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CARDIOVASCULAR GENOMICS (KG ARAGAM, SECTION EDITOR)

Use of Polygenic Risk Scores for Coronary Heart Disease in Ancestrally Diverse Populations

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Abstract

Purpose of review A polygenic risk score (PRS) is a measure of genetic liability to a disease and is typically normally distributed in a population. Individuals in the upper tail of this distribution often have relative risk equivalent to that of monogenic form of the disease. The majority of currently available PRSs for coronary heart disease (CHD) have been generated from cohorts of European ancestry (EUR) and vary in their applicability to other ancestry groups. In this report, we review the performance of PRSs for CHD across different ancestries and efforts to reduce variability in performance including novel population and statistical genetics approaches.

Recent Findings PRSs for CHD perform robustly in EUR populations but lag in performance in non-EUR groups, particularly individuals of African ancestry. Several large consortia have been established to enable genomic studies in diverse ancestry groups and develop methods to improve PRS performance in multi-ancestry contexts as well as admixed individuals. These include fine-mapping to ascertain causal variants, trans ancestry meta-analyses, and ancestry deconvolution in admixed individuals.

Summary PRSs are being used in the clinical setting but enthusiasm has been tempered by the variable performance in non-EUR ancestry groups. Increasing diversity in genomic association studies and continued innovation in methodological approaches are needed to improve PRS performance in non-EUR individuals for equitable implementation of genomic medicine.

Keywords Coronary heart disease · Polygenic risk score · Risk prediction · Multi-ancestry · Diverse · Transethnic

Introduction

Coronary heart disease (CHD), a leading cause of morbidity and mortality worldwide [1, 2], has an estimated heritability of 40–60%. Monogenic CHD is typically a result of pathogenic variants in *LDLR*, *APOB*, or *PCSK9*, leading

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to familial hypercholesterolemia (FH), and significantly elevated plasma low density lipoprotein cholesterol levels [3]. The prevalence of heterozygous FH is estimated to be ~ 1:250. In most of the population, heritable risk for CHD is polygenic, i.e., due to aggregation of low-impact effects across many genetic variants [3]. Genetic testing for CHD typically involves sequencing of FH-related genes alone and does not account for polygenic risk.

A polygenic risk score (PRS) for CHD (PRS_{CHD}) is the (effect-size) weighted sum of risk alleles, and provides a measure of genetic predisposition to CHD [3]. As a summation of many small effect size risk alleles, a PRS inherently has a normal distribution in the population. Those at the tail ends of this distribution may possess significantly greater or reduced genetic predisposition to CHD compared to those in the middle of the distribution.

PRSs for CHD have been evaluated in several studies [4–6, 7•, 8••, 9–14] and found to be associated with CHD independent of clinical risk factors such as diabetes, hypercholesterolemia, smoking, obesity, hypertension, and family history of CHD [7•, 8••, 9, 12, 15, 16]. Individuals likely to be impacted the most would be those at intermediate risk where initiation of lipid-lowering therapy is subject to uncertainty, younger individuals among whom prevalence of clinical risk factors is low, and those at the extremes of the PRS distribution since their risk category is more likely to change [17•, 18]. These studies collectively highlight the potential of PRS to refine CHD risk estimates, thereby guiding management since genetic risk is modifiable by lifestyle and medical therapy such as the use of lipid lowering drugs. Initial PRSs included only genome-wide significant variants and were modestly associated with CHD; typically the hazard ratio (HR) was 1.1–1.3 for incident CHD events per 1-standard deviation (1-SD) increase in PRS [4, 5, 19] and the loci explained only a small proportion of CHD heritability [20]. Recent PRSs include millions of variants across the genome and are more strongly associated with CHD—with a HR/OR as high as 1.7 per 1-SD increase in PRS and conferring roughly threefold increased risk at the tail end of the PRS distribution, similar to the risk associated with a monogenic cause such as FH [7•, 8••, 9]. This observation suggests that heritability of CHD is highly polygenic [21].

The majority of genomic association studies to date have consisted of European-ancestry (EUR) populations; in 2009 ~ 14% of GWAS participants were of non-European descent which increased to ~ 20% by 2016 [22, 23]. There is insufficient empirical data for other ancestry groups, resulting in subpar performance of PRSs in non-EUR individuals [17•, 24–26]. A large-scale multi-ancestry GWAS for CHD [25] recently identified the first eight genome-wide significant loci among AFR and Hispanic ethnicity groups, 15 years after the first GWAS for CHD were published [31–33]. Before the goal of using polygenic risk prediction in the clinical setting can be realized, there is a need to improve performance of PRS across ancestrally diverse populations.

In this paper, we review the performance of PRSs for CHD across different ancestry populations, current efforts to improve genomic risk prediction in these groups, and clinical implications of these findings.

Reduced Transferability of PRS_{CHD} Across Diverse Ancestries

The portability of PRSs to non-EUR groups is affected by differences in allele frequencies, effect sizes, and the degree of correlation of alleles between nearby variants (i.e., linkage disequilibrium) among ancestral groups [27, 28]. The discrepancy in performance is most noticeable when EUR-derived scores are applied to individuals of African ancestry (AFR) since this population differs the most in terms of stretches of sequences of allele combinations across the genome (i.e., haplotype structure) which influences the correlation between measured and causal variants [27–29]. In the electronic Medical Records and Genomics (eMERGE) Network, a US-based multi-site cohort with EHR-linked biorepositories [17•], a 1-SD increase in a genome-wide PRS_{CHD} derived and validated using UK Biobank cohort [7•] was associated with a relative risk of 1.53 in EUR individuals but only 1.27 in the AFR subpopulation of the same cohort ($p\text{-}interaction = 0.003$) (Table 1) [17•]. Another study assessed the strength of association of a EUR-derived genome-wide PRS_{CHD} with CHD derived from six studies across five major ancestral/ethnic groups [24]. Based on 1-SD increase in PRS_{CHD} in ancestry-level meta-analyzed results, the strength of association with CHD for EUR, South Asian, East Asian, and Hispanic groups was similar with an OR of 1.60, 1.47, 1.66, and 1.52, respectively. The association was noticeably weaker in AFR individuals with an OR of 1.25 [24] (Table 1). This same genome-wide PRS_{CHD} [7•] when applied to a diverse validation cohort within the Million Veteran Program showed, based on ratio of log-transformed ORs, a relative strength of association of 80% and 35% in EUR- and AFR-subpopulations, respectively [25]. Similar results were also observed in another study [30] where a PRS_{CHD} was associated with CHD with an OR per 1-SD of 1.52, 1.50, and 1.2 among EUR, Hispanic, and AFR subgroups of the Mount Sinai Bio*Me* cohort, respectively (Table 1).

Table 1 Ancestry-stratified evaluation of PRS_{CHD}

Evaluated PRS (PGS Catalog ID)	Ancestry	Sample Size	Study Reference	CHD	PRS Effect Size per 1-SD increase [95% CI]	Discrimination Metrics
GPS_CAD (PGS000013)	African Ancestry	6,979	[30]	Prevalent	OR: 1.29 [1.23, 1.34]	AUROC: 0.58
GPS_CAD (PGS000013)	European Ancestry	10,344	[30]	Prevalent	OR: 1.52 [1.46, 1.58]	AUROC: 0.63
GPS_CAD (PGS000013)	Hispanic or Latin American Ancestry	7,048	[30]	Prevalent	OR: 1.50 [1.44, 1.57]	AUROC: 0.63
GPS_CAD (PGS000013)	European Ancestry	39,758	[17•]	Incident	HR: 1.50 [1.43, 1.56]	C-index: 0.72
metaGRS_CAD (PGS000018)	European Ancestry	39,758	[17•]	Incident	HR: 1.53 [1.46, 1.60]	C-index: 0.72
GPS_CAD (PGS000013)	African Ancestry	7,070	[17•]	Incident	HR: 1.19 [1.07, 1.33]	C-index: 0.66
metaGRS_CAD (PGS000018)	African Ancestry	7,070	[17•]	Incident	HR: 1.27 [1.13, 1.43]	C-index: 0.66
GPS_CAD (PGS000013)	Hispanic or Latin American Ancestry	2,194	[17•]	Incident	HR: 1.16 [0.96, 1.41]	C-index: 0.66
metaGRS_CAD (PGS000018)	Hispanic or Latin American Ancestry	2,194	[17•]	Incident	HR: 1.53 [1.23, 1.90]	C-index: 0.68
GPS_CAD (PGS000013)	European Ancestry	474,498	[24]	Prevalent	OR: 1.60 [1.44, 1.78]	N/A
GPS_CAD (PGS000013)	African Ancestry	16,755	[24]	Prevalent	OR: 1.25 [1.12, 1.40]	N/A
GPS_CAD (PGS000013)	East Asian Ancestry	3,988	[24]	Prevalent	OR: 1.66 [1.47, 1.86]	N/A
GPS_CAD (PGS000013)	Hispanic or Latin American Ancestry	9,085	[24]	Prevalent	OR: 1.52 [1.43, 1.62]	N/A
GPS_CAD (PGS000013)	South Asian Ancestry	8,102	[24]	Prevalent	OR: 1.47 [1.36, 1.59]	N/A
GPS_CAD (PGS000013)	European Ancestry	3,081	[11]	Early-onset mycardial infarction (age ≤ 55 years)	OR: 2.06 [1.89, 2.25]	N/A
GPS_CAD (PGS000013)	African Ancestry	1,298	[11]	Early-onset mycardial infarction (age ≤ 55 years)	OR: 1.46 [1.28, 1.66]	N/A
GPS_CAD (PGS000013)	Asian Ancestries	544	[11]	Early-onset mycardial infarction (age ≤ 55 years)	OR: 2.16 [1.35, 1.59]	N/A
GPS_CAD (PGS000013)	East Asian Ancestry	919	[11]	Early-onset mycardial infarction (age ≤ 55 years)	OR: 1.56 [1.29, 1.88]	N/A
MetaPRS_CAD (PGS000337)	East Asian Ancestry	10,999	[44]	Prevalent	OR: 1.84 [1.74, 1.94]	AUROC: 0.67 [95% CI 0.66, 0.69]
metaGRS_CAD (PGS000018)	African Ancestry	64,840	[25]	Prevalent and Incident	OR: 1.21 [1.10–1.14]	N/A
metaGRS_CAD (PGS000018)	European Ancestry	225,603	[25]	Prevalent and Incident	OR: 1.38 [1.36–1.39]	N/A
metaGRS_CAD (PGS000018)	Hispanic or Latin American Ancestry	30,641	[25]	Prevalent and Incident	OR: 1.39 [1.34–1.43]	N/A
GPS_CAD (PGS000013)	African Ancestry	64,840	[25]	Prevalent and Incident	OR: 1.10 [1.08–1.12]	N/A

Table 1 (continued)

Evaluated PRS (PGS Catalog ID)	Ancestry	Sample Size	Study Reference	CHD	PRS Effect Size per 1-SD increase [95% CI]	Discrimination Metrics
GPS_CAD (PGS000013)	European Ancestry	225,603	[25]	Prevalent and Incident	OR: 1.36 [1.35–1.37]	N/A
GPS_CAD (PGS000013)	Hispanic or Latin American Ancestry	30,641	[25]	Prevalent and Incident	OR: 1.32 [1.28–1.36]	N/A
GPS_CAD_SA (PGS000296)	South Asian Ancestry	491	[43]	Myocardial infarction (first-ever)	OR: 1.60 [1.32, 1.94]	AUROC: 0.66
GPS_CAD_SA (PGS000296)	South Asian Ancestry	2,963	[43]	Prevalent and Incident	OR: 1.66 [1.53, 1.81]	AUROC: 0.71
GPS_CAD (PGS000013)	South Asian Ancestry	2,963	[43]	Prevalent and Incident	OR: 1.58 [1.42, 1.76]	AUROC: 0.71
GPS_CAD (PGS000013)	South Asian Ancestry	7,244	[43]	Prevalent and Incident	OR: 1.53 [N/A]	AUROC: 0.80

*PRS performance metrics obtained from PGS catalog. PRS = polygenic risk score; CHD = coronary heart disease; SD = standard deviation; CI = confidence interval; OR = odds ratio; HR = hazard ratio; AUROC = area under the receiver operating characteristic curve

New Insights into Predictive Performance of PRS in Diverse Ancestry Groups and Novel Methods Development

In general, the accuracy of PRS risk prediction is highest in the population from which GWAS summary statistics were derived [27]. The strong Euro-centric bias in large GWAS and lack of well-powered studies in minority groups [22, 23] lead to poor generalizability of PRS [28]. Due to lack of available data, attempting to extend existing PRS to other populations or to create de novo PRS in these groups is challenging regardless of the phenotype of interest.

In a recent study [29], 245 different PRSs were constructed for a large set of traits in the UK Biobank and applied to nine ancestry groups in the same cohort. When averaged over 245 phenotypes, in reference to Northwest European ancestry individuals from the United Kingdom, relative predictive ability of PRS was highest in Northeast (93.8%) and Southern Europeans (85.6%), progressively decreasing in Middle Eastern (72.2%), South Asians (64.7%) and East Asians (48.6%), and lowest in the West African group (18%). These findings illustrate how prediction performance decays with increasing genetic distance between derivation and validation cohort [29].

An example of how large diverse consortia can improve performance of PRSs in non-EUR groups is the Global Lipids Genetics Consortium which published one of the largest and most diverse GWAS to date for blood lipid traits including ~ 1.6 M individuals across 201 studies and five genetic ancestry groups with roughly 1.3 M EUR, 146 k East Asian, 100 k AFR, 48 k Hispanic, and 41 k South Asian individuals [34]. This study demonstrated a significant increase in statistical power to identify potential causal variants within trait-associated regions in GWAS (i.e., fine-mapping) in multi-ancestry analyses rather than analyses including EUR, alone. Interestingly, PRSs derived from multi-ancestry meta-analysis showed equivalent or better performance across ancestry groups compared to ancestry-specific or EUR-derived PRS [34]. These results suggest that increasing diversity in GWAS as opposed to studying additional EUR individuals will improve fine-mapping of causal variants and increase portability of PRS across ancestry groups.

Several population and statistical genetics methods are being explored to increase the performance of PRSs across ancestry groups [35–38]. This is a rapidly evolving field of research and we describe a few examples below. Amariuta et al. [36] used functional annotations, which involves linking biological information such as impact on gene expression and protein structure/function, to risk associated variants, prioritizing those with regulatory roles to improve trans-ancestry portability of PRS. This approach assumes that causal variants are largely shared between populations but obscured by population-specific linkage disequilibrium patterns. The authors demonstrated high-concordance of variant-heritability of shared regulatory elements between EUR and East Asian populations as well as an average increase of 49.9% in explained trait variability by PRS (as measured by R^2) across 21 phenotypes when applying EUR-derived functional variant prioritized PRS versus traditional PRS to East Asian individuals [36]. Another method, PolyPred [37], similarly uses fine-mapping to improve cross-population risk scores. Across 49 phenotypes, this method improved prediction accuracy by 7% to 77% in South Asians

and 32% to 164% in AFR individuals in comparison to traditional PRS methods. Finally, PRS-CSx [35], a novel Bayesian method, aims to overcome hurdles in PRS transferability by integrating GWAS summary statistics from multiple populations via a continuous shrinkage prior shared across ancestry groups, to facilitate information sharing among ancestry-specific GWAS summary statistics and increase accuracy of variant effect size estimates. This method increased prediction accuracy by 53.3% in East Asians and 45.1% in AFR individuals in the UK Biobank compared to another popular method LDpred2 which performs single ancestry PRS prediction [35, 39].

Accounting for Admixture in PRS Construction

PRS methods will also need to account for recently admixed individuals' unique mosaic of ancestry. Estimates of local ancestry (e.g., 0, 1, or 2 African ancestry alleles), such as based on a conditional random-field based approach, RFMix [40], can be used to weigh the contribution of each genetic variant's regression coefficient to the PRS. In a recent study, local-ancestry deconvolution, i.e., elucidating unique tiling of ancestry blocks for each admixed individual, was used to compute ancestry-specific partial PRSs [38]. The authors demonstrated improvement in trait prediction, but the study was limited in the number of studied phenotypes (i.e., type 2 diabetes, breast cancer, height, and BMI) and ancestry groups. This approach will likely perform best when the effect size of a genetic variant has a large difference among different populations but may over-adjust when the effect sizes are not very different and lose predictive power [41].

Current Efforts to Develop Trans-Ancestry PRS_{CHD}

There is growing interest in derivation of ancestry-specific and trans-ancestry PRSs with increasing availability of diverse datasets (Fig. 1a and b). To date, the majority of the scientific efforts have been concentrated on either validating existing EUR-derived PRS_{CHD} across closely related EUR-individuals [42] or across non-EUR individuals [17•, 24, 25, 30]. Ancestry-specific PRS_{CHD} for groups such as South

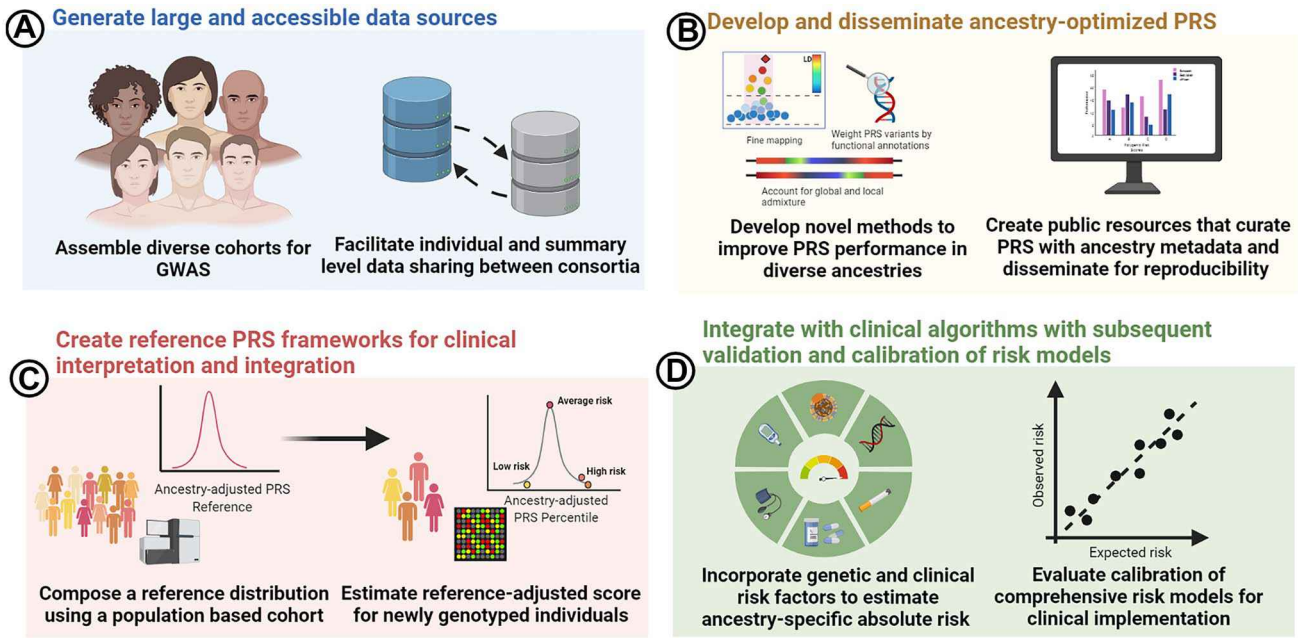

Fig. 1 Polygenic risk scores for diverse ancestry groups. **A** Assembling large multi-ancestry consortia for GWAS and sharing of individual and/or summary level data between these initiatives is a critical step to generate ancestrally diverse datasets for PRS development. **B** Development of novel methods to derive ancestry optimized PRS and public resources enabling fast and reliable dissemination of these scores to researchers will help close the gap in PRS performance between EUR and non-EUR populations. **C** Creation of population-based reference frameworks will help adjust scores for population structure and facilitate clinical interpretation. **D** Finally, incorporation of PRSs into clinical risk factors to create comprehensive risk prediction models, following validation of performance and calibration, is needed for clinical implementation of genomic risk prediction across globally diverse populations. GWAS = Genome-wide association study; PRS = Polygenic risk score; EUR = European ancestry. This figure was created with BioRender.com

Asians [43] and East Asians [44] have revealed performance comparable to that in EUR cohorts (Table 1).

CARDIoGRAMplusC4D [45], a large consortium established to facilitate genomic discovery for CHD, is currently leading efforts to create a multi-ancestry PRS for CHD by leveraging its extensive collaboration network including the Million Veteran Program, UK Biobank, Biobank Japan, eMERGE network, and several National Heart, Lung, and Blood Institute (NHLBI) studies. Furthermore, eMERGE network [46] in its current phase (IV) is validating PRSs for diverse ancestries for several common complex diseases including CHD as well as communicating genomic risk profiles and relevant clinical recommendations based on PRS, family history, and other clinical data.

The National Human Genome and Research Institute (NHGRI) has initiated the multi-site Polygenic Risk Methods in Diverse Populations (PRIMED) consortium, to improve the applicability of PRS in diverse populations by optimizing the integration of large-scale, harmonized genomic and phenotypic data [47]. The consortium is composed of 7 US-based institutions and includes working groups such as genotype and phenotype harmonization of both individual level DNA-linked health data and GWAS summary statistics and development of methods and software for PRS construction with a focus on non-EUR ancestry and admixed populations [47]. CHD is one of the main phenotypes of interest in the PRIMED consortium. Additionally, diverse genomic datasets include the All of Us research program [48], the Million Veteran Program from the Department of Veterans Affairs [49] and NHLBI's Trans-Omics for Precision Medicine (TOPMed) program [50]. Other global initiatives that will improve genomic diversity include The Emirati Genome Program [51], H3Africa [52], Qatar Cardiovascular Biorepository [53], Biobank Japan [54], United Kingdom Biobank [55], China Kadoorie Biobank [56], and Taiwan Biobank [57]. Creation of these resources will ultimately enable construction of robust multi-ancestry PRS_{CHD} with performances comparable to what is currently available for EUR populations.

Practical Considerations Regarding Clinical Application of PRS_{CHD} in Globally Diverse Populations

Performance of PRS_{CHD} across ancestry groups can be compared using relative risk measures including OR/HR, discriminatory ability with metrics such as AUROC and C-statistic, risk reclassification measures like net reclassification index, and the amount of phenotypic variance explained with metrics such as pseudo R^2. In clinical practice, clinicians use absolute risk to make medical decisions, e.g., 10-year or lifetime risk of a cardiovascular event for patients [58–61]. Commonly used cardiovascular risk calculators include American College of Cardiology (ACC)/American Heart Association (AHA) Pooled cohort equation [58], Framingham risk score [59], QRISK [60], SCORE2 [62, 63], and MESA risk scores [61]. Both the US and European guidelines incorporate these clinical risk scores with certain risk thresholds to guide clinical decision making for primary prevention such as initiation of lipid lowering therapy [64, 65].

When using PRSs in different ancestry groups, differences in disease epidemiology such as incidence and mortality rates need to be accounted for to estimate absolute risk. For example, South Asians and African Americans have higher risk of cardiovascular disease than whites in the USA [66, 67]. We explored use of PRS in modeling absolute risk of CHD using age, sex, and race/ethnicity-specific CHD incidence rates in the US as well as non-CHD mortality rates as competing risk [17•]. In reference to the EUR cohort, a lower yet substantial proportion of AFR participants were reclassified from intermediate to high 10-year risk category (24.1% versus 19.5%) using a genome-wide PRS_{CHD} , due to higher incidence of CHD among African Americans versus whites in the USA. Despite a narrower relative risk gradient in the non-EUR populations, PRS_{CHD} could still facilitate clinical decision-making regarding prevention and treatment based on estimates of absolute risk of cardiovascular disease.

Clinical implementation of PRS_{CHD} in diverse groups also requires assessment of calibration [68, 69], i.e., discrepancy between estimated versus observed risk (Fig. 1d). Despite high prediction performance of a risk model including genetic and non-genetic risk factors, poor calibration can be misleading and potentially harmful in clinical decision making [68] such as by unnecessarily increasing the burden of medical testing for an individual. Although certain studies explored calibration of models incorporating both genetic and clinical data [18, 70, 71], the majority of studies omit these evaluations. The Polygenic Score (PGS) catalog [72] created a public resource of published PRSs with consistently curated metadata required for reproducibility and independent applications [72]. This platform currently stores 2,149 PRSs across 524 traits obtained from over 262 publications and incorporates expert curation for this data including ancestry distribution of source GWAS for published PRS and cohorts used in validation studies. Additionally, PGS catalog, in collaboration with the Clinical Genome Resource (ClinGen) Complex Disease Working Group, published a comprehensive reporting framework based on input from experts on epidemiology, statistics, disease-specific applications, implementation and policy, to improve reporting standards for PRS studies including an emphasis on definition and reporting of ancestry in study populations [69]. Following these guidelines, future studies should include relevant aspects of model performance for PRS.

Additionally, to quantify polygenic risk in an individual, one must determine where an individual's PRS falls within a representative cohort of the respective ancestry group while accounting for population structure [73]. Wang et al. [43] sequenced a group of individuals drawn from a population-based cohort and used principal components of ancestry to adjust the raw PRS_{CHD} for population structure, thus creating a reference PRS distribution. As a result, a newly genotyped individual could have an ancestry adjusted PRS_{CHD} along with its percentile rank in the general population based on the built reference distribution (Fig. 1c). In conjunction with a risk calculator integrating both genetic and environmental risk factors, such frameworks can streamline the entire process starting from genotyping to calculation of 10-year risk estimation for CHD and facilitate PRS interpretation in the clinical setting [73].

For translation of PRS from bench to bedside, risk prediction models will need to incorporate both genetic and non-genetic (i.e., environmental) risk factors and use reference frameworks to account for population structure in order to generate ancestry-specific absolute risk of cardiovascular disease [74] (Fig. 1c and d) that can inform screening/diagnostic workup and selection of treatment modalities [17•, 24, 75].

Conclusions

PRSs can be integrated into clinical risk prediction tools to refine risk estimates of future cardiovascular events. Such clinical risk prediction tools should estimate ancestry specific absolute risk to guide clinical decision making in primary prevention of CHD. PRSs perform robustly in EUR populations but lag in performance across non-EUR groups, particularly individuals of African descent. The use of EUR-derived PRS for non-EUR populations (except African ancestry) is an alternative until the availability of mature trans-ancestry or ancestry-specific PRSs for CHD. Ongoing efforts to assemble large and diverse consortia to power future genomic studies, and innovation in PRS methodologies for multi-ancestry applications, will be necessary for equitable implementation of genomic medicine globally and fulfill the promise for precision medicine.

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Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

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