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Polygenic Risk Scores for Cardiovascular Disease: A Scientific Statement From the American Heart Association

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Abstract

Cardiovascular disease is the leading contributor to years lost due to disability or premature death among adults. Current efforts focus on risk prediction and risk factor mitigation, which have been recognized for the past half-century. However, despite advances, risk prediction remains imprecise with persistently high rates of incident cardiovascular disease. Genetic characterization has been proposed as an approach to enable earlier and potentially tailored prevention. Rare

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mendelian pathogenic variants predisposing to cardiometabolic conditions have long been known to contribute to disease risk in some families. However, twin and familial aggregation studies imply that diverse cardiovascular conditions are heritable in the general population. Significant technological and methodological advances since the Human Genome Project are facilitating population-based comprehensive genetic profiling at decreasing costs. Genome-wide association studies from such endeavors continue to elucidate causal mechanisms for cardiovascular diseases. Systematic cataloging for cardiovascular risk alleles also enabled the development of polygenic risk scores. Genetic profiling is becoming widespread in large-scale research, including in health care–associated biobanks, randomized controlled trials, and direct-to-consumer profiling in tens of millions of people. Thus, individuals and their physicians are increasingly presented with polygenic risk scores for cardiovascular conditions in clinical encounters. In this scientific statement, we review the contemporary science, clinical considerations, and future challenges for polygenic risk scores for cardiovascular diseases. We selected 5 cardiometabolic diseases (coronary artery disease, hypercholesterolemia, type 2 diabetes, atrial fibrillation, and venous thromboembolic disease) and response to drug therapy and offer provisional guidance to health care professionals, researchers, policymakers, and patients.

Keywords

AHA Scientific Statements; atrial fibrillation; diabetes, type 2; genome-wide association studies; multifactorial inheritance; predictive genetic testing; venous thromboembolism

Cardiovascular disease is the leading cause of morbidity and mortality in the United States and globally.[1] In the United States, 121.5 million people have cardiovascular disease[1] and 26 million have diabetes (estimates from 2013 to 2016 data), each with continually increasing prevalences.[1] Furthermore, cardiovascular diseases and their complications contribute to the substantial and ever-increasing health care costs in the United States.[1]

In an effort to reduce cardiovascular disease prevalence and its complications, much effort has focused on prevention.[2] The cornerstone of prevention is early risk prediction coupled with risk mitigation. The Framingham Risk Score, now nearly 25 years old, represents an early example of synthesizing multiple clinical risk factors into a single estimated risk for coronary artery disease (CAD) and stroke.[3,4] With the incorporation of additional cohorts, including individuals of non-European ancestry, the Pooled Cohort Equations (PCE) provide the contemporary 10-year risk estimator for atherosclerotic cardiovascular disease (ASCVD) recommended by cardiovascular professional societies in the United States.[5,6] However, the PCE may systematically underperform in some groups and has reduced discrimination among younger adults and older adults.[7–11]

Incorporation of genetics into risk prediction frameworks offers the opportunity to refine risks, potentially earlier in life, toward the creation of earlier and tailored risk reduction strategies.[11a] Having a parent with a history of premature CAD is associated with an ≈50% higher odds of developing cardiovascular disease independent of clinical risk factors.[12] Furthermore, twin studies (comparing monozygotic twins with dizygotic twins) have shown that variation in the development of CAD,[13] atrial fibrillation (AF),[14] and diabetes[15,16]

is attributable to common genetic variations. These observations support the notion that genetics may be additive in risk prediction.[13,14,16,17]

Monogenic risk variants (defined in Table 1) are typically rare and confer a large risk of disease (such as low-density lipoprotein [LDL] receptor variants causing familial hypercholesterolemia [FH]).These variants have been recognized for decades and represent the current scope of clinical cardiovascular genetics.[18] However, monogenic risk variants are present in only a small minority of patients and explain only a small proportion of heritable cardiovascular disease risk in familial aggregation studies (eg, many families do not have monogenic variants and still have cardiovascular disease).[19,20] This phenomenon, as well as evidence from twin studies,[21] supports the polygenic basis of the development of cardiometabolic diseases: Common genetic variation (ie, present in at least 1% of the population) contributes substantially to risk.

Indeed, over the past 15 years, increasingly larger genome-wide association studies (GWAS) have confirmed the polygenic basis of cardiometabolic diseases. GWAS has shown that many single nucleotide variants (SNVs) scattered across the genome are associated with many cardiometabolic diseases. Each of these variants is of individually small risk, but collectively, they account for substantial cardiovascular disease risk.[20,22,23]

GWAS showed the association of many SNVs and cardiometabolic disease. Polygenic risk scores (PRSs; also known as polygenic scores) are the weighted summations of these SNVs. The summation of these SNVs (eg, PRS) has been shown to confer significant risk (Figure 1). For multiple cardiovascular diseases, PRSs are independently associated with respective cardiovascular diseases.[20] Thus, PRSs are proposed as tools to improve the prediction of common, complex cardiovascular diseases.[24]

Universities, academic medical centers, and direct-to-consumer genetics companies are now able to provide PRSs to research participants, patients, and consumers.[25,26] This scientific statement reviews the current science, clinical implementation considerations (eg, efficacy and cost) across stakeholders (health care professionals, patients, and health care administrators), and outstanding questions about the clinical use of PRSs for selected cardiovascular diseases. We focus on 5 cardiometabolic diseases (CAD, hypercholesterolemia, type 2 diabetes [T2D], AF, and venous thromboembolic disease) and offer provisional guidance to health care professionals, researchers, policymakers, and patients on the use of PRSs in cardiovascular disease risk assessment and risk reduction.

In line with the National Heart, Lung, and Blood Institute 2020 guidelines on the use and reporting of race, ethnicity, and ancestry[27] and the American Heart Association (AHA) presidential advisory on structural racism,[28] throughout this scientific statement, we use the term ethnicity to refer to social categories including both race and ethnicity. We support the AHA presidential advisory definition of race as "a social construct primarily based on phenotype, ethnicity, and other indicators of social differentiation that results in varying access to power and social and economic resources."[28] The term ancestry is used for inferences from genetic data. When we state the ethnicity or ancestry of participants, we

attained this information directly from the primary literature. Last, we note that the concepts of ethnicity and ancestry are not synonymous but may be correlated.[29]

WHAT ARE PRSs?

PRSs (or polygenic scores) are the weighted sum of the risk conferred by multiple disease-associated SNVs across the genome. Constructing a PRS requires a list of SNVs with their accompanying effect sizes (a quantification of the association of the SNV with the disease) from an external data set, typically acquired from a GWAS (Figure 1). Next, methods are used to account for the extensive correlation between SNVs throughout the genome (known as linkage disequilibrium [LD]).[18] Common methods include *P* value thresholding (only including SNVs that are below a predefined *P* value), LD pruning (randomly removing a SNV from a pair that are in LD, in which LD is typically classified by the correlation between SNVs, quantified by r^2), and clumping (similar to LD pruning but the SNVs with the lower *P* value [of the pair] is selected). All of these earlier methods exclude several SNVs on the basis of an arbitrarily selected *P* value threshold or at random. Advances in statistical genetics have led to a number of new methods that do not exclude SNVs. These methods include bayesian approaches (such as LDpred,[22] Bayesian Sparse Linear Mixed Models,[30] AnnoPred,[31] LDpred-funct,[32] PRS-CS,[33] and PleioPred[34]) and penalized regression (Lassosum[35]) and include all SNVs but with reweighted effect sizes baselined on at least the *P* and r^2 values.

Current research is focused on ensuring equity of PRS use and predictive ability across all ancestry groups. Transethnic PRSs from meta-analyses of GWAS across multiple ancestries may help with portability.[36,37] Large biorepositories such as the UK Biobank, Million Veteran Program, and Electronic Medical Records and Genomics Network have aided in the performance of high-throughput and high-sample-size genome-wide discovery efforts of a wide range of cardiometabolic disease.[20,38] In addition, biobanks located in areas with higher levels of ancestry diversity have contributed a critical view of genetic association in understudied populations.[39,40]

POLYGENIC VERSUS MONOGENIC RISK VARIANTS

Monogenic risk variants are rare (minor allele frequency <1%, defined as the frequency of the second most common allele that occurs within a selected population[41]) and are typically disruptive or truncating coding sequence variants that confer a large risk of disease. In this scientific statement, rare variants are denoted as minor allele frequency <1%; common polygenic risk variants are denoted as minor allele frequency ≥1%. Monogenic risk variants follow classic mendelian patterns of inheritance. For example, monogenic risk variants in the genes encoding the LDL receptor (*LDLR*), apolipoprotein B (*APOB*), and proprotein convertase subtilisin/kexin type 9 (*PCSK9*) are examples of causes of FH, a monogenic disease that causes severe hypercholesterolemia and is a significant risk factor for early-onset myocardial infarction.[42–45] Other examples of monogenic risk variants include variants in *GCK* for diabetes,[46] *KCNQ1* for AF,[47] and *F5* for venous thromboembolic disease.[48,49]

The risk of developing a disease is influenced by both monogenic and polygenic risk variants. In those with FH monogenic risk variants, LDL cholesterol (LDL-C) concentrations varied, as did their risk of developing CAD. This variation aligned each participant's LDL-C PRS; that is, those with a low LDL-C PRS and monogenic FH had, on average, lower LDL-C and a lower risk of CAD compared with those with a high LDL-C PRS and monogenic FH.[19,50] This concept has also been extended to cardiomyopathies; for example, the risk of developing hypertrophic cardiomyopathy depends on monogenic risk variants (eg, *MYH7*) and a person's PRS.[51] These observations support the liability threshold model, that is, the notion that multiple factors—monogenic, polygenic, and nongenetic—may each contribute to a threshold necessary for disease development.[18]

Because genetic testing for monogenic causes of suspected inherited cardiovascular conditions was covered in a prior scientific statement,[52] we focus on PRSs in the present scientific statement.

Atrial Fibrillation

AF is the most prevalent cardiac arrhythmia in the United States, with >12 million individuals projected to be diagnosed with AF by 2030.[1,53] AF prevalence increases with age and commonly coexists with other cardiovascular diseases.[54] It is a well-recognized independent risk factor for stroke[55] and can contribute to and worsen heart failure.[56]

Although many common cardiovascular diseases are risk factors for developing AF,[57] genetic variation also has been shown to contribute.[20,58] Loss-of-function variants in the Titin (*TTN*) gene are enriched among individuals with early-onset AF (2.1% prevalence) versus control subjects (1.1% prevalence; odds ratio, 1.76 [95% CI, 1.04–2.97]).[59,60]

Common genetic variation also contributes to AF risk. The first appreciation of this was in twin studies, which showed that the likelihood of developing AF was higher in monozygotic twins compared with dizygotic twins (hazard ratio [HR], 2.0 [95% CI, 1.3–3.0]).[14] More recently, 134 distinct AF-associated loci have been identified through GWAS meta-analyses, all of which are common and of individually small effect.[61,62]

The increasing number of common genetic variants associated with AF has enabled the development of AF PRSs (Table 2).[23,63] PRSs constructed to date have shown a consistent predictive benefit (C statistic, or area under the receiver-operating characteristics curve [AUC], varying from 0.61–0.78).[20,23,64–69] Recent advancement in statistical methods, most notably the liberalizing of included SNVs in PRSs, has led to increased predictive accuracy (see the What Are PRSs? section).[23,64,65] These improvements contributed to the accuracy of risk prediction in 2 ways. First, they improve the accuracy of the prediction of AF in the absence of clinical risk factors (eg, early-onset AF). Second, they enhance prediction when PRSs and clinical risk factors are combined. Concerning the latter, AF prediction is improved with the addition of PRSs to clinical risk factors (age, height, weight, systolic and diastolic blood pressures, smoking status, blood pressure–lowering medication, diabetes, heart failure, and history of myocardial infarction) through both discrimination (the C statistic changed from 0.725 [95% CI, 0.719–0.732] to 0.734 [95% CI, 0.728–0.741]) and reclassification (net reclassification index [NRI], 10% (95% CI, 4.2%–15.7%]) metrics

(Figure 2).[23,63] Concerning the former, PRSs are consistently predictive of early-onset AF[23,70]; 1 study showed that those in the top 10th percentile of PRS risk had an odds ratio of 5.70 (95% CI, 2.60–13.95) for developing early-onset AF compared with those in the bottom 90th percentile of PRS risk.[70] Another study showed that those in top 2.5th percentile of PRS risk developed the disease ≈6.64 years before those in the 20th to 80th percentile.[23] Similarly, of those who developed AF before 60 years of age, 27.9% were at high PRS risk (>5% 5-year risk of developing AF determined by the PRS model only), whereas only 4.9% of these participants with early AF were deemed high risk by the common clinical risk tool, CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology model for AF).[23]

Diversity of included participants remains an issue; only 1 study of AF PRS focused primarily on non-European participants. This study included Japanese participants and showed results consistent with the studies focused on Europeans (the AUC for the model combining clinical risk factors and PRSs in Japanese participants was 0.84 [95% CI, 0.80–0.86], 6% higher than the model including clinical risk factors alone without PRS).[64]

In addition to the prediction of AF, AF PRSs may have a role in the prediction of AF-associated complications such as ischemic stroke.[71] Evidence from GWAS shows a shared genetic cause between AF and ischemic stroke: Loci at the *PITX2* and *ZFHX3* genes are associated with risk of AF and ischemic stroke.[72,73] Several AF PRSs are predictive of stroke.[62,74,75] Similarly, ischemic stroke PRSs appear to be predictive of strokes specifically in patients with AF, even beyond conventional clinical risk factors (eg, CHA_2DS_2-VASc score).[71] Early analyses of the ability of PRSs to predict AF recurrence are inconclusive, with larger studies likely required to investigate whether PRSs play a role.[69]

For adult patients, established AF risk prediction tools (CHARGE-AF[76]) are improved with the addition of PRSs (across sexes and age groups [18–85 years]; Figure 2).[23] Furthermore, given the lack of clinical risk factors, only PRSs can predict the development of early-onset AF.[23,70] Future studies should focus on AF surveillance and risk mitigation strategies for high AF PRSs, as well as cost-effectiveness. The decreasing costs of genetic testing and the ability to calculate PRSs for a large number of diseases from 1 test increase the likelihood of cost-effectiveness, but this is yet to be formally studied for AF.

Coronary Artery Disease

Given the aggregation of CAD in families, particularly when occurring earlier in life, genetic variation has long been expected to influence CAD risk.[77] CAD heritability, or the proportion of phenotype explained by the additive sum of genetic factors, is estimated to be 40% to 60%.[13,78]

FH is a well-recognized monogenic condition.[44] Retrospective analyses indicate that those with FH variants have a greater relative and absolute clinical benefit from statins for the prevention of incident CAD.[79] Current guidelines and US Food and Drug Administration (FDA) labels support additionally aggressive pharmacological LDL-C lowering among individuals recognized to have FH.[80]

GWAS of CAD in the general population has shown that common genetic variation also influences the risk for CAD.[81] Increasingly large CAD GWAS continues to identify novel genomic loci; 167 separate genomic loci have been identified to be significantly associated with CAD to date.[82] Systematic pleiotropy analyses indicate that the majority of these loci do not influence CAD risk through well-recognized risk factors.[83]

The discovery of common genetic variants associated with CAD has enabled the development of PRSs for the prediction of CAD (Table 2).[23,63] Initial PRSs focused on the simple summation of significantly associated independent CAD risk alleles, and subsequent PRSs weighted these alleles by predicted CAD effects. Contemporary scores have focused on liberalizing variant inclusion through varied statistical approaches.[20,38] Scores have been shown to be strong predictors of subclinical coronary atherosclerosis and independently prognostic of CAD risk (1.4- to 1.6-fold per SD of the CAD PRS), including self-reported family history and comparable or more powerful predictors of CAD than individual clinical risk factors (smoking, T2D, lipid measures, hypertension; Figure 3).[20,23,38,63,84–88] Because the top fifth percentile of CAD PRS is associated with an 8–mg/dL increase in LDL-C, conventional clinical risk scores do not readily detect high CAD PRSs.[85,89] Furthermore, the top 95th percentile (1 in 20) of a CAD PRS score is associated with a 3-fold odds for CAD, similar to that associated with FH (1 in 313) without accompanying severe hypercholesterolemia.[20,85] Furthermore, in analyses among individuals with prevalent ASCVD, a CAD PRS was independently associated with incident major cardiovascular events (1.1- to 1.2-fold per SD of the CAD PRS).[90–92] An initial study in ARIC (Atherosclerosis Risk in Communities) and MESA (Multi-Ethnic Study of Atherosclerosis; n=7237) showed little improvement in the C statistic with the addition of PRSs to PCE to predict incident events.[93] More recent studies using more contemporary statistical approaches and validation in larger cohorts (n=352 660 and n=≈250 000) have shown slightly greater performance.[63,94] Furthermore, it is likely that different age groups will derive varying benefit from PRSs. For example, NRI reached a peak of 15.4% (95% CI, 11.6%–19.3%) for younger subgroups and an improvement of the C statistic of 5% (0.05 [95% CI, 0.03–0.07]).

Although they represent vastly different technologies, comparisons are often made with coronary artery calcium (CAC) scoring and PRSs. These diagnostic approaches have not been compared directly. However, data suggest that both technologies improve the predictive accuracy of clinical risk factors alone (PCE),[63,95] and their predictable abilities appear to be at least comparable. For example, in a cohort of 1688 middle-aged adults, CAC scoring improved prediction when combined with the PCE: the C statistic increased from 0.633 with clinical risk factors alone (PCE) to 0.678 with PCE and CAC (ΔC, 0.045 [95% CI, 0.015–0.101]). Furthermore, there was significant improvement in NRI when CAC was added to the PCE: NRI, 6.7% (95% CI, 1.8%–11.6%).[95] In comparison, a recent PRS validated in 186 451 participants showed that the C statistic increased from 0.76 with clinical risk factors alone (PCE) to 0.79 (ΔC, 0.03 [95% CI, 0.02–0.04]), and there was significant improvement in NRI when combined with the PCE (C statistic, 0.76 [95% CI, 0.75–0.76]; NRI, 5.8% [95% CI, 4.7%–7.0%]).[63] These data were ascertained from different cohorts of varying sample sizes and not directly compared. Evidence also suggests a correlation between PRS

and CAC scores.[96,97] This indicates that stratified use of the respective technologies may be beneficial, but this topic requires further prospective study.

Observational analyses in epidemiological studies or post hoc analyses within completed randomized controlled trials for CAD prevention have yielded hypotheses for strategies to reduce CAD risk in the setting of a high CAD PRS. Because a CAD PRS is largely additive of nongenetic factors, adherence to a healthful diet mitigates CAD risk regardless of CAD PRS; however, given the worse prognosis, the absolute risk reduction from a healthful diet among those with a high CAD PRS may be greater than for those without a high CAD PRS.[88,98] In a single-arm study, disclosure of a higher CAD PRS may influence favorable lifestyle behaviors.[99] Beyond lifestyle changes, it appears that PRS risk correlates with medication efficacy. Subgroup analyses in primary prevention statin trials indicated that those with high CAD PRS versus others derived greater relative and absolute clinical benefit from statins versus placebo (46% versus 26%; $P_{heterogeneity}$=0.05) without differences in LDL-C reduction.[86,91] Similarly, among individuals with established ASCVD on statins, greater benefit from PCSK9 monoclonal antibodies was observed among those with high versus low CAD PRS (37% versus 13%; $P_{interaction}$=0.04).[90,92] Data exploring the correlation between PRS and medication efficacy are further explored in the PRSs for Pharmacogenomics section. Similarly, a healthy lifestyle has been shown to reduce disease risk across all deciles of PRS risk, although the greatest reductions are in those with highest PRS risk.[100] A randomized controlled trial among patients without CAD showed that disclosure of a high CAD PRS versus low CAD PRS or no PRS disclosure to patients and clinicians led to lower LDL-C concentrations.[101]

The integration of PRS for CAD into clinical practice will likely rely on its inclusion in current cardiovascular risk prediction tools. Currently, the AHA, American College of Cardiology (ACC), and many other international organizations recommend determining the 10-year cardiovascular risk for all adult patients 40 to 75 years of age with the AHA/ACC ASCVD risk calculator.[2] For adult patients, the addition of PRS to the AHA/ACC ASCVD risk calculator significantly improves prediction for cardiovascular events (Figure 2).[23,38,63,89,94] This enhanced prediction is independent of conventional clinical risk factors (Figure 3), is detectable before the emergence of clinical risk factors, and is appreciable across a spectrum of ages, sexes, and, increasingly, ancestries and ethnicities (South Asian, Black/African American/Black Caribbean/Black African, Chinese, and Japanese).[23,36,38,63,84,94,102,103] The inclusion of PRS in the AHA/ACC ASCVD risk calculator significantly improves prediction, and early evidence suggests that targeted screening may be cost-effective (further discussed in the Considerations for Payers section),[104] particularly because evidence suggests that conventional tools are missing participants at high PRS risk.[89]

Among asymptomatic middle-aged adults at borderline/intermediate risk by conventional clinical risk factors, a high CAD PRS has been shown to aid in reclassifying statin prescriptions.[89] Among asymptomatic younger adults, a high CAD PRS may prompt more intensive earlier efforts for lifestyle modification and potentially earlier statin initiation akin to severe hypercholesterolemia to mitigate high lifetime risk for CAD.[105]

Hypercholesterolemia

Lipids, or cholesterol and triglycerides, are carried in the blood by lipoprotein macromolecules such as LDL and high-density lipoprotein. The properties of circulating lipoproteins are dictated by the relative concentrations of cholesterol, triglycerides, phospholipids, and proteins and biochemical alterations thereof. A reduction of apolipoprotein B–containing lipoproteins such as LDL-C is associated with a reduction in major adverse cardiovascular disease events through multiple pharmacological classes in randomized controlled clinical trials.[37,106–109]

Common genetic variants, summed as a PRS, can also predict lipid concentrations (Table 3). For example, the top 95th percentile of an LDL-C PRS carries an LDL-C effect (≈30 mg/dl) similar to that in individuals with an FH variant among those of European ancestry. Among those with severe hypercholesterolemia, 2% have an FH variant, whereas 23% are in the top fifth percentile of an LDL-C PRS.[111] Furthermore, an LDL-C PRS explains some variation in LDL-C concentrations among individuals with FH variants.[50]

LDL-C PRSs, in addition to predictive LDL-C concentrations, are predictive for ASCVD events.[19,112] Recent work has indicated that an LDL-C PRS may predict ASCVD event risk in addition to cross-section LDL-C measures. Among nearly 49 000 participants of the UK Biobank, ASCVD risks were compared for those with FH variants, the top 95th percentile of an LDL-C PRS, and those with hypercholesterolemia to a similar degree without the aforementioned genetic factors.[113] Compared with nongenetic hypercholesterolemia, FH and polygenic hypercholesterolemia were associated with a 1.93- and 1.26-fold risk, respectively, for ASCVD events (coronary and carotid revascularization, myocardial infarction, ischemic stroke, and all-cause mortality).

LDL-C PRSs have also been correlated with risks for other cardiovascular disease, including aortic stenosis,[114] abdominal aortic aneurysm, peripheral arterial disease, and venous thromboembolic disease.[110] However, the prognostic capabilities of LDL-C PRSs that are independent of LDL-C measurement for these conditions have not been well studied to date.

PRSs for other lipid fractions also have been evaluated for ASCVD risk prediction. High-density lipoprotein cholesterol PRSs have limited prognostic utility for ASCVD prediction. Although triglyceride PRSs generally support an association with CAD events, the clinical utility of a triglyceride PRS is not well established. Lipoprotein(a) is a highly heritable LDL-like lipoprotein, additionally harboring apolipoprotein a, which is independently predictive of ASCVD events.[115] An *LPA* PRS is strongly predictive of both lipoprotein(a) and ASCVD events.[116] In fact, an *LPA* genetic risk score performs similarly to lipoprotein(a) measurement for the prediction of CAD events.[117]

For individuals undergoing genetic testing for severe hypercholesterolemia, comprehensive evaluation for monogenic and polygenic determinants will increase genetic testing diagnostic yield compared with FH gene panel testing alone and may refine CAD risk prediction beyond conventional lipid measures. Lipid and CAD PRSs will likely have distinct yield, according to the presence and extent of hypercholesterolemia. Both may have roles in identifying individuals for whom aggressive and early lipid-lowering therapies are

indicated; this hypothesis requires prospective evaluation. Future work focusing on lipid and lipoprotein PRSs in the context of therapeutic interventions may better clarify clinical relevance.

Type 2 Diabetes

Epidemiological research has long appreciated the clustering of T2D within families.[16] The scientific pursuit of monogenic causes of T2D has identified some causal genes (eg, peroxisome proliferator-activated receptor γ [*PPARG*])[118]; however, recent GWAS has revealed that a polygenic, rather than monogenic, predisposition accounts for substantially more T2D heritability.[119]

The advent of GWAS revealed the polygenic architecture of T2D,[119,120] which, in turn, facilitated the development of PRSs for T2D.[20,121] Early T2D PRSs showed the predictive ability of summated genetic loci.[122] With increasing GWAS sample sizes and improvements in PRS methodology, recent T2D PRSs have become more accurate (Table 2).[20,23,63,121] For instance, a 2018 meta-analysis of 32 GWAS including participants of exclusively European ancestry included 171 249 variants and showed a 9-fold increase in risk between the lowest 2.5% and the highest 2.5% PRSs.[121] This same study showed that T2D prediction with PRS alone was similar to the prediction from body mass index, age, and sex (AUC reported as 66% for both, no 95% CI reported). Similarly, a 2018 study of participants of European ancestry in the UK Biobank included 6 917 436 variants and showed a linear increase in risk with higher PRS[20]; participants in the highest 10% PRS had a 2.5-fold risk, and participants in the highest 1% PRS were at a 3.3-fold risk (compared with the remaining 90% and 99%, respectively). This same study showed an AUC of 0.72 (95% CI, 0.72– 0.73) for PRS (inclusive of age, sex, genotyping array, and the first 4 principal components of ancestry as covariates).[20] Last, a 2020 study showed those in the top 2.5th percentile risk were at 3.5-fold increased risk compared with those in the middle 20th to 80th percentile risk, and those in the bottom 2.5th percentile risk had an ≈80% reduction in lifetime risk compared with the middle 20th to 80th percentile risk.[23] This same study showed a modest improvement in risk prediction when PRS was added to clinical risk factors: The C statistic modestly improved from 0.84 (95% CI, 0.83–0.84) with clinical risk factors only to 0.85 (95% CI, 0.84–0.85) with the inclusion of PRS.[23] This same study showed more convincing improvement in prediction with the NRI metric: The addition of PRS to the above American Diabetes Association clinical risk factors criteria showed an NRI of 4.5% (95% CI, 3.0%–6.1%; Figure 2).[23] Although older studies previously showed little improvement in discrimination compared with cumulative clinical risk factor models, more recent studies, substantially improved with the inclusion of a larger number of SNVs and trained on a larger sample size, showed improvement in prediction with the inclusion of PRS.[122–124] For example, a 2010 study that used a 40-SNV PRS[123] reported an AUC of 0.54 (95% CI, 0.50–0.58) compared with a 2020 study that used a 6 437 380–SNV PRS (0.763 [95% CI, 0.758–0.767]).[23]

Nevertheless, the early identification of those at high risk of T2D is just one potential application of PRS and one that remains of unclear therapeutic value. Whether determined by clinical or genetic risk (or both), the primary benefits of early identification of T2D

risk are targeted prevention through lifestyle modification and more rigorous surveillance. Recent evidence suggests that stratifying risk by PRS may help identify high-risk subgroups for whom successful lifestyle modification is associated with greater absolute reduction in the risk of incident diabetes.[125] However, older evidence suggests more modest effects across T2D PRS strata.[98,126] Therefore, it may be argued that those who are identified as high risk through PRSs should be screened at a younger age or at more frequent intervals, but data supporting the use of PRSs for this application are needed.

A T2D PRS may also predict treatment responsiveness. This is further described in the PRSs for Pharmacogenomics section. In brief, a 2020 study showed that participants with a higher T2D PRS had greater reductions in hemoglobin A1c (HbA1c) in response to sulfonylurea therapy (P=0.02).[127] The authors also investigated the relationship between PRS and glycemic surrogates of metformin response but found no association.[127]

In regard to glycemic control, a 2016 study showed that a PRS modified the effect of intensive glycemic control on cardiovascular mortality in the ACCORD randomized trial (Action to Control Cardiovascular Risk in Diabetes)[128]: Participants with a high T2D PRS were found to have a 3-fold risk of cardiovascular mortality with intense glycemic control (HR, 3.08 [95% CI, 1.82–5.21]), whereas those with a low T2D PRS had a substantial mortality benefit from intensive glycemic control (HR, 0.24 [95% CI, 0.07–0.86]).[128]

This application of genetic data to guide risk stratification of T2D complications and treatment response mirrors efforts to cluster patients with T2D with the use of clinical factors, which has demonstrated some early promise for guiding clinical care.[129,130] Five genetically defined subtypes of diabetes (severe autoimmune diabetes, severe insulin-deficient diabetes, severe insulin-resistant diabetes, mild obesity-related diabetes, and mild age-related diabetes)[131] have distinct underlying pathophysiologies with varying diabetes-associated complications.[130,132]

The predictive accuracy of the American Diabetes Association risk tool is increased with the addition of a PRS.[23] The cost-effectiveness of screening remains less clear. Although the cost of genetic testing continues to fall, the effect of therapies that may be offered to those at high risk remains an active area of research. Given that an advantage of PRS is the possibility to calculate numerous PRSs from 1 test, cost-effectiveness analyses that consider risk prediction of both CAD and T2D may be advantageous (because the cost of a PRS to calculate a number of diseases will be the same as the cost to calculate 1 disease). Furthermore, a scientific opportunity remains for PRSs to help personalize T2D pharmacological management in terms of medication responsiveness and earlier prevention of microvascular and macrovascular complications.

Venous Thromboembolic Disease

Acute venous thromboembolism (VTE), which comprises deep venous thrombosis and pulmonary embolism, occurs in around 1000 000 individuals yearly in the United States[1] and is the among the leading causes of acquired harm and preventable death in hospitalized patients.[133] Although inherited monogenic thrombophilias (eg, factor V Leiden and prothrombin G20210A) increase the relative risk of VTE by ≈3- to 5-fold, the role of

genetic testing in informing therapy has remained limited[134,135] because of uncertainties about the effects of inherited thrombophilias on recurrent VTE risk,[136–138] the lack of data demonstrating that thrombophilia testing improves outcomes,[139] and the risks of prolonged anticoagulation.

Recent advances in the genetics of VTE have produced increasingly robust GWAS summary statistics enabling the development of PRS predictive of VTE. With the use of summary statistics from a GWAS comprising 30 234 VTE cases, a 37-variant VTE PRS was recently constructed (Table 3).[140] Among 6573 cases and 20 515 controls from the UK Biobank, individuals in the lowest fifth percentile of genetic risk had a 50% lower odds of having had VTE (odds ratio, 0.51 [95% CI, 0.42–0.6]), and those in the upper 95th percentile had a 3.2-fold odds of having had VTE (odds ratio, 3.2 [95% CI, 2.9–3.5]) compared with those in the intermediate range. Similarly, another recent analysis of 26 066 separate VTE cases ultimately yielded a 297-variant PRS for VTE, inclusive of many of the SNVs or correlated SNVs in the 37-variant score.[110] After exclusion of the factor V Leiden and prothrombin G20210A variants, the 297-variant PRS was applied to an independent set of 2100 cases with VTE and 53 865 VTE controls.[110] In the same study, across 10 975 women in the Women's Health Initiative with 690 incident VTE events over 25 years, the women in the top 95th percentile of polygenic risk had a 2.5-fold risk of incident VTE (HR, 2.5 [95% CI, 2.0–3.2]); this was comparable in effect size to the risk conferred by factor V Leiden (HR, 2.4 [95% CI, 1.9–3.4]) and prothrombin G20210A (HR, 3.3 [95% CI, 1.1–10.2]).[110]

Current guidelines recommend prophylactic anticoagulation for patients with factor V Leiden in certain clinical situations (surgery, hospitalization, peripartum, and postpartum).[141] Given the comparable risk of factor V Leiden and those at highest PRS risk, future research could examine whether there are groups who would benefit from VTE PRS–aided use of prophylactic anticoagulation in high-risk scenarios. Furthermore, future studies can examine the predictive performance of the current risk scores (the Padua score for medical inpatients[142] and the Caprini score for surgical inpatients[143]) with the integration of PRS. Because prophylaxis for VTE is generally anticoagulation, the potential risks should also be studied in prospective studies.

PRSs FOR PHARMACOGENOMICS

Evidence supporting PRSs for cardiovascular pharmacogenomics is evolving. Until recently, candidate gene studies including only 1 or a few genes have been the focus of most pharmacogenomic research studies[144–146] and clinical implementation programs.[147] The development of pharmacogenomic PRSs has been hindered by unique challenges for pharmacogenomic GWAS such as securing adequate sample sizes of patients treated with the same drug, along with the necessary drug and phenotypic data (eg, dose, frequency, adherence, drug response metrics).[148] Large consortia are working toward overcoming this barrier (eg, International Clopidogrel Pharmacogenomics Consortium[149] and International Warfarin Pharmacogenetics Consortium[150]). Researchers are also using creative approaches to calculate pharmacogenomic PRSs such as scanning multiple candidate genes[151,152] or testing disease-associated PRSs for associations with cardiovascular drug responses.[86,91]

These efforts have led to several currently published studies applying PRSs to cardiovascular pharmacogenomics.

These pharmacogenomic PRSs have been applied with 4 different goals: (1) predicting drug efficacy, (2) predicting drug toxicity, (3) reviving drugs that failed in clinical trials (ie, by finding a genetic subgroup of responders, although successful examples have not been demonstrated to date), and (4) predicting adverse cardiovascular reactions for noncardiovascular drugs. For the prediction of drug efficacy, the strongest evidence currently supports PRSs predicting statin response. A PRS predictive of CAD risk also predicted the absolute and relative benefit from statins for the primary and secondary prevention of CAD.[86,91] Similarly, a 2019 study showed that patients with a high PRS for CAD had a larger risk reduction (absolute and relative) in major adverse cardiovascular events and death when treated with alirocumab (a PCSK9 inhibitor): Participants at high PRS risk (>90th percentile) had a 6% absolute reduction (95% CI not reported) compared with a 1.5% absolute reduction in those at low PRS risk (≤90th percentile).[90] Participants at high PRS risk had a relative risk reduction by alirocumab of 37% (HR, 0.63 [95% CI, 0.46–0.86]) compared with a 13% reduction in the low-PRS group (HR, 0.87 [95% CI, 0.78–0.98]).[90] A 2020 study of another PCSK9 inhibitor, evolocumab, found a similar relationship in which patients with higher PRS risk benefited more from evolocumab therapy.[92] The absolute risk reduction for major vascular events improved significantly across an increase in the genetic risk category: 0.7%, 0.9%, and 4.0% absolute risk reduction in low-, intermediate-, and high-genetic-risk groups, respectively (P_{trend}=0.04). Participants at high PRS risk had a relative risk reduction by evolocumab of 31% (HR, 0.69 [95% CI, 0.55–0.86]) compared with 9% (HR, 0.91 [95% CI, 0.79–1.03]) in the intermediate-PRS-risk group and 8% in the low-PRS-risk group (HR, 0.92 [95% CI, 0.72–1.18]; P_{trend}=0.07).

Beyond CAD, there is also a building body of evidence to support the correlation between T2D PRS and treatment responses. A 2020 study showed that a T2D PRS was predictive of a reduction in HbA1c in patients taking a sulfonylurea[127]; for every 1-SD increase in T2D PRS, there was a 0.06% (0.07 mmol/mol) decrease in HbA1c level in response to sulfonylurea therapy (P=0.02).[127] Similarly, participants in the highest decile of the T2D PRS had a 0.27±0.12% greater HbA1c reduction compared with those in the lowest decile (P=0.03).[127] The authors also investigated the relationship between PRS and glycemic surrogates of metformin response but found no association.[127]

Evidence also supports PRS predicting clinical benefit from β-blockers (predicting survival benefit in patients with heart failure with reduced ejection fraction),[153] angiotensin-converting enzyme inhibitors (predicting cardiovascular mortality, nonfatal myocardial infarction, or resuscitated cardiac arrest),[154] calcium channel blockers (predicting all-cause death, nonfatal myocardial infarction, or nonfatal stroke),[155] and clopidogrel (predicting ischemic events and cardiovascular mortality).[152] These PRSs for clinical responses to β-blockers, angiotensin-converting enzyme inhibitors, and calcium channel blockers were not based on disease PRS; rather, they were derived from drug×SNV interaction tests for clinical outcomes in GWAS or multiple candidate genes. The PRS for clopidogrel was also not derived from disease PRS but rather candidate SNVs independently associated with high on-clopidogrel platelet reactivity.

A further study assessed the ability of a PRS derived from a GWAS of the QT interval to predict the outcome of drug-induced QT interval prolongation and torsades de pointes,[156] demonstrating the potential for PRSs derived from intermediate phenotypes to predict cardiovascular drug toxicities. PRSs have also been used in an attempt to revive a drug that failed in clinical trials. However, a CAD PRS did not successfully identify a genetic subgroup of patients who benefited from evacetrapib, a cholesterol ester transfer protein inhibitor.[157]

CONSIDERATIONS FOR HEALTH CARE SYSTEMS

Criteria for Implementing PRSs in Cardiovascular Clinical Practice

We suggest 3 broad criteria to be considered by health care systems before implementation of PRSs for cardiovascular care: (1) efficacy, (2) harm, and (3) logistics. First, estimations of benefit overall and across subgroups from observational data sets are likely to be key initial driving forces. Although issuing definitive criteria for the clinical implementation is beyond the scope of this scientific statement, we suggest in broad terms that the clinical efficacy of PRS is likely appropriate when either of the following is achieved: (1) The integration of PRS into clinical risk tools substantially improves their accuracy, or (2) PRS risk tools can identify participants at a risk at least equivalent to that of individuals with monogenic risk variants (such as *LDLR* for FH; Table 4). In regard to the first point, for most of the disease examples in this scientific statement (AF, CAD, and T2D), the predictive accuracy of established clinical risk factor models is improved with the addition of PRS (ie, PRS improves prediction when incorporated into the PCE for ASCVD, the CHARGE-AF risk model [AF], and the American Diabetes Association risk model [T2D]).[23,63]

Furthermore, statin allocation, particularly in scenarios of clinical equipoise for primary CAD prevention among middle-aged adults, is harmonized with the 2019 ACC/AHA cholesterol guidelines.[2] Therefore, recent analyses in 3 ethnically and geographically distinct hospital biobanks have shown the capability of using a CAD PRS to allocate statins for primary prevention among middle-aged adults when 10-year estimated risk by clinical risk factors is borderline to intermediate.[89] Post hoc pharmacogenomic analyses in randomized controlled trials may also help with refining treatment allocation.[90] Whether screening earlier in life identifies individuals at sufficiently high lifetime risk to treat with statins on the basis of a CAD PRS alone, akin to the risk conferred by severe FH, requires further study. Preliminary analyses indicate that disclosure alone of a CAD PRS may improve health-related behaviors, but results are inconsistent to date.[99,101,158] Limited experience with T2D PRS has not shown behavioral modification after disclosure.[159] Improved risk prediction and allocation of established effective and safe therapies may be sufficient to motivate clinical use.

Second, with increasingly widespread availability, it is important for any guidance on responsible clinical use to address the potential harms. Although most current studies may estimate prognosis or treatment effects with retrospective analyses, estimations of harms remain challenging. There have been concerns about exacerbating existing racial disparities in health care with the use of existing PRSs. Initial and large GWAS still largely comprise individuals of European ancestry,[40] which poses recalibration challenges, although ongoing

efforts to genetically profile non-Europeans and novel methods are continuing to bridge this gap and have shown comparable predictive accuracy between multiple ethnicities (Figure 3).[18,84] In addition, in some scenarios such as a high AF PRS or high VTE PRS, higher-risk prevention strategies such as initiation or extension of the duration of anticoagulation prophylaxis may be considered. For these riskier protocols, prospective randomized controlled trials addressing both safety and efficacy are necessary.

Third, several logistical and educational considerations exist. To date, genomic data for PRS calculation are largely external to the health care system (ie, research study or direct-to-consumer testing product) with few exceptions.[160] Although germline genetic profiling is a static biomarker, associations are also functions of age and other potential nongenetic factors, as well evolving evidence refining interpretation of the human genome. Information technology systems should be robust to new knowledge to use new algorithms and to revise clinical decision support on the basis of static genotypes. Furthermore, population genetics literacy among both clinicians and patients remains limited, potentially hindering putative benefits and potentially exacerbating harms.[1–3,5] The extent to which ancillary support such as specialized clinicians, including genetic counselors, is needed will likely vary across health systems. Last, health care systems should consider the regulatory guidance for use of PRSs (described in the Considerations for Commercial Genetics Organizations section)

Calibrating PRSs to the Population of a Health Care System

Similar to prediction equations based on clinical risk factors, performance of PRSs for disease prediction is sensitive to characteristics of the population in whom they are applied.[39,40,161–163] Systemic underperformance will be strongly correlated with the extent of dissimilarity between the derivation and applied data sets. For example, ASCVD risk estimation from the PCE varies when applied to different cohorts.[161,164,165] Cohort-specific calibration approaches have been demonstrated to improve performance for the PCE for ASCVD.[161,164,165] Similarly, recalibration of PRS models for distinct genetic ancestries in target populations has been shown to improve performance. For example, a T2D PRS derived from individuals of European ancestry was reweighted according to Latino haplotypes with resulting improvement in T2D prediction among people of Hispanic ancestry.[166] However, simple variant filtration based on predicted functional impact may also improve transancestry transferability.[167] Similarly, prediction approaches tailored separately for men and women may improve on current approaches. For admixed individuals, partial PRSs corresponding to deconvoluted ancestries recombined[168] and linear combinations of ancestry-specific PRSs[166] have shown recent promise.

Current PRS studies are presented in percentiles according to the cohort studied. Therefore, varying genotyping platforms limit the ability to generate universal raw scores. Because percentiles are therefore a function of cohort ethnicity, admixture, and genotyping platform, internal calibration procedures are likely also necessary. Nevertheless, universal harmonization efforts would improve generalizations of PRS applicability beyond single health systems. The ultimate goal for application of PRSs should be their representation in absolute risks, not percentiles.

CONSIDERATIONS FOR COMMERCIAL GENETICS ORGANIZATIONS

Genetic testing in the United States falls under the College of American Pathologists (CAP) and the Clinical Laboratory Improvement Amendments (CLIA; part of the Centers for Medicare & Medicaid Services).[169] The FDA has traditionally asserted its authority to oversee all diagnostic tests, including laboratory developed tests (LDTs). However, the FDA has for decades practiced "enforcement discretion," leaving regulation of LDTs almost entirely to the CLIA/CAP process. The FDA clarified direct authority in 2010, intervening with several direct-to-consumer genetic testing companies,[170] and in 2019 to 2020 with several pharmacogenomics testing companies.[171,172] In 2020, however, in a ruling that derived direction from a Presidential Executive Order, the Department of Health and Human Services made FDA regulation of LDTs harder, requiring the agency to implement notice-and-comment rulemaking in any regulation of LDTs.[173] Although the high-level regulatory authority for LDTs remains unclear and unstable, in practical terms, the FDA is not resourced to regulate the thousands of LDTs. This means that implementation of tests such as PRSs currently continues to fall under CLIA/CAP regulation.[173] There are no specific guidelines for CLIA/CAP certification of PRS tests, but CLIA/CAP certification of any new test has relied on peer-reviewed publications.

Furthermore, commercial genetics companies need to consider how they report an individual's risk and those responsible for medical follow-up when deemed necessary. The most easily understood and meaningful way of presenting one's PRS remains somewhat unclear. Future research addressing effective PRS risk communication is needed.

Commercial direct-to-consumer genetics companies also need to consider medical follow-up workflows for individuals with a high PRS. For example, if an individual is determined to be in the top 1% of PRSs for T2D, should the commercial genetics company alert the patient's primary care physician, recommend visiting with their primary care physician, recommend increased frequency of HbA1c screening tests, or provide some other guidance? These difficult-to-resolve questions highlight the advantage of commercial genetics companies collaborating with established health care systems.

Last, it would be advantageous if genetics companies welcomed open science practices. Both the advancement and integrity of genomic science have been greatly aided by collaborations, sharing of data (although maintaining privacy and confidentiality of the individuals who contributed their DNA), and open examination of methods. A continuation of these practices will help ensure the integrity and accuracy of both commercial and academic PRSs.

CONSIDERATIONS FOR PAYERS

How to Consider the Financial Integration of PRSs Into Clinical Practice

The goal for any health care system is to maximize population health, and payers are tasked with considering interventions that will achieve this in a financially responsible manner.[174] Once the scientific accuracy of PRS is confirmed in its intended population (described in the Considerations for Health Care Systems section) and the regulatory standards are

met (described in the Considerations for Commercial Genetics Organizations section), policymakers can begin to consider the financial implications.

For cost-effectiveness studies for PRS, the following costs should be considered: the one-off costs of genotyping (and the associated infrastructure) and algorithm development and ongoing costs such as laboratory and bioinformatics staff.[175] Assessing these direct costs is particularly challenging, given the rapidly decreasing costs of genetic profiling; sequencing technology costs have dropped substantially over the past 10 years.[176,177]

Conversely, there are unique potential savings with the use of PRSs. With 1-time broad genetic profiling, PRSs for numerous conditions can be generated with trivial incremental costs. In addition, PRSs may provide health care savings through earlier targeted prevention and mitigation of future costly medicines or procedures, for example, through deimplementing screening for PRS-determined lower-risk groups. Such estimates are likely to vary per condition according to condition heritability, prognostic performance of the PRS, the intervention invoked, including efficacy by PRS, and several others.

There is a paucity of cost-effectiveness studies for cardiometabolic PRS. Those that are available focus largely on CAD.[178–180] The existing literature uses different methodological approaches, includes a variety of populations, and shows mixed results. A 2018 simulation study of people 45 to 65 years of age examined the cost-effectiveness of a 27-SNV PRS guiding statin treatment in the primary prevention for ASCVD for those at low borderline 10-year ASCVD risk (2.5%–7.5%).[178] Although the authors conclude that this strategy is not more cost-effective than treating all at low borderline risk, secondary analyses indicated that the use of a 27-SNV PRS might be cost-effective in some scenarios, including when 10-year ASCVD risk was closer to 7.5%. Because the majority of patients at low borderline risk are not currently recommended for statins, this scenario may not suitably reflect the anticipated use of a CAD PRS. Furthermore, PRSs have become more sophisticated since this study; among many other advances, the inclusion of more SNVs has significantly enhanced predictive accuracy (contemporary CAD scores include millions of SNVs).[35,181] These methodological advances are reflected in a 2019 study that assessed the cost-effectiveness of a 49 310–SNV CAD PRS.[180] This study used a bayesian decision-tree approach based on adults >45 years of age living in Finland and found that the addition of a PRS to clinical risk factors may be cost saving compared with clinical risk factors alone for certain patient segments.[180] More recent data suggest that targeted screening with PRSs in addition to clinical risk factors is likely to be cost-effective through the prevention of "7% more cardiovascular disease events than conventional risk prediction alone."[104] As PRSs continue to improve, this benefit is expected to increase. It is notable that a PRS alone has a predictive accuracy that comparable to or greater than that of many individual clinical risk factors (including T2D and hypercholesterolemia).[38,63] Further research would likely be beneficial, but the decreasing costs of genetic testing, the comparable cost to current biomarker tests (eg, the cost of an HbA1c test is comparable to the cost of a PRS),[182] and the ability to calculate PRSs for a large number of diseases from 1 test increase the likelihood of cost-effectiveness. These data support cost-effectiveness among middle-aged adults at intermediate risk. Last, there are encouraging data on the cost-effectiveness of PRSs for noncardio-metabolic diseases, which has led to the inclusion of PRSs in current

clinical risk tools such as in the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm/CanRisk for breast cancer.[183,184]

Interpretation and Relevance of PRSs in the Context of Insurance Policies

In the United States, the Genetic Information Nondiscrimination Act prohibits the use of genetic information in the provision of health insurance or employment hiring, firing, pay, or promotion.[185] However, this protection does not extend to life and disability insurance. Numerous other countries have government policies (on a spectrum of government intervention) that protect patients from insurance exclusion while maintaining market sustainability.[186]

CHALLENGES AND FUTURE DIRECTIONS

The overarching goals of a cardiovascular PRS include disease prevention by identifying at-risk individuals for improved disease surveillance and better-informed treatment plans. Although there are promising applications for PRS, several limitations should be acknowledged that would benefit from future work.

One limitation is that the current state-of-the-art polygenic risk models include only common variants.[20,22,187–189] The advantages of including rare variants in PRS models have yet to be investigated. Recent studies have shown how rare and low-frequency variants can explain a substantial fraction of heritability.[190–193] The number of discoveries of this type of variants is limited by lack of power; for cardiovascular diseases, only a few studies have identified rare and low-frequency variants that confer a high risk of disease (similar to variants that cause monogenic disease).[194–197] To be able to capture information across the allele frequency and effect size spectrum, PRS models built from common variants can be improved by incorporating well-characterized, rare, high-risk variants. This is likely to be achieved as sequencing moves to whole-genome sequencing. Future studies should prioritize data from whole-genome sequencing to facilitate PRS models that incorporate common and rare variants, that is, a full allelic spectrum polygenic score. In the absence of whole-genome data on patients for whom a PRS is to be calculated, genotyping array data can be imputed to whole-genome sequencing data. However, imputation accuracy is typically low for rare variants, and poorly imputed variants can affect the quality of the PRS. Other options include high-coverage whole-genome sequencing,[85] whole-exome sequencing and genotyping array, and high-coverage sequencing of individual genes and low-coverage sequencing across the genome.[66] Technology developments that improve cost and efficiency will improve the accessibility for this type of test in the clinical practice.

A second limitation is the reduced transferability of PRSs across many different populations. Most training data are derived from a single population, typically of European ancestry. This limits the utility of current data for use in non-European populations,[198] although there are promising data that current PRSs show similar predictive accuracy across ethnicity groups (Figure 3).[36,84,103] Despite the increase in the proportion of GWAS and PRSs that include non-Europeans, having more non-Europeans in future biobanks and studies remains an urgent priority.[166,199–203] To some degree, this has already begun. The Million Veteran Program has nearly 30% non-European individuals[204]; Biobank Japan has recruited

exclusively from Japan[205]; and East London Genes and Health was established to recruit British South Asians.[206] Increasingly large health care–associated biobanks represent the genomic diversity of their sociodemographically diverse patients.[207] Newer biobanks such as All of Us Research Program and East London Genes and Health have focused on the recruitment of individuals traditionally underrepresented in biomedical research through parallel recruiting strategies[206]: recruiting from community settings aided by local organizing groups and recruiting from health care settings. Community engagement approaches that seek to understand more prevalent conditions among diverse ancestral groups may serve as a research engagement strategy. In the short term, computational strategies to improve PRS transferability to non-European populations will complementarily improve PRS generalizability.[84,203,208] Similarly, future PRS studies may consider tailoring risk models by sex. Because there is substantial variation in the incidence of and risk factors for cardiovascular disease between sexes, enhanced prediction may be achieved by future cardiovascular risk models that include sex-specific PRSs and sex-specific clinical risk factors. This should be a focus of future research.

Future PRS research should be encouraged in existing and planned randomized controlled trials to conduct post hoc analyses to further assess clinical utility. Specifically, further work should examine the incremental value of PRSs over clinical scores, as well as treatment changes based on PRSs and resultant clinical outcomes. Although this strategy has already been effective in identifying subgroups who may benefit from PRS-directed treatment,[86,91] there is a paucity of data for non-CAD diseases and for nondrug interventions. Moreover, given the cumulative lifetime effect of genetic risk, it would be of particular value to recruit younger adults (eg, <40 years of age) or even children and adolescents (eg, <18 years of age) into PRS research studies. PRSs have the unique advantage of assessing risk before the emergence of clinical risk factors and therefore can act as a modulator of screening practices; the intensification or deintensification of screening of children and young adults on the basis of a PRS would be a valuable focus of future research.

The apparent correlation in PRSs among family members has implications for cascade screening, particularly if a PRS is not already available for family members of a proband with a high PRS.[209] Furthermore, earlier identification of at-risk individuals and earlier treatment that reduces causal risk factors such as LDL-C will likely provide stronger mitigation of risk for atherosclerotic diseases such as CAD. However, the clinical efficacy and cost-effectiveness of cascade screening with PRSs are yet to be fully explored.

Beyond the technical and analytical limitations, potential negative consequences of PRS adoption into cardiovascular clinical practice should be carefully considered. These potential considerations include, but are not limited to, widening care disparities related to access to PRSs,[40] unequal benefit of PRSs across race and ethnicity groups, misinterpretation or misapplication of PRS information attributable to clinician knowledge or patient understanding, threats to patient well-being related to genetic data security and to coverage practices of insurers, and escalating health care costs.

The use of PRSs for CAD also merits further discussion. As the most studied phenotype to date, the efficacy of PRSs for CAD has been examined in numerous studies and produced

mixed results. These mixed results may be attributable to varying sample sizes, varying statistical approaches, reliance on single accuracy metrics, and aggregated results across various subgroups. Studies in smaller biobanks (MESA and ARIC) have generally produced nonsignificant results compared with studies of larger biobanks (UK Biobank,[63,94] Malmö Diet and Cancer Study,[87] Women's Genome Health Study[88]), and statistical approaches continue to advance and produce more accurate PRSs.[36,63]

The transparency and reproducibility of PRSs are essential as clinical integration is considered. In an effort to improve transparency, the PRS reporting standards writing committee recently published a reporting guideline.[169] The guideline acts as a checklist for researchers performing PRS studies, outlining the minimum information that should be stated in a research article to ensure that the work is transparent and able to be reproduced. In broad terms, the reporting guideline includes information on study design and recruitment, participant demographics (including ancestry), genetic data, nongenetic variables, risk model development, and evaluation, including discrimination and calibration. This reporting guideline can act as a checklist not only for researchers but also in the appraisal of PRS studies by payers, health care systems, and policymakers considering implementation and reimbursement of certain PRSs. Furthermore, the polygenic score catalog is a freely available, open-access resource of published PRSs.[210]

Although we review 5 cardiometabolic diseases in this scientific statement, the polygenic bases for other cardiometabolic diseases are increasingly being characterized. Examples include stroke (hemorrhagic and ischemic), left ventricular end-systolic volume,[211] hypertrophic cardiomyopathy,[51] and heart failure.[212] Similar encouraging data exist for channelopathies and related traits, including QT interval prolongation[213,214] and Brugada syndrome.[215]

CONCLUSIONS

The identification of monogenic risk variants predisposing to cardiovascular conditions has been used clinically to inform surveillance and management plans. Relatively recent advances in population genetics have uncovered the polygenic basis of these and other cardiovascular conditions in most patients. These observations point to the possibility of using genetic profiling to inform clinical practice in significantly larger groups of individuals than for whom monogenic cardiovascular variants are considered. As a result of exponential increases in the proportion of individuals with broad genetic profiling, cardiovascular PRSs are beginning to enter clinical practice. Such PRSs may be appropriately considered in select scenarios, given the current evidence base. The evolving literature aims to continue to narrow the current knowledge gaps and to improve the performance and communication of PRSs.

Below, we recap the pertinent points covered in previous sections:

1. What Are PRSs? PRSs are single scores reflecting the cumulative weighted risk of individual genetic variation for a set of traits. These individual genetic variants confer an incrementally small disease risk, but summated, they have been shown to be predictive of many cardiovascular diseases.

2. Polygenic Versus Monogenic Risk Variants: Monogenic risk variants are typically single, protein-truncating variants conferring a relatively large risk of disease. Examples of monogenic risk variants for cardiovascular disease include *LDLR* for FH, *GCK* for diabetes,[46] *KCNQ1* for AF,[47] and *F5* for venous thromboembolic disease.[48] PRSs independently associate with disease risk and, at particularly high scores, may yield similar estimated disease risk as monogenic risk variants.[20]

3. Atrial Fibrillation: PRSs for AF have consistently shown incremental predictive capabilities in addition to clinical risk factors.[20,23,64–69] Proposed utility has been to refine the identification of individuals meriting close surveillance for AF development.

4. Coronary Artery Disease: CAD is perhaps the most studied cardiovascular phenotype for PRSs.[20,23,38,85–88,90–94] Among middle-aged adults, a CAD PRS performs similarly to conventional risk factors and provides additional prognostic information for CAD,[23,38,63,94] but the clinical significance of this improvement is contentious.[24,94] Observational evidence suggests that CAD PRSs may have utility in guiding pharmacological management (particularly for LDL-C lowering) attributable to increased estimated disease risk and greater estimated treatment benefit.[88,98]

5. Hypercholesterolemia: LDL-C PRSs have been shown to be predictive of LDL-C concentrations,[111] including severe hypercholesterolemia.[111] Because an LDL-C PRS is predictive of ASCVD events independently of LDL-C,[112] whether it should be used to help allocate novel LDL-C–lowering medicines (as FH variants currently allow) requires further study.

6. Type 2 Diabetes: Early research suggested that PRSs for T2D had a predictive ability similar to that of clinical risk factors.[122–124] More recent evidence suggests that PRSs may be additive to clinical risk factors.[23] However, the identification of those at high risk of T2D currently has unclear value; lifestyle modification and metformin treatment for T2D prevention did not appear to have different effects across genetic risk strata.[98,126] Nevertheless, T2D PRSs may help guide T2D management through both sulfonylurea responsiveness[127] and intensity of glucose management.[128]

7. Venous Thromboembolic Disease: A VTE PRS is associated with incident venous thromboembolic disease (VTE) risk.[110,140] Because the clinical utility of identifying inherited thrombophilias is unknown, the clinical utility of a VTE PRS also remains unknown. The benefits and risk of prolonged anticoagulation in those at high risk (determined using both clinical and genetic factors) require further study.

8. PRSs for Pharmacogenomics: Pharmacogenetic PRSs have addressed the following: In regard to PRSs for drug efficacy, most research has focused on statins with CAD PRSs,[86,91] sulfonylureas with T2D PRSs,[127] and PCSK9 inhibitors with CAD PRSs,[90] whereas drug toxicity PRSs have focused

on QTc prolongation with QTc PRSs.[156] Ongoing disease-associated PRS analyses in completed clinical trials will continue to inform pharmacogenetics. Discovery genetic association analyses within clinical trials may enable novel pharmacogenomic PRSs.

9. Criteria for Implementing PRSs in Cardiovascular Clinical Practice: Estimates of incremental efficacy and harm and logistical challenges are key aspects for health care systems to consider when evaluating PRSs. Clinician and patient education on their interpretation and limitations may require additional infrastructure and personnel.

10. Calibrating PRSs to the Population of a Health Care System: Recalibration of PRSs to target populations may improve performance but may lead to challenges in transferability.[166]

11. Considerations for Commercial Genetics Organizations: Commercial genetics organizations should be aware of the current, but likely changing, regulatory approval process for LDTs. Currently, LDT regulation falls largely under CLIA/CAP regulation,[173] but a series of decisions by the FDA over the past couple years seem to indicate that this may change in the future.

12. How to Consider the Financial Integration of PRSs Into Clinical Practice: There are a paucity of cost-effectiveness studies addressing cardiovascular PRSs. Decreasing genotyping costs and the negligible incremental direct costs of virtually limitless PRSs lead to modeling challenges.

13. Interpretation and Relevance of PRSs in the Context of Insurance Policies: The Genetic Information Nondiscrimination Act protects people in the United States from being discriminated against on the basis of their genetic information, specifically the provision of health insurance or employment hiring, firing, pay, or promotion.[185] However, this protection does not extend to life and disability insurance.

14. Challenges and Future Directions: The addition of PRSs to clinical risk tools consistently enhances the predictive ability. However, significant but surmountable challenges exist. The lack of diversity of participant inclusion in biobanks, GWAS, and consequently PRSs is a major current limitation. The lack of inclusion of non-Europeans in PRS construction makes the use of PRS in non-European populations suboptimal. Recognizing this major limitation, large samples of non-Europeans are being enrolled in newer biobanks. For some populations, study of large numbers of non-European participants has already begun (ie, Japan Biobank, Million Veteran Program), but much work is still required. Further future work should address the inclusion of rare variants in scores, improvement in phenotyping in biobanks, and inclusion of PRSs within randomized controlled trials; future work on other cardiometabolic diseases also is needed.

Disclosures

Writing Group Disclosures

Writing group member	Employment	Research grant	Other research support	Speakers' bureau/ honoraria	Expert witness	Ownership interest	Consultant/ advisory board	Other
Jack W. O'Sullivan	Stanford Cardiology	None	None	None	None	None	None	None
Pradeep Natarajan	Massachusetts General Hospital Cardiovascular Research Center	Apple †; Amgen *; Astra-Zeneca *; Boston Scientific *; Fondation Leducq †; Novartis *; NIH † (all investigator-initiated grants)	None	Allelica *	None	Named as inventors on a government-owned US patent application related to the use of genetic risk prediction for venous thromboembolic disease filed by the US Department of Veterans Affairs in accordance with federal regulatory requirements *; TenSixteen Bio †; geneXwell *; Vertex (immediate family members) †	Apple †; AstraZeneca *; Genentech/ Roche †; Novartis †; Blackstone Life Sciences *; Foresite Labs †; TenSixteen Bio †; Invitae *	Massachusetts General Hospital (Paul and Phyllis Fireman Chair in Vascular Medicine) †; Vertex (medical director; immediate family members) †
Euan A. Ashley	Stanford University School of Medicine Center for Inherited Cardiovascular Disease	Bristol Myers Squibb (academic grant) *; Takeda (academic grant) *; Google *; Verily *	None	None	None	Personalis *; DeepCell *; Silicon Valley Exercise Analytics *	Nuevocor *; Cathay Capital (unpaid) *; Third Rock Ventures (unpaid) *; Medical Excellence *; Foresite Capital *; Novartis (unpaid) *; Samsung (unpaid) *; Analog Devices (unpaid) *; Apple †; Illumina (unpaid) *; Nanopore (unpaid) *; SequenceBio (unpaid) *; Genome Medical (unpaid) *; Disney (unpaid) *	AstraZeneca (non-executive director) *
Scott M. Damrauer	University of Pennsylvania School of Medicine	US Department of Veterans Affairs (genetic research on cardiovascular	Pending patent (named as a coinventor on a government-owned US patent application	None	None	Abbott *; United Health *; Gilead *; Daiichi Sankyo *; Abbvie *; Teva *	None	None

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		disease)[†]; Renalytix AI (precision medicine approaches to CKD progression)[†]	related to the use of genetic risk prediction for venous thromboembolic disease filed by the US Department of Veterans Affairs in accordance with federal regulatory requirements)[*]					
Jasmine A. Luzum	University of Michigan Clinical Pharmacy College of Pharmacy	NHLBI (K08 HL146990)[*]	None	None	None	None	None	None
Carla Marquez-Luna	Icahn School of Medicine at Mount Sinai	None	None	None	None	None	None	None
Christopher J. O'Donnell	VA Boston Healthcare System	None	None	None	None	None	None	Novartis Institute for Biomedical Research (global head, translational medicine cardiovascular and metabolic disease)[†]
Sridharan Raghavan	Denver Veterans Affairs Medical Center	Department of Veterans Affairs (active research grant funding, including partial salary support)[†]; US National Institutes of Health (active research grant funding)[*]; Boettcher Foundation (active research grant funding, including partial salary support)[†]	None	None	None	None	None	None
Cristen J. Willer	University of Michigan Medical School	None	None	None	None	None	None	None

This table represents the relationships of writing group members that may be perceived as actual or reasonably perceived conflicts of interest as reported on the Disclosure Questionnaire, which all members of the writing group are required to complete and submit. A relationship is considered to be "significant" if (a) the person receives $10 000 or more during any 12-month period, or 5% or more of the person's gross income; or (b) the person owns 5% or more of the voting stock or share of the entity, or owns $10 000 or more of the fair market value of the entity. A relationship is considered to be "modest" if it is less than "significant" under the preceding definition.

[*] Modest.

† Significant.

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Samuli Ripatti	Institute for Molecular Medicine, Finland, FIMM (Finland)	None	None	None	None	None	None	None
Jerome I. Rotter	Lundquist Institute for Biomedical Innovation at Harbor-UCLA Medical Center	NIH*; Sanford Health System*	None	None	None	None	None	None

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* Significant.

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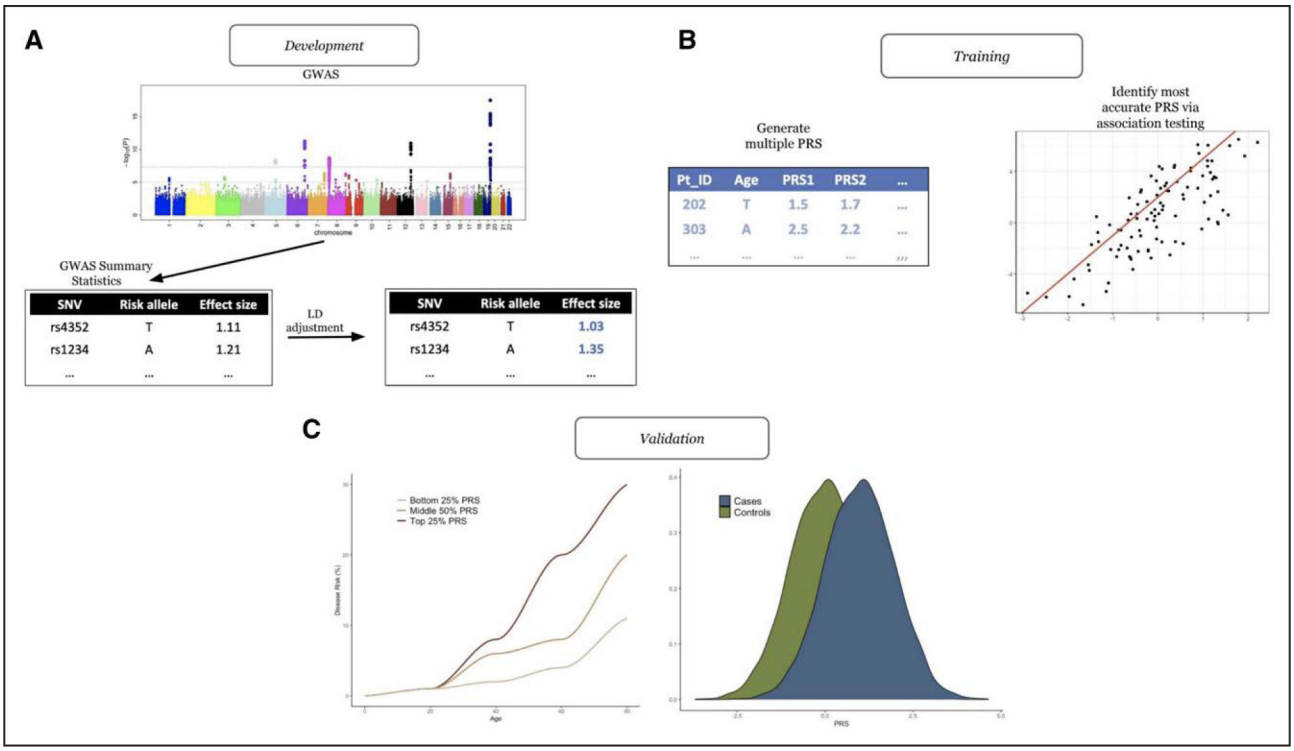

Figure 1. Development of a PRS.

A, Development of polygenic risk scores (PRSs). This typically involves attaining single nucleotide variant (SNV) effect sizes from a genome-wide association study (GWAS) and then adjusting these SNV effect sizes to account for linkage disequilibrium (LD). **B**, Training of the PRS. Typically, numerous PRSs are created per participant. Each PRS is then assessed through various association testing, and the most accurate PRS is collected. **C**, Validation of the PRS. The most accurate PRS is then validated in an independent cohort of participants.

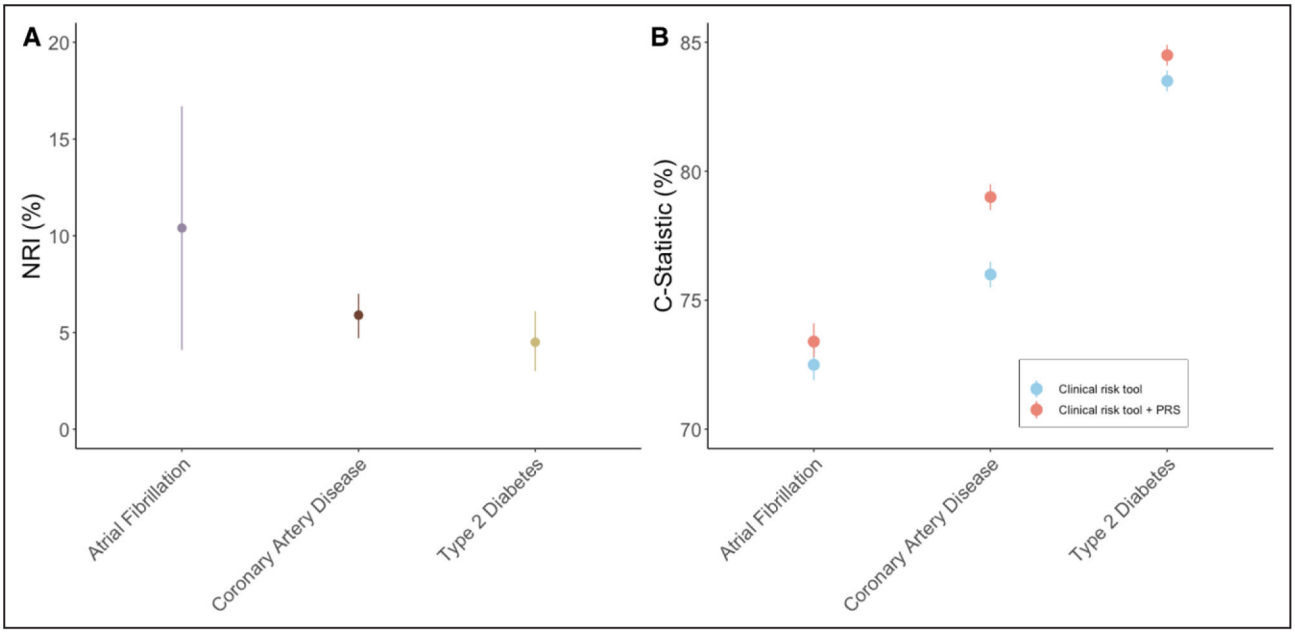

Figure 2. Predictive accuracy of polygenic risk scores when combined with clinical risk tools, compared to clinical risk tools alone.

A, Net reclassification index (NRI). Comparison of clinical risk tools with and without the integration of polygenic risk score (PRS).[23,63] The clinical risk tool used atrial fibrillation was CHARGE-AF (Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation) with a risk threshold of >5% over 5 years. Variables included in CHARGE-AF were age, height, weight, systolic blood pressure (SBP), diastolic blood pressure (DBP), smoking status, blood pressure–lowering medication, diabetes, heart failure, and history of myocardial infarction. The clinical tool for coronary artery disease was the American Heart Association/American College of Cardiology Pooled Cohort Equation with a 7.5% risk threshold over 10 years and included the following variables: age, diabetes, sex, race, smoking, total cholesterol, high-density lipoprotein (HDL), systolic blood pressure, and treatment for hypertension. The clinical tool for type 2 diabetes was the American Diabetes Association risk score, which had a 33% risk threshold over 10 years and included the following variables: age, sex, body mass index, history of stroke or coronary heart disease, parental history of diabetes, SBP, DBP, HDL, and triglycerides. All differences are statistically significant. **B**, Comparison of C statistics between clinical risk scores (same as stated in **A**) and a risk tool with a PRS integrated into the clinical risk tool. All differences are statistically significant.[23,63]

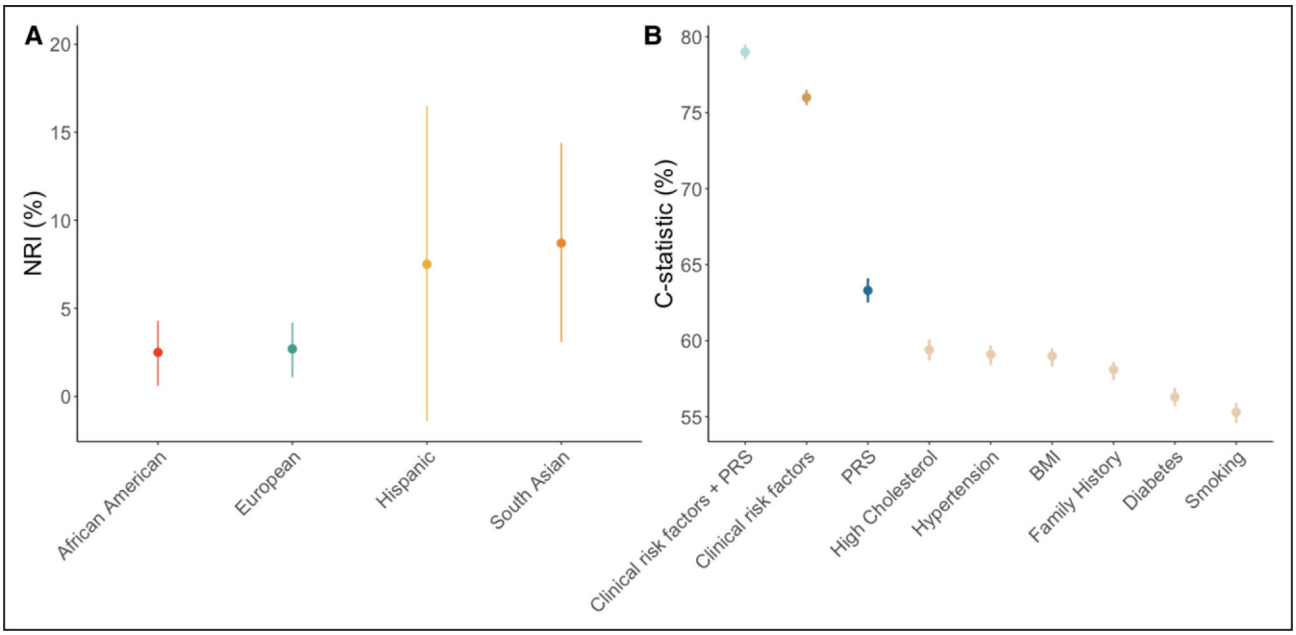

Figure 3. Predictive ability of polygenic risk scores for coronary artery disease.

A, Net reclassification index (NRI) comparing clinical risk tools and a risk tool with a polygenic risk score (PRS) integrated into the clinical risk tool for coronary artery disease across multiple ethnicities.[84] African American includes Black Caribbean and Black African, and South Asian includes Indian, Bangladeshi, or Pakistani. **B**, NRI for the American Heart Association/American College of Cardiology Pooled Cohort Equations (AHA/ACC PCE) tool+PRS, clinical risk factors collectively as the AHA/ACC PCE tool, PRS, and individual clinical risk factors for coronary artery disease.[38,63] BMI indicates body mass index.

Table 1.

Common Statistical Genetics Terms Used in This Scientific Statement

Terms	Definition
AUC	The probability that the statistical model will correctly classify a participant as having or not having a disease (discrimination)
C statistic	The probability that the statistical model will correctly classify a participant who will go on to develop or not go on to develop a disease (discrimination)
NRI	A measure of how a new model, typically with the addition of ≥1 more risk factors, reclassifies participants
SNV	A variation in nucleotide base pair compared with what is expected at that location in the human genome, ie, an A instead of a G
LD	The nonrandom association of alleles that tend to be inherited together more often than chance; a function of allele ages, genomic distance, and local recombination rates
Minor allele frequency	The prevalence of the least common allele among the possible allele combinations at a genomic site
Monogenic risk variants	Rare and typically disruptive or protein-truncating variants that confer large risks of disease; typically follow classic mendelian patterns of inheritance
Polygenic risk variants	Commonly occurring variants in the population that typically confer an individually small risk of developing a disease

AUC indicates area under the receiver-operating characteristic curve; LD, linkage disequilibrium; NRI, net reclassification index; and SNV, single nucleotide variant.

Table 2.

Characteristics of Studies of PRSs With the Highest NRI When Comparing a Clinical Risk Tool With a Clinical Risk Tool With PRSs Integrated Within

Disease, authors (y)	SNVs, n	Participants, n cases/N total*	Biobank	Participants: ancestry/ ethnicity, age, y	Outcome 1: HR/OR (95% CI) (included covariates controlled for)*	Outcome 2: AUC/C statistic (95% CI) (included covariates controlled for)*	Outcome 3: AUC/C-statistic (95% CI): clinical risk tool vs PRS+clinical risk tool	Outcome 4: NRI (95% CI) comparison
AF, Mars et al[23] (2020)	6 171 733	12 809/135 300 For model comparing clinical risk model, 229/21 030	FinnGenn	European, 59.2±16.6	HR per SD, 1.62 (1.59–1.65) (collection year, genotyping array/batch and the first 10 principal components of ancestry, and stratified the models by sex)	C statistic, 0.751 (0.744–0.757) (collection year, genotyping array/batch and the first 10 principal components of ancestry, and stratified the models by sex)	CHARGE-AF, 0.725 (0.719–0.732) CHARGE-AF+PRS, 0.734 (0.728–0.741)	Using >5% risk threshold over 5 y, 10.4 (4.1–16.7) CHARGE-AF vs CHARGE-AF+PRS
CAD, Riveros-Mckay et al[63] (2021)	>3 500 000	4247/186 541	UK Biobank	European, 40–69	HR per SD, 1.90 (1.86–1.95) (age, sex, principle components of ancestry)	C statistic, 0.633 (0.625–0.641) (age, sex, principle components of ancestry)	AHA/ACC PCE, 0.76 (0.75–0.76) AHA/ACC PCE+PRS, 0.79 (0.78–0.79)	Using >7.5% threshold over 10 y, 5.9% (4.7%–7.0%) AHA/ACC PCE vs AHA/ACC PCE+PRS
T2D, Mars et al[23] (2020)	6 437 380	17 519/135 300 For model comparing clinical risk model, 1346/10 561	FinnGenn	European, 59.2±16.6	HR per SD, 1.74 (1.72–1.77) (collection year, genotyping array/batch and the first 10 principal components of ancestry, and stratified the models by sex)	C statistic, 0.763 (0.758–0.767) (collection year, genotyping array/batch and the first 10 principal components of ancestry, and stratified the models by sex)	ADA, 0.835 (0.831–0.839) ADA+PRS, 0.845 (0.841–0.849)	NRI using 10-y risk ≥33% risk threshold, 4.5% (3.0%–6.1%) ADA criteria

ADA indicates American Diabetes Association; AF, atrial fibrillation; AHA/ACC, American Heart Association/American College of Cardiology; AUC, area under the receiver-operating characteristic curve; CAD, coronary artery disease; CHARGE-AF, Cohorts for Heart and Aging Research in Genomic Epidemiology model for atrial fibrillation; HR, hazard ratio; NRI, net reclassification index; OR, odds ratio; PCE, Pooled Cohort Equation; PRS, polygenic risk score; SNV, single nucleotide variant; and T2D, type 2 diabetes.

*Data from validation data set/analysis.

Table 3.

Characteristics of Published Studies That Compared Risk Estimates for Carriers of Monogenic-Risk Variants Versus Individuals With a High Polygenic Score

Disease, author (y)	SNVs, n	Participants: n cases/N total	Biobank	Participants: ancestry/ ethnicity, age, y, other	HR/OR PRS (95% CI) (included covariates controlled for)	HR/OR monogenic risk (95% CI) (included covariates controlled for)	HR/OR PRS+monogenic risk (95% CI) (included covariates controlled for)
Hypercho-lestolemia, Fahed et al[19] (2020)	6 630 150	6432/12 852	UK Biobank	European, 40–69	OR for top 20% PRSs, 2.28 (2.10–2.48) (age, sex, and the first 4 principal components of ancestry) vs 20%–80% PRS risk	OR for FH carriers (*LDLR*, *APOB*, or *PCSK9* mutations), 3.21 (1.72–5.99) (age, sex, and the first 4 principal components of ancestry) compared with noncarriers	OR for FH carriers (*LDLR*, *APOB*, or *PCSK9* mutations) and top 20% PRS risk, 12.61 (2.96–53.62) (age, sex, and the first 4 principal components of ancestry) OR for FH carriers (*LDLR*, *APOB*, or *PCSK9* mutations) and bottom 20% PRS risk, 1.30 (0.39–4.32). Both compared noncarriers and 20% to 80% PRS risk.
VTE, Klarin et al[110] (2019)	297	WHI: 690/10 975 MVP: 2100/55 965	MVP 2.1, UK Biobank: development, MVP 3.0, WHI: validation	European, 19–100	HR for top 5% risk in WHI, 2.51 (1.97–3.19) (age, 10 principal components of ancestry, and hormone therapy intervention status during the active phase of the WHI-HT) OR for top 5% risk in MVP, 2.89 (2.52–3.30) (age, sex, and 5 principal components of ancestry) compared with the bottom 95% risk	HR for factor V Leiden in WHI (F5 p.R506Q), 2.34 (1.86–3.35) HR for factor V Leiden in WHI (F2 G20210A), 3.35 (1.10–10.23) (age, 10 principal components of ancestry, and hormone therapy intervention status during the active phase of the WHI-HT) OR for factor V Leiden in MVP (F5 p.R506Q), 2.97 (2.63–3.36) OR for factor V Leiden in MVP (F2 G20210A), 2.61 (2.19–3.12) (age, sex, and 5 principal components of ancestry)	"In addition, we observed that this risk was further compounded for individuals among the top 5% with increased polygenic VTE risk who were also F5 Leiden or F2 G20210A carriers."[110]

FH indicates familial hypercholesterolemia; HR, hazard ratio; MVP, Million Veteran Program; OR, odds ratio; PRS, polygenic risk score; SNV, single nucleotide variant; VTE, venous thromboembolism; WHI, Women's Health Initiative; and WHI-HT, Women's Health Initiative hormone therapy.

Because monogenic carriers meet current clinical guidelines for intervention, a logical extension would be considering individuals with similar risk levels attributable to polygenic risk status.

Table 4.

Potential Clinical Utility of PRSs

Disease/risk factor	Potential clinical utility of PRS
CAD	Earlier identification for lifestyle therapies and statins, potentially for those with very high CAD PRSs Earlier screening for subclinical atherosclerosis to time the initiation of pharmacotherapies Use as a risk-enhancing factor for primary prevention in middle-aged patients at borderline-intermediate 10-y ASCVD risk
AF	Earlier AF detection and resultant prophylactic anticoagulation, potentially with monitoring devices Rigorous control of additive clinical risk factors for AF
T2D	Earlier lifestyle modification Potential consideration of prophylactic hypoglycemic medications with concomitant additional T2D clinical risk factors Genomic stratification may optimize hypoglycemic choice
VTE	Rigorous VTE risk-reducing strategies in the context of high-risk scenarios (prolonged travel, major surgery, etc)
Hypercholesterolemia	Earlier institution and earlier uptitration of lipid-lowering pharmacotherapies analogous to FH
Pharmacogenomics	Personalized drug therapy regimens that increase drug efficacy and decrease toxicities, eg, personalized β-blocker target dose in patients with HFrEF or the prevention of drug-induced QT prolongation

AF indicates atrial fibrillation; ASCVD, atherosclerotic cardiovascular disease; CAD, coronary artery disease; FH, familial hypercholesterolemia; HFrEF, heart failure with reduced ejection fraction; PRS, polygenic risk score; T2D, type 2 diabetes; and VTE, venous thromboembolism.

Lone AF refers to AF in the absence of other cardiovascular risk factors (typically in young adults).