



PRIMED Consortium

Polygenic Risk Methods Development



PRIMED at ASHG

Motivation

Due to the historical oversampling of populations with European ancestry in genetic research, polygenic risk scores (PRS) currently perform less well in other, understudied populations, leading to concerns that clinical use in their current forms could widen health care disparities. **The PRIMED Consortium is developing and evaluating methods to improve PRS performance and overall risk prediction in diverse ancestry populations.**

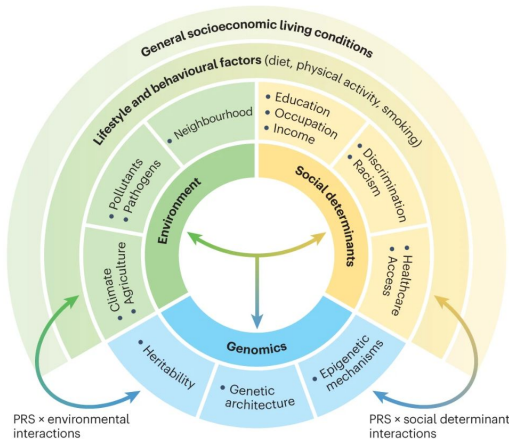


Figure 3a from Kachuri et al. (2023), showing the complex interrelationship among different genomic, environmental, and social risk factors. PMID:37620596

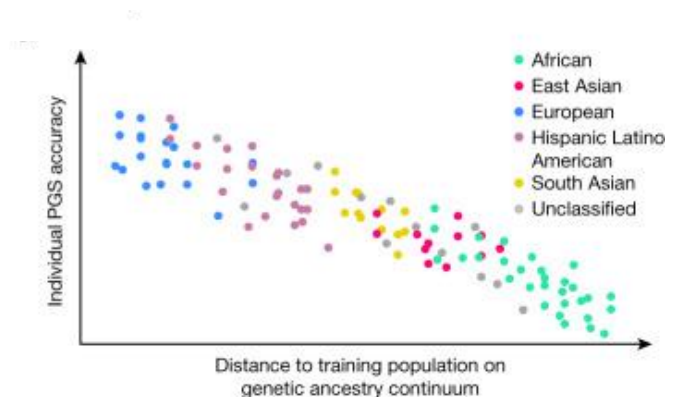
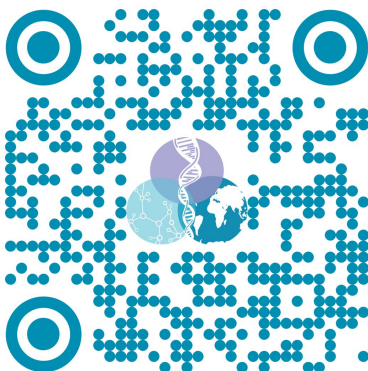


Figure 1d from Ding et al. (2023), illustrating how individual PRS accuracy decreases with increased genetic distance from the training population. PMID:37198491

Connect with PRIMED online



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Bluesky - [@prsmethods.bsky.social](https://bsky.app/profile/prsmethods.bsky.social)



X - [@PRSmethods](https://twitter.com/PRSmethods)



LinkedIn - [/company/primed-consortium/](https://www.linkedin.com/company/primed-consortium/)



Website - primedconsortium.org

PRIMED Overview

Consortium Goals



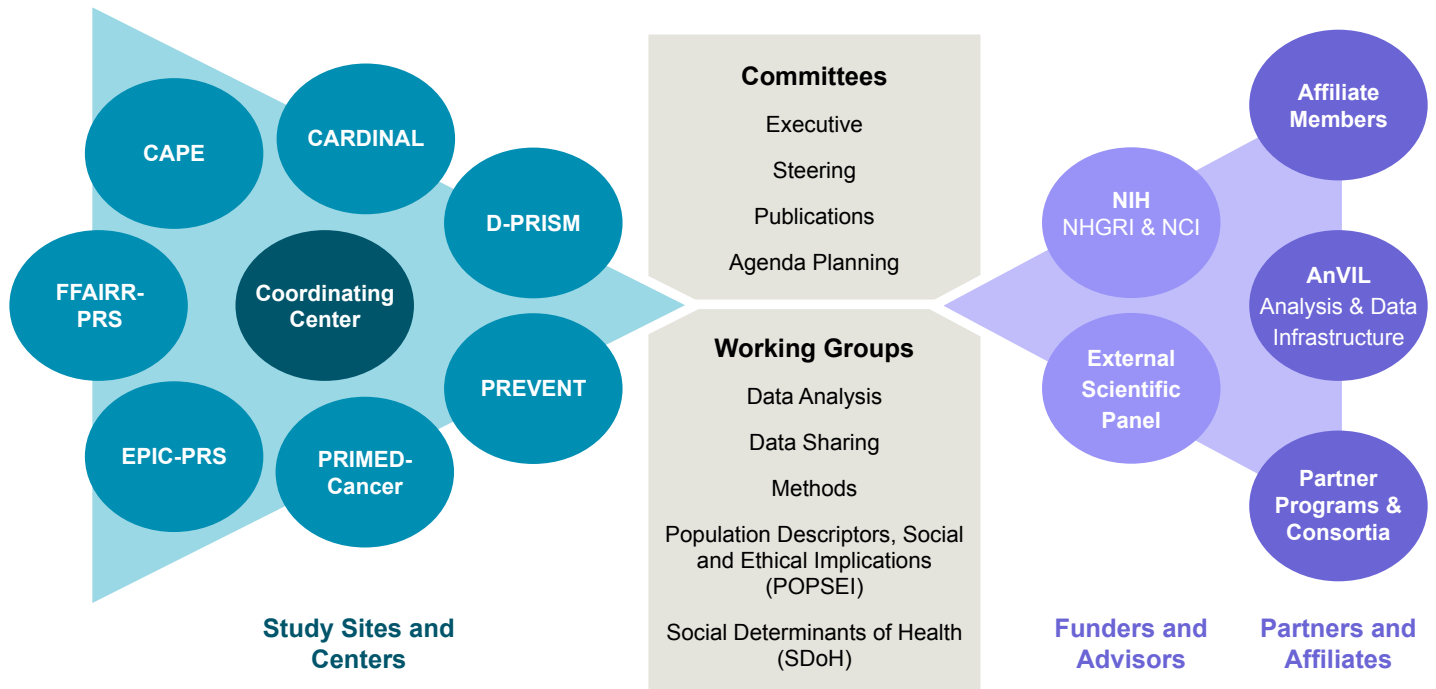
Gather diverse datasets



Develop new PRS methods



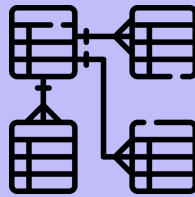
Foster global collaboration



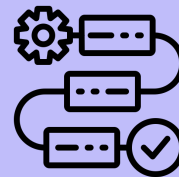
Consortium Products



Population descriptors recommendations



PRIMED common data model



Analysis workflows



Methods innovation



PRIMED
consortium



NHGRI & NCI funding

U01HG011697
U01HG011717
U01CA261339
U01HG011719
U01HG011720
U01HG011723
U01HG011715
U01HG011710

Research Highlights



Perspectives on the field of PRS methods and development

PRS methods and software to improve prediction across diverse and admixed populations



PRS models for key traits to reduce health inequities

PRS models to improve biomarker accuracy



Environmental and social determinants to refine risk estimation

Innovative approaches to representing and using diversity in PRS

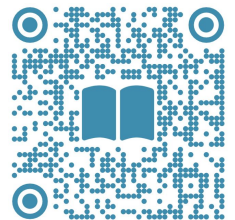


Social and ethical considerations to responsibly develop and implement PRS

Cloud-based approach to collaboratively share and analyze data on the AnVIL platform

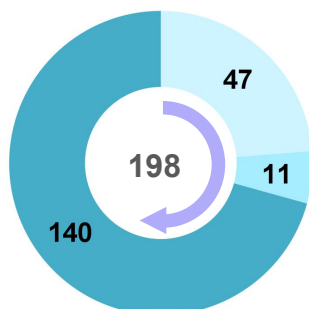


Research Highlights with select publications

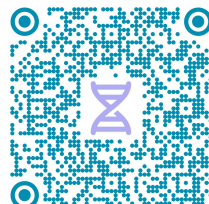


Publications

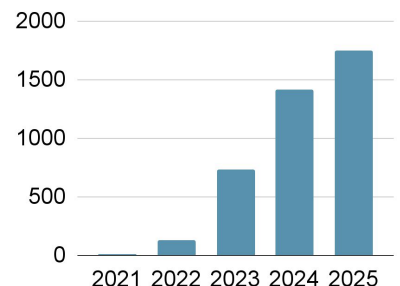
- Proposals in Progress
- Pre-prints
- Publications



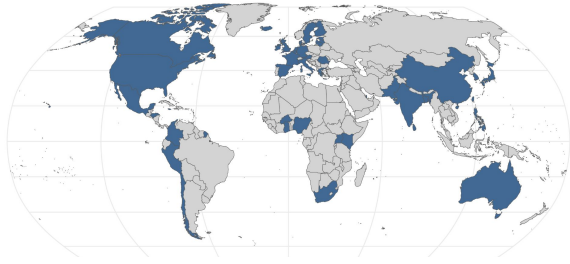
PRIMED Publications in PGS Catalog



Citations by year cited
(4,025 total)
Median RCR: 2.27



Data Overview

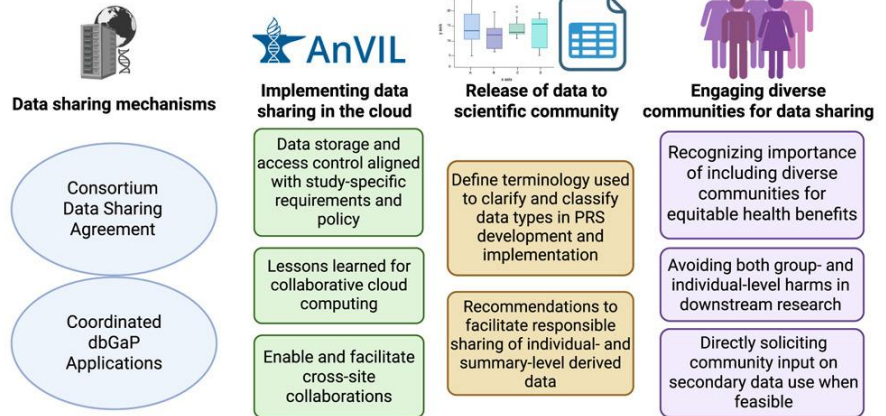


Over **40 countries** are represented among study participants whose data are used by the PRIMED Consortium to improve PRS development and use in diverse genetic ancestry populations.

PRIMED developed multiple **data sharing mechanisms** to accommodate different data sources, types, and use restrictions. Data is shared and analyzed on the **NHGRI AnVIL cloud platform**. PRIMED has outlined **policy recommendations** to facilitate responsible sharing and future re-use of data products to improve polygenic risk prediction. (Smith et al. 2025; PMID 40628271)



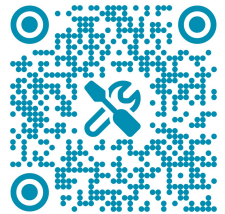
Data sharing recommendations for future research based on experience from the PRIMED Consortium



Created in BioRender.

Methods

PRIMED researchers are **developing methods** that improve PRS performance across diverse ancestry populations (two examples below). Analysis tools and workflows are made available in the **PRIMED Dockstore Organization**.



Haplotypes of individual i

variant j

x_{ij1} haplotype 1

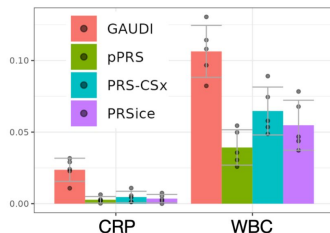
x_{ij2} haplotype 2

Ancestry A

Ancestry B

$l_{ij1} = A, l_{ij2} = B$

Effect of variant j on individual i : $x_{ij1} \beta_{A,j} + x_{ij2} \beta_{B,j}$



$$f(\beta | \lambda, \gamma, p_i) = \frac{1}{2} \|Y_{n \times 1} - G_{n \times 2p_i} \beta_{2p_i \times 1}\|_2^2 + \lambda \|D_{3p_i \times 2p_i} \beta_{2p_i \times 1}\|_1$$

$$D_{3p_i \times 2p_i} = \begin{pmatrix} D_1 \\ D_2 \end{pmatrix} = \begin{pmatrix} 1 & -1 & 0 & 0 & \cdots & 0 & 0 \\ 0 & 0 & 1 & -1 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 1 & -1 \\ \gamma & 0 & 0 & 0 & \cdots & 0 & 0 \\ 0 & \gamma & 0 & 0 & \cdots & 0 & 0 \\ \vdots & \vdots & \vdots & \vdots & \ddots & \vdots & \vdots \\ 0 & 0 & 0 & 0 & \cdots & 0 & \gamma \end{pmatrix}$$

GAUDI explicitly models ancestry-specific effect sizes while encouraging them to be similar. It achieves higher accuracy by detecting variants with large ancestry-differential effects (Sun et al. 2024, PMID: 38310129)

PRSmix integrates PRSs from secondary traits with a penalized regression to improve PRS accuracy (Truong et al. 2024, PMID:38642556)



Image by Ricardo Job-Reese, Broad Communications

