in press

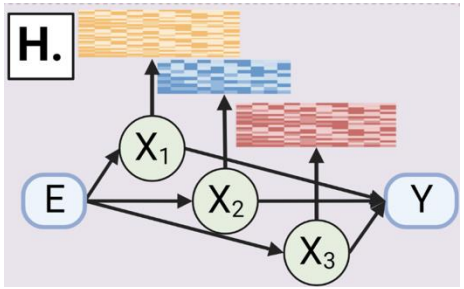
Multiomic Mediation Framework For Precision Environmental Health

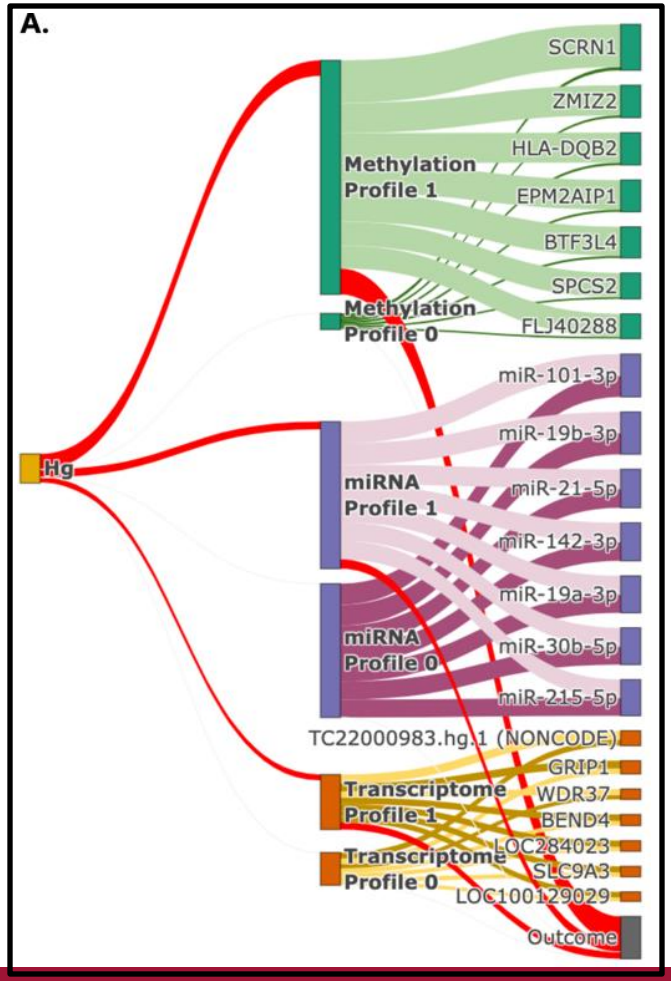


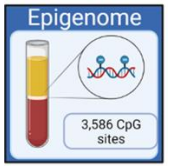
Goodrich et al. 2024; Zhao et al 2024; Zhao et al in press; Peng et al. 2020

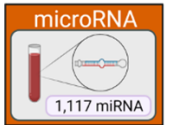
Joint Analysis, Intermediate Integration

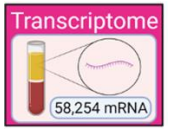
Integrated information on environmental exposures, DNA methylation, miRNA levels, and transcripts can identify groups of children at elevated **risk of liver injury**





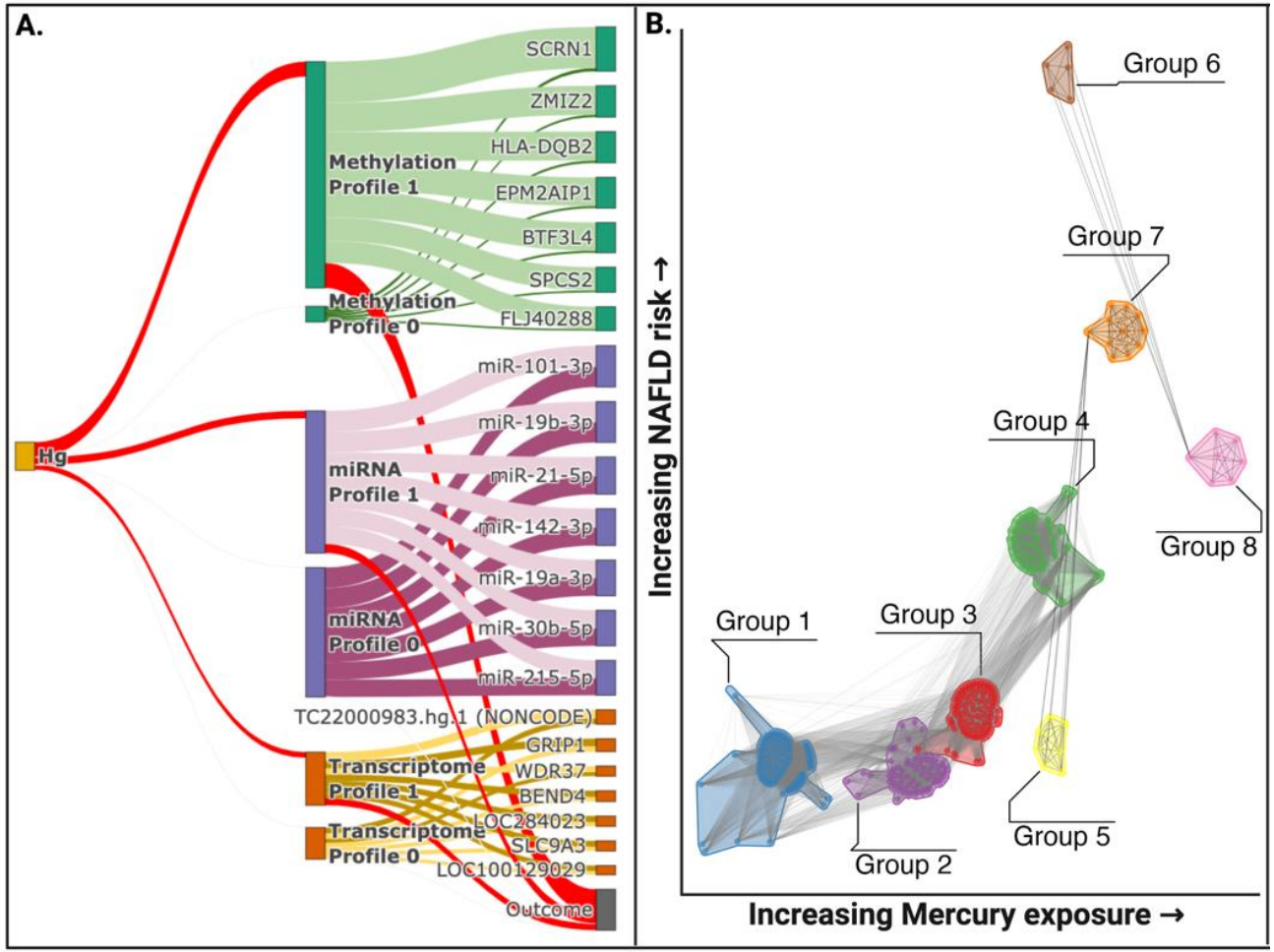






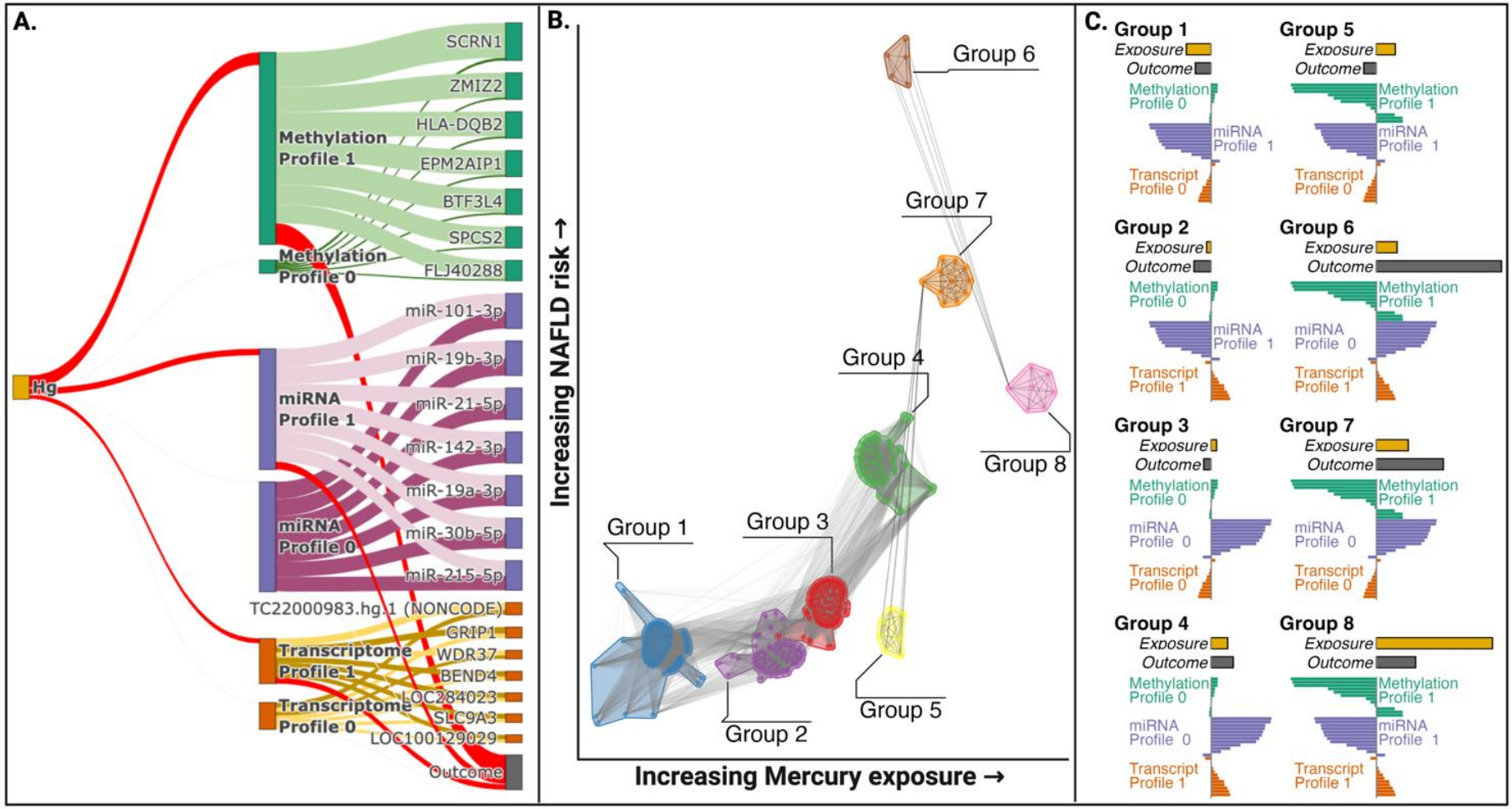
Goodrich et al. *Environ Int.* 2024

Joint Analysis, Interactions Between Omic

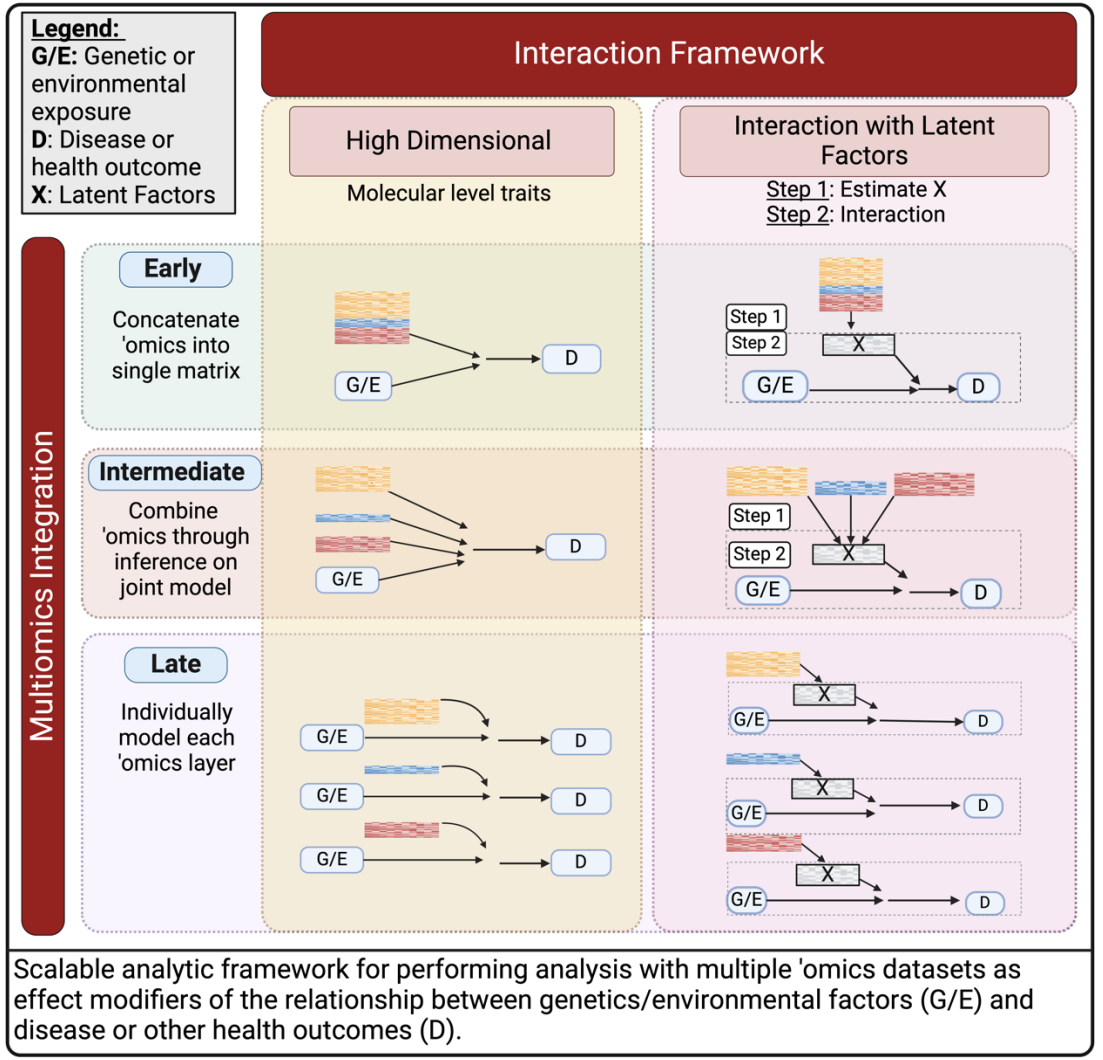


- Eight groups: defined by their exposure and outcome levels
- Here, each point represents an individual from our data. Lines connect individuals with similar omics profiles

Joint Analysis, Interactions Between Omic



Multiomic Interaction



Scalable analytic framework for performing analysis with multiple 'omics datasets as effect modifiers of the relationship between genetics/environmental factors (G/E) and disease or other health outcomes (D).

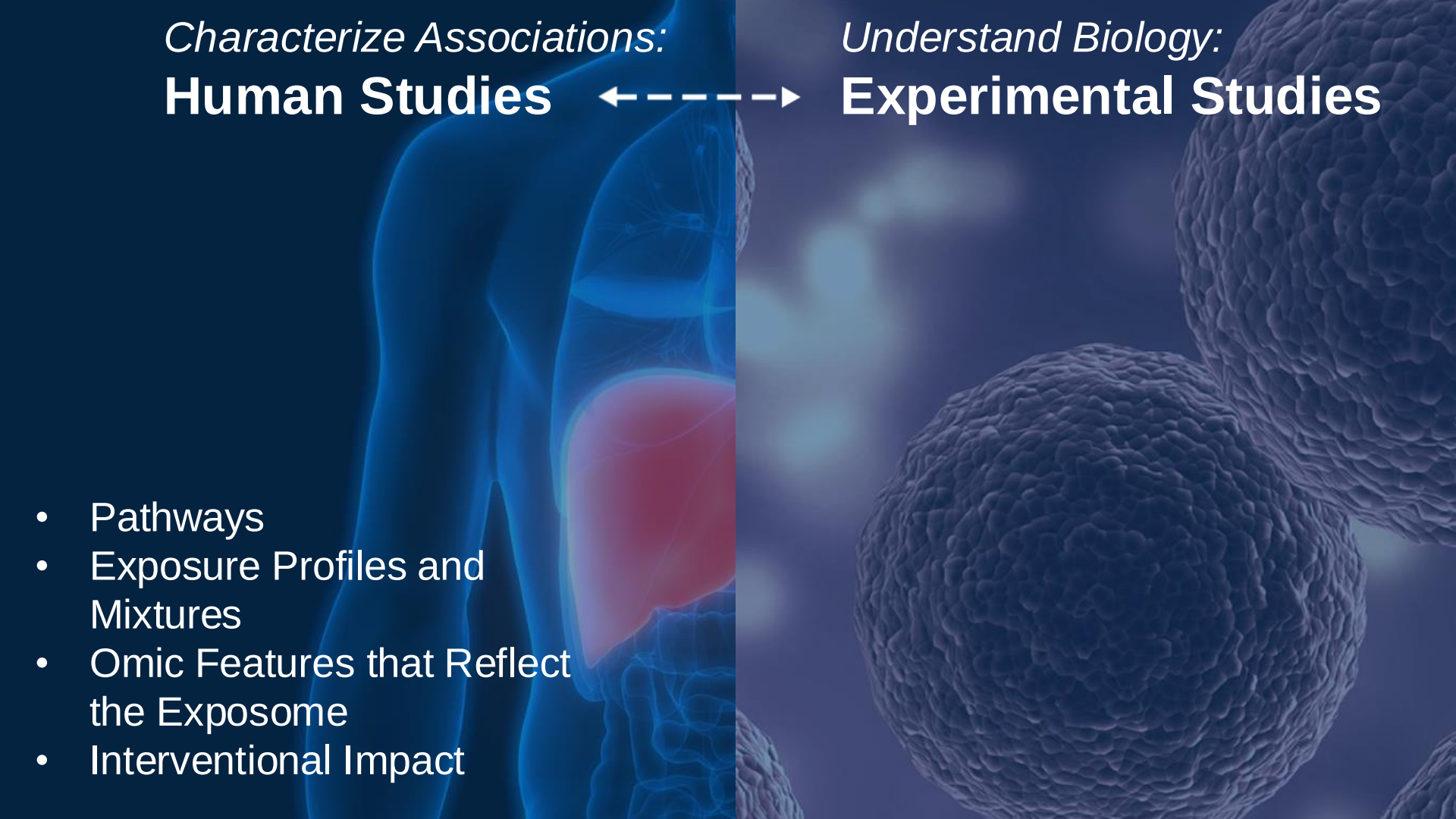
Characterize Associations:

Human Studies

Discovery:

Large Biobanks
Cohorts
Databases

- AI and Analytic Methods that Leverage Prior Information
  - Pathways
  - Exposure Profiles and Mixtures
  - Omic Features that Reflect the Exposome



Characterize Associations:

Human Studies

Understand Biology:

Experimental Studies

- Pathways
- Exposure Profiles and Mixtures
- Omic Features that Reflect the Exposome
- Interventional Impact

Multi-Omics for Health and Disease (MOHD*)

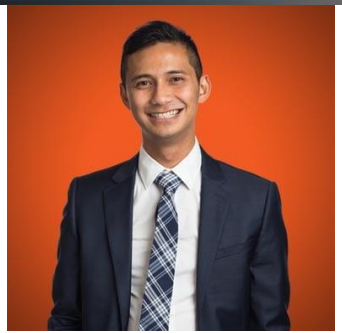
Contributing NIH Institutes:
National Human Genome Research Institute (NHGRI)
National Cancer Institute (NCI)
National Institute of Environmental Health Sciences (NIEHS)

*MOHD: pronounced "mode"

Jesse Goodrich, PhD

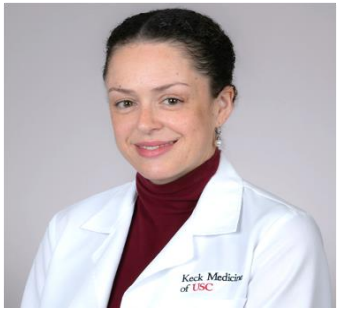
Rob McConnell, PhD

Lida Chatzi, PhD

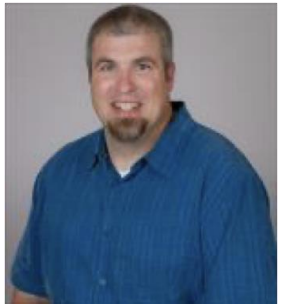


Max Aung, PhD

Lucy Golden, PhD



Ana Maretti-Garcia, PhD



Matthew Salomon, PhD

Southern California Superfund Research and Training Program for PFAS Assessment, Remediation, and Prevention (ShARP)

USCIMAGE
Integrative Methods of Analysis for Genetic Epidemiology

R01ES030691,P30ES007048, R01ES029944, R01ES030364

PRIMED-Cancer

USC
- David Conti, Chris Haiman, Dan Stram

Stanford
- John Witte

Kaiser
- Lori Sakoda

Harvard:
- Mingyang Song

Fred Hutch
- Riki Peters, Charles Kooperberg

Hawaii Cancer Center
- Loic Le Marchand, Lynne Wilkens

NCI
- Stephen Chanock, Sonja Berndts, Pete Kraft

USCIMAGE

Integrative Methods of Analysis for Genetic Epidemiology

- MPIs: Jim Gauderman and Kim Siegmund

- PROJECT 1: INTEGRATION OF OMIC DATA TO ESTIMATE MEDIATION OR LATENT STRUCTURES:
  - David Conti, Josh Millstein, Nick Mancuso

- PROJECT 2: INTEGRATION OF OMIC DATA IN THE ANALYSIS OF GENE x ENVIORNMENT INTERACTION:
  - Jim Gauderman, Juan Pablo Lewinger, Eric Kawaguchi, Lu Zhang

- PROJECT 3: STATISTICAL METHODS FOR GENOME CHARACTERIZATION:
  - Paul Marjoram, Huaiyu Mi, Kim Siegmund, Kelly Street, Paul Thomas

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Special Thanks to All the Students and Post-Docs

Environmental Genomics (T32 ES013678 NIEHS)

Thank You!

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