

Polygenic Risk Scores in Psychiatry

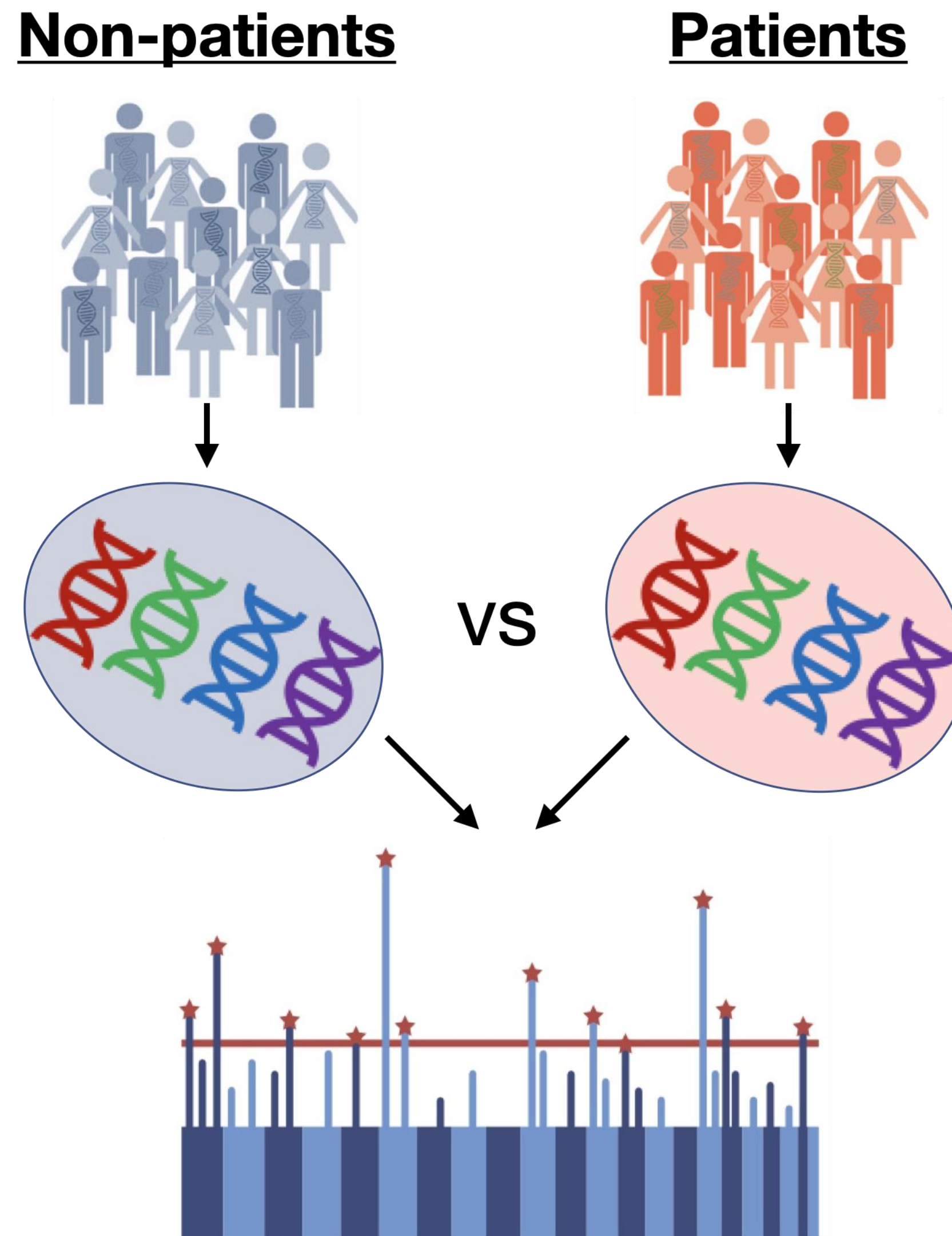
Alicia Martin, PhD

From Molecular Insights to Patient Stratification for Neurological and
Psychiatric Disorders: A workshop, NASEM
October 5, 2021

Genetics can provide objective biomarkers, critically needed in psychiatry

Genetics is about:

1. providing biological insight into disease mechanism
2. assessing risk among individuals

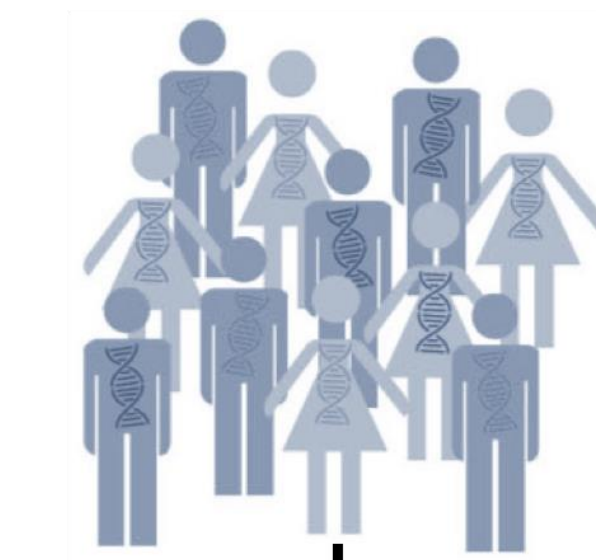


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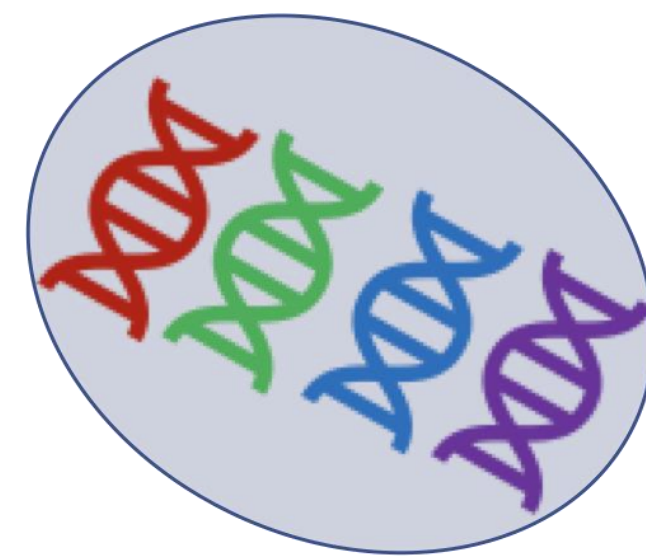
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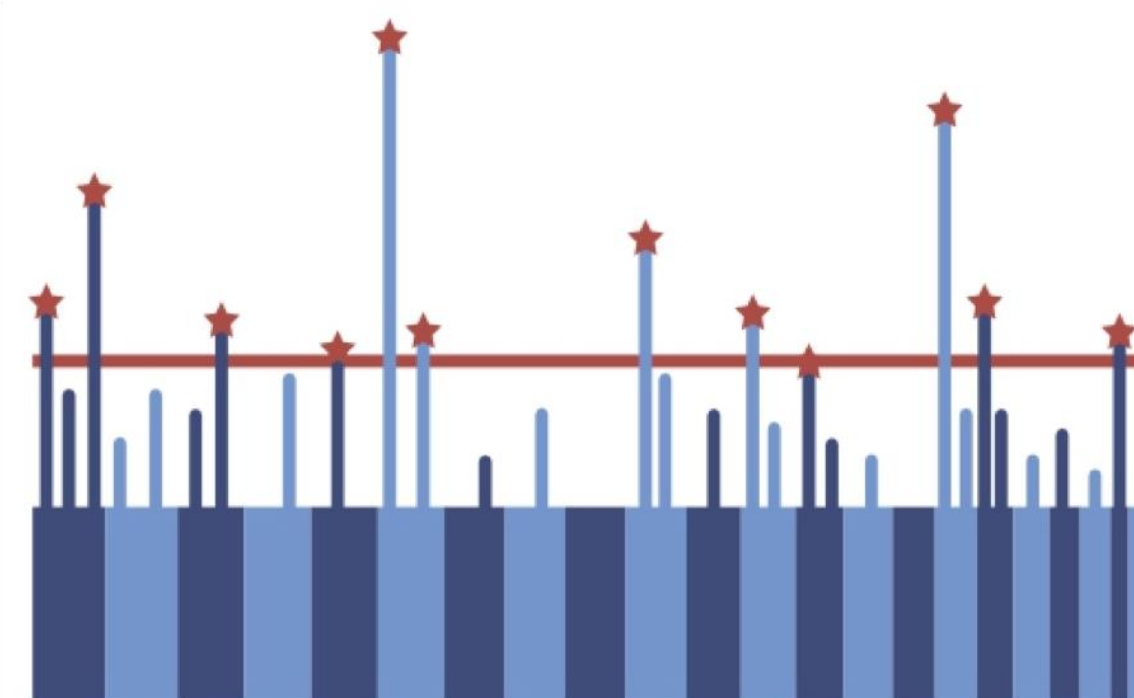
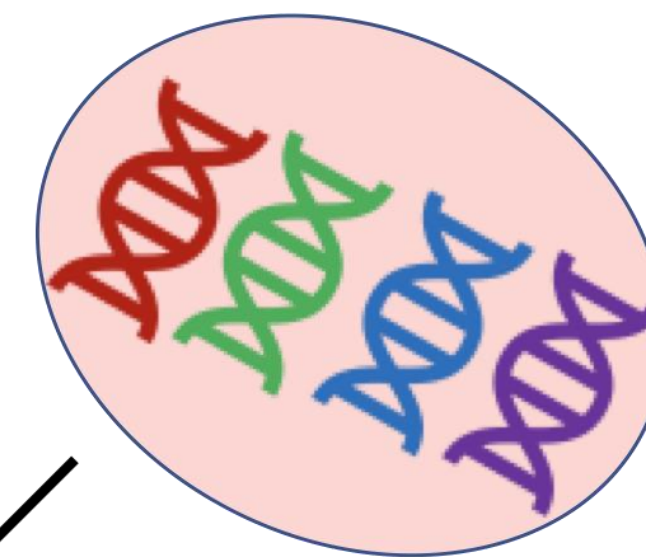
Non-patients



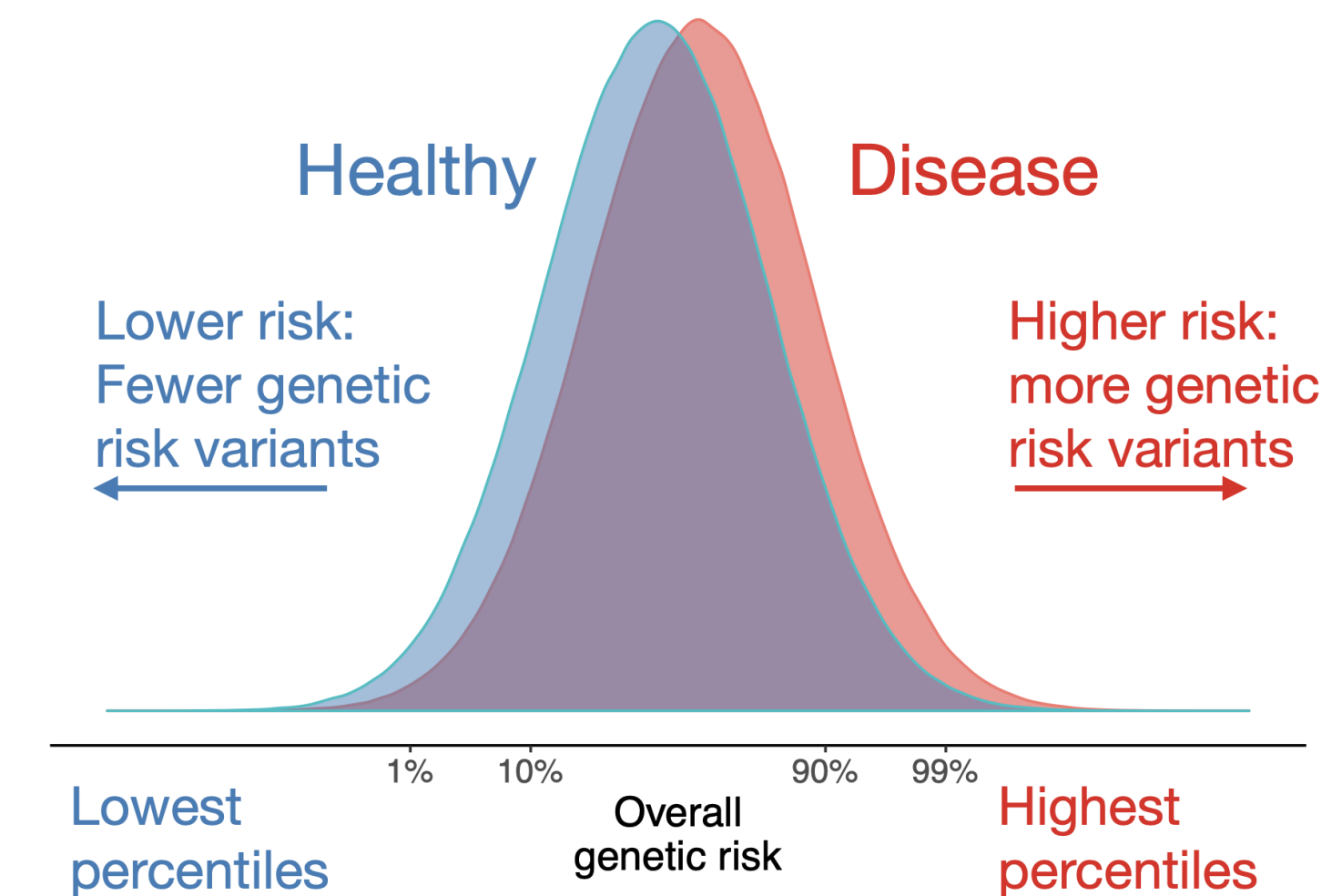
Patients



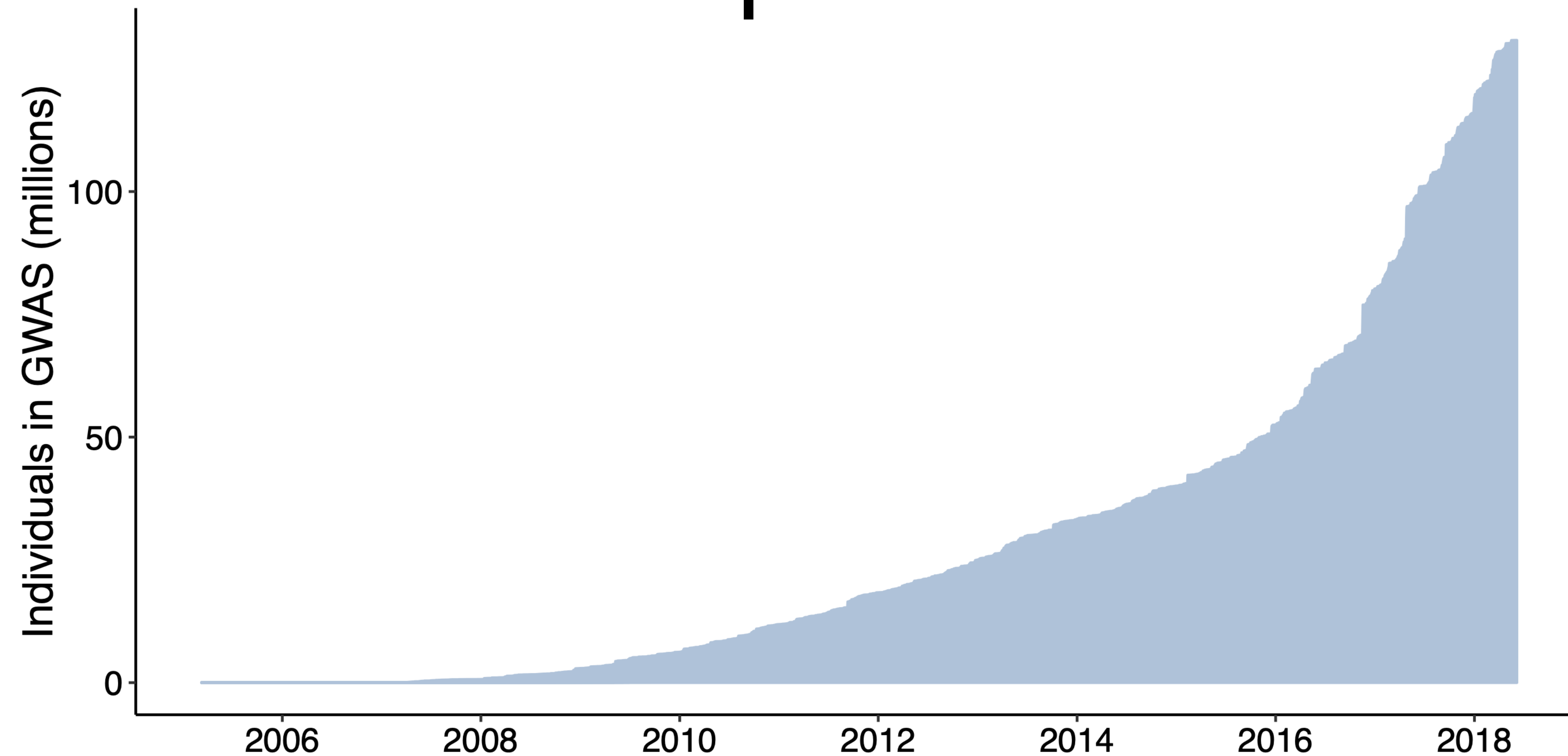
vs



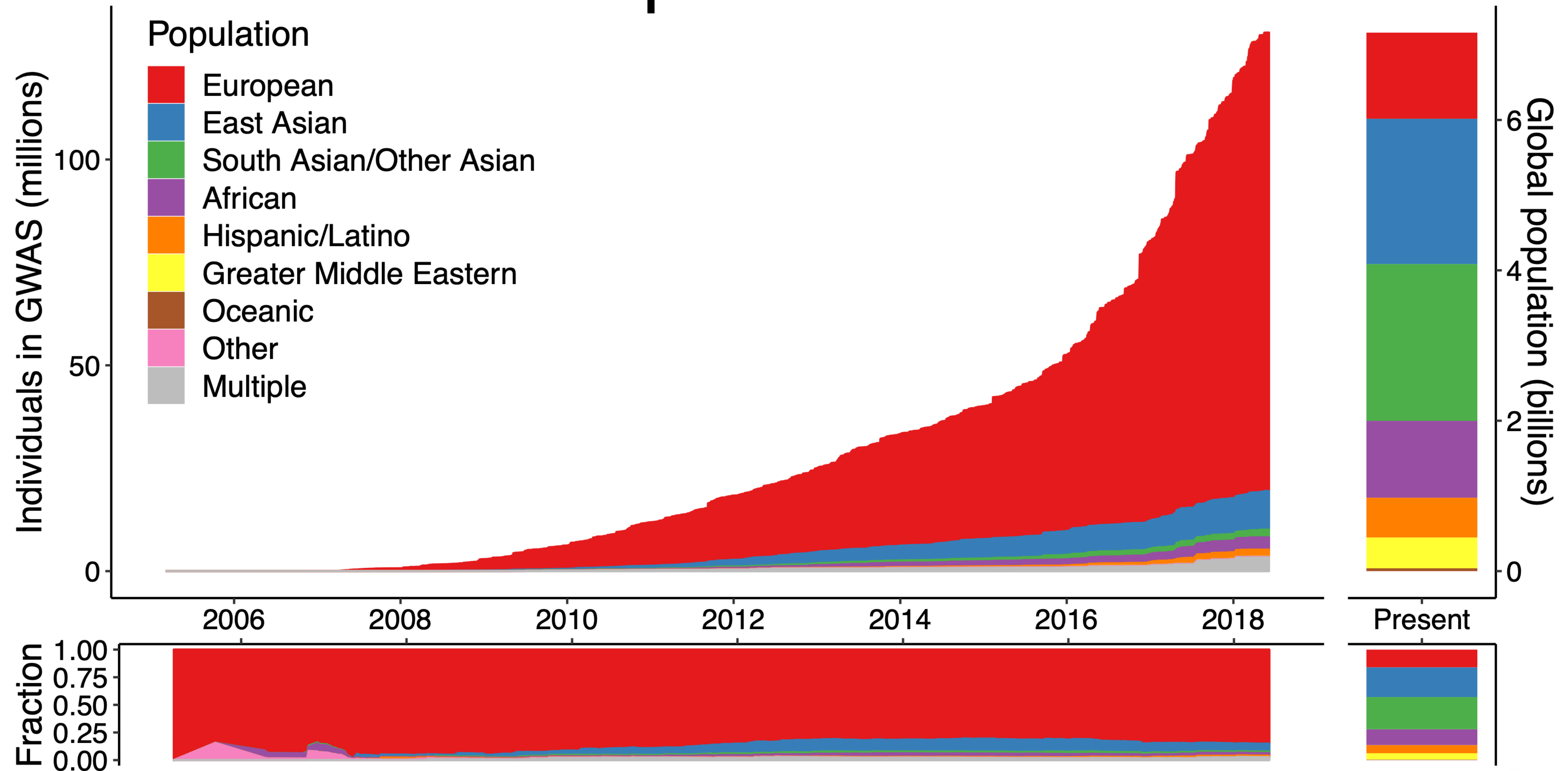
Polygenic risk score:
predicted risk of a phenotype
from a people's DNA



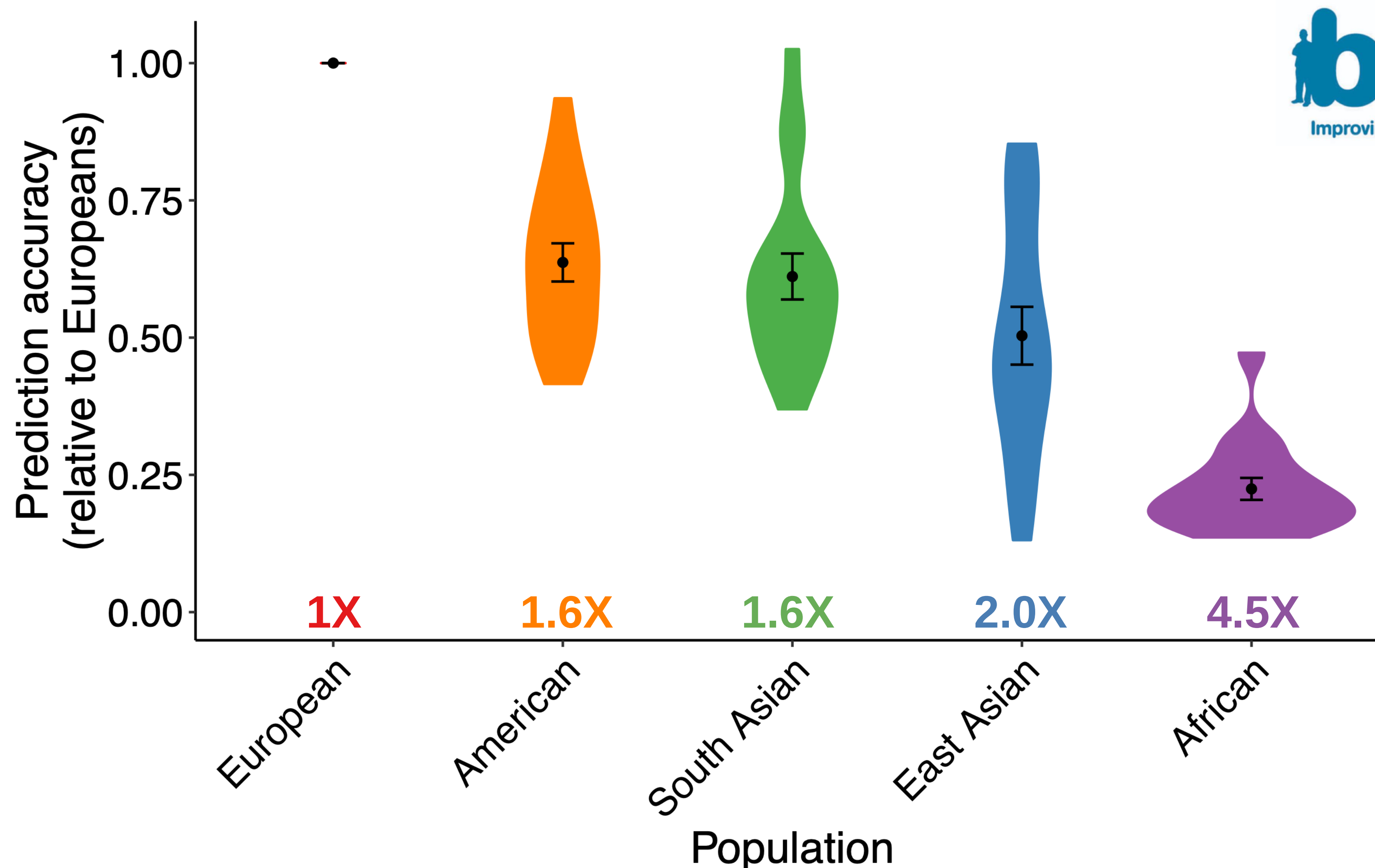
Genetic studies are increasingly powerful



...but genetics has a **HUGE** diversity problem



Staggering disparities in accuracy

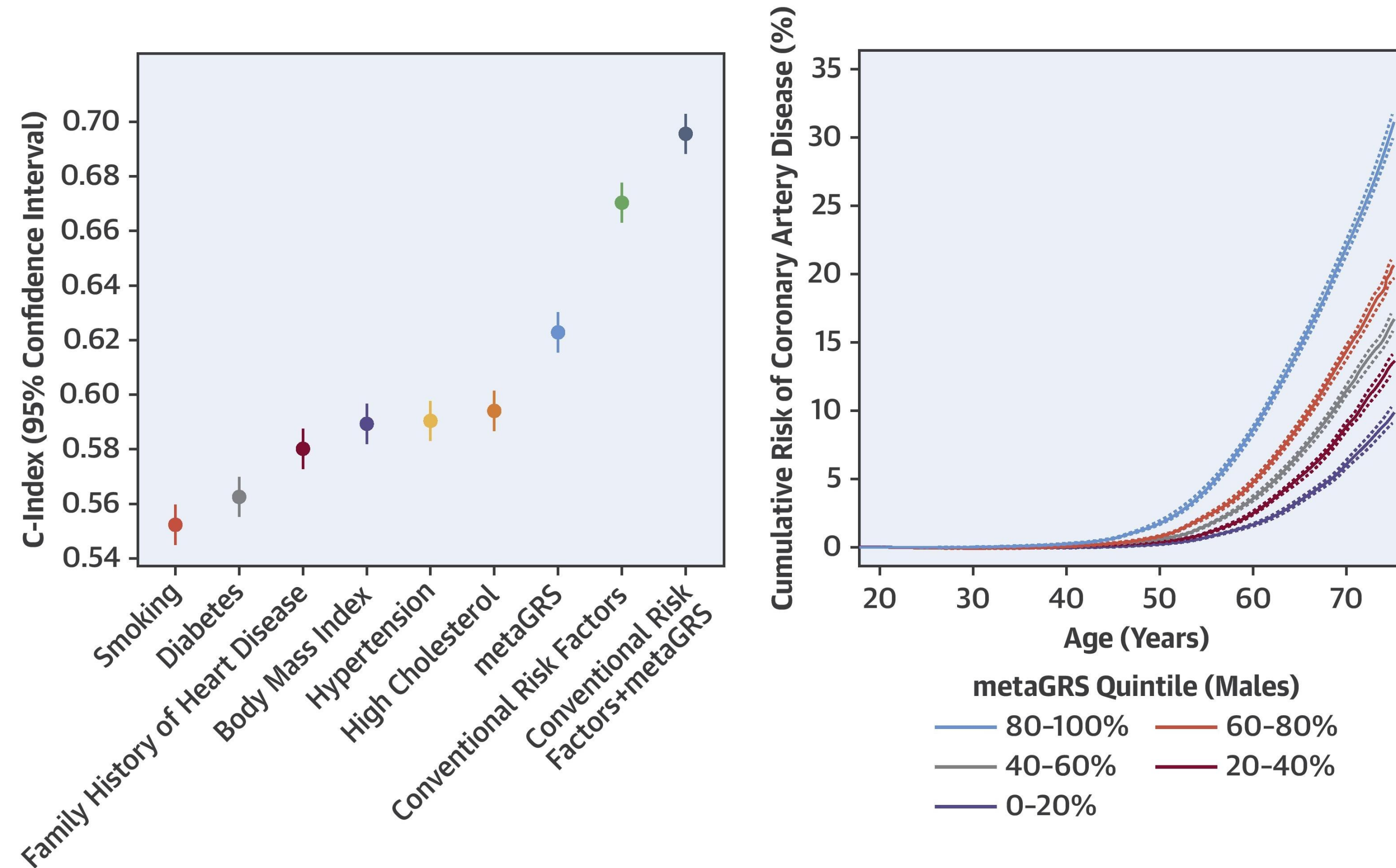


Computed for 17 quantitative traits

Genetic basis:

- Correlated variants, not causal effects
- Differences in allele frequency, LD

Clinical potential for heart disease w/ actionable interventions



Inouye, M., et al. (2018).
Genomic Risk Prediction
of Coronary Artery
Disease in 480,000
Adults: Implications for
Primary Prevention. J.
Am. Coll. Cardiol. 72,
1883–1893.

PRS (in European ancestry) already perform better than well-known *individual* heart disease risk factors, improves existing models

Differential polygenic score accuracy for schizophrenia across populations

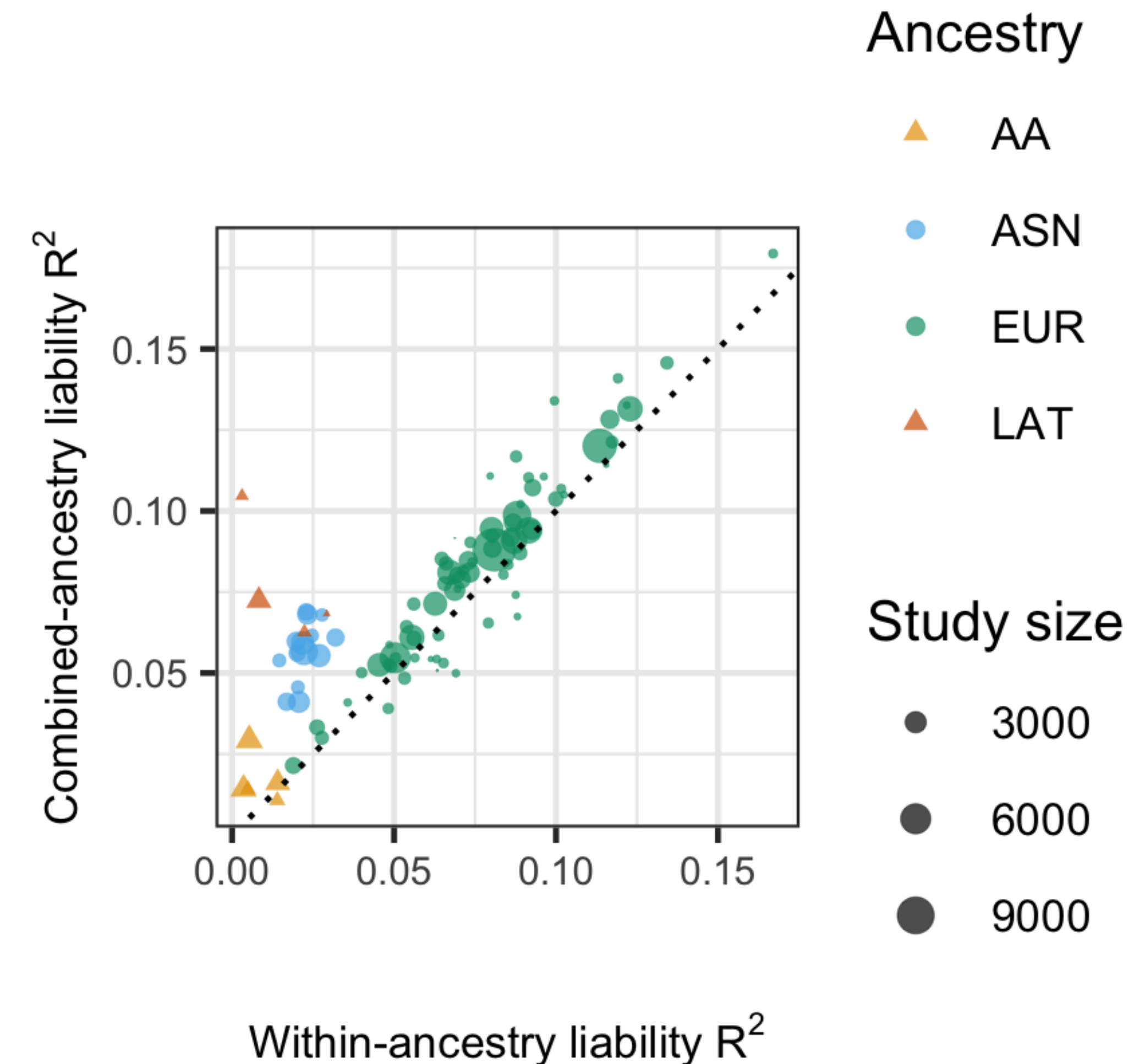
Ancestry	N	Liability R^2 (median)	Top 10% vs rest OR	Top 1% vs bottom 1% OR
African American	9,824	0.02	1.57	4.82
Asian	31,456	0.06	3.60	28.32
European	100,468	0.09	4.94	45.01
Latino	2,377	0.08	3.40	58.87

- *Actionability?*
- Future potential utility: medication response, readmission rates, etc



Issued: MAY 2021

*Advisory on the Use of Polygenic Risk Scores
to Screen Embryos for Adult Mental Conditions*



The Schizophrenia Working Group of the Psychiatric Genomics Consortium. (2020). Mapping genomic loci prioritises genes and implicates synaptic biology in schizophrenia (medRxiv).

Facilitating diverse population genetic studies towards health equity

Needs

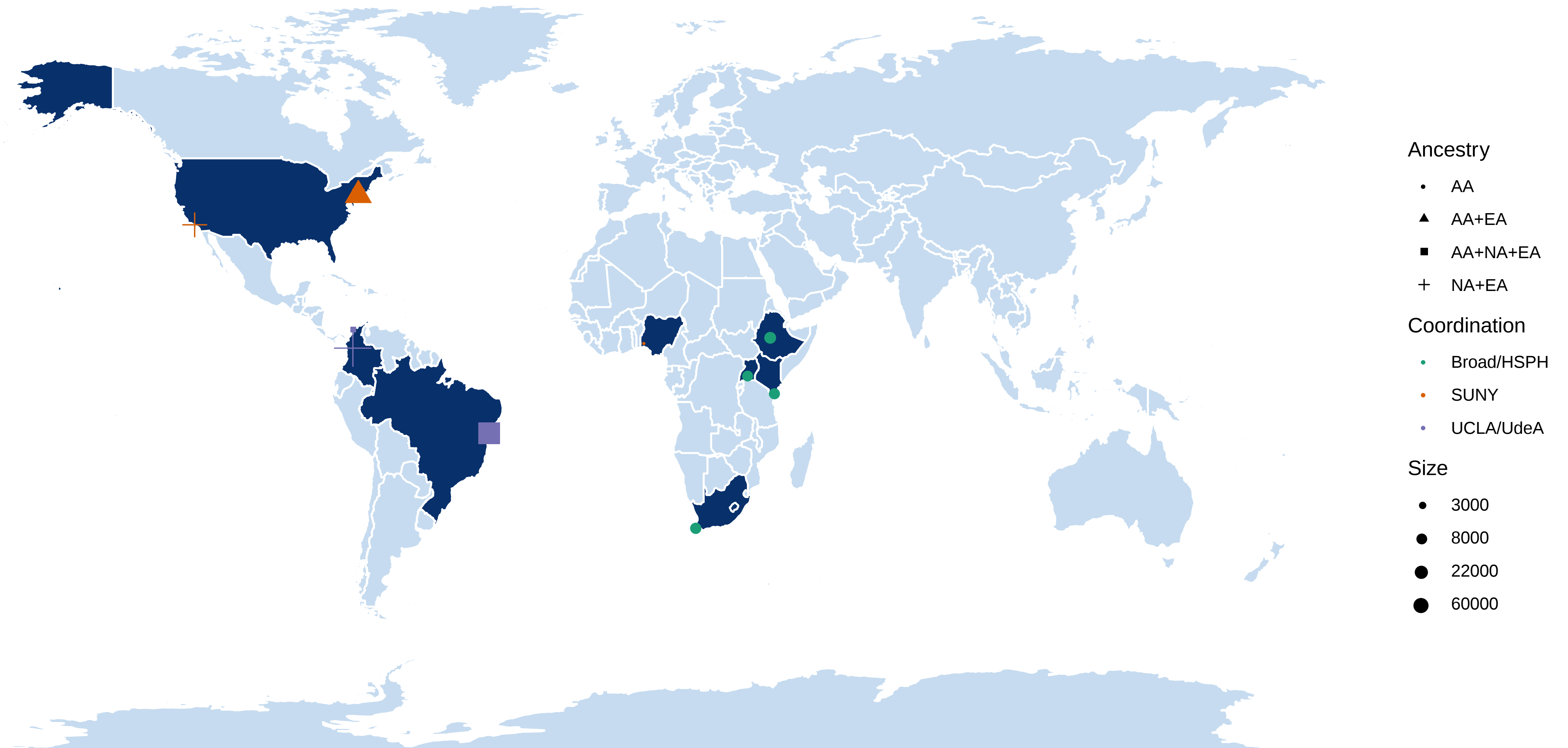
- **Methods:** most assume homogeneity
- **Data + community resources:**
 - Make better use of existing data
 - Collate data across previous boundaries
 - Develop resources (imputation, cell lines, etc)
 - Grow to address gaps
- **Research capacity:** training the next generations of diverse researchers to lead in home communities, countries



Opportunities

- **Novel associations:** identify low-hanging fruit
- **Fine-mapping:** pinpoint causal variants for functional follow-up
- **Genetic risk prediction:** improve accuracy for all, especially underrepresented populations
- **Genetic and environmental determinants of health:** shared and unique population risk factors

Populations Underrepresented in Mental illness Association Studies (PUMAS)



Next steps



- Polygenic scores may provide objective biomarkers in psychiatry and improve clinical models, but are currently likely to **increase health disparities** due to Eurocentric GWAS biases
- We need more **diverse GWAS studies** and **new methods** to address these major issues
- Communicate culturally sensitive topics responsibly and widely, anticipating implications of your research

**How Genetics Is Changing
Our Understanding of 'Race'**

*Why White Supremacists Are Chugging
Milk (and Why Geneticists Are Alarmed)*

**Genetics has learned a ton —
mostly about white people.
That's a problem.**

Thank you!

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Questions/comments?

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