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Review article

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Clinical use of polygenic risk scores: current status, barriers and future directions

Iftikhar J. Kullo ✉

Abstract

Genome-wide association studies have identified thousands of single-nucleotide variants that are associated with complex traits, including cardiometabolic diseases, cancers and neurological disorders. Polygenic risk scores (PRSs), which aggregate the effects of these variants, can help to identify individuals who are at increased risk of developing such diseases. As PRSs are typically only weakly associated with conventional risk factors for these diseases, they have incremental predictive value and are beginning to be incorporated into clinical practice to guide early detection and preventive strategies. However, challenges to their use — such as suboptimal precision, poor transferability across diverse populations and low familiarity among patients and providers with the concept of polygenic risk — must be addressed before their broader clinical adoption. This Review explores the current state of the field, highlights key challenges and outlines future directions for the use of PRSs to improve risk prediction and to advance personalized prevention in clinical care.

Sections

Department of Medicine, Division of Cardiovascular Medicine, the Cardiovascular Research Center and the Mellowes Center for Genomic Sciences and Precision Medicine, Medical College of Wisconsin, Milwaukee, WI, USA.
✉e-mail: ikullo@mcw.edu

Introduction

Most common human diseases, such as cardiometabolic diseases, cancers and neurological disorders, result from multiple aetiological factors, including both genetic and environmental factors. These conditions are leading causes of morbidity and mortality worldwide, and risk assessment has a crucial role in devising screening strategies and guiding preventive or therapeutic interventions. Traditionally, risk estimation has relied on risk factors identified in large cohort studies (such as age, male sex, smoking, hypertension, diabetes and hypercholesterolaemia for coronary heart disease (CHD)), and for some diseases, validated algorithms are available to estimate absolute risk over defined time periods based on these factors. However, the accuracy of risk prediction for common diseases is modest, partly owing to the limited availability of sufficiently predictive biomarkers. In this context, the development of polygenic risk scores (PRSs), based on genetic variants identified in genome-wide association studies (GWAS)[1,2], represents an important advance in disease risk assessment[3].

A historical perspective

The origin of PRSs can be traced back to the principles of complex trait genetics and statistical genetic prediction, first proposed in the early twentieth century[4]. At that time, the scientific divide between biometricians, who analysed continuous variation in traits, and 'Mendelians', who focused on discrete patterns of inheritance, was reconciled by Ronald Fisher[5] in a seminal paper published in 1918. Fisher proposed that complex traits are influenced by the additive effects of many genetic variants of small effect and that these traits could be studied using quantitative statistical approaches[4]. He proposed analysis of variance as a statistical method to partition phenotypic variation into genetic and environmental components, introducing the concept of heritability. Importantly, these early models of genetic architecture were based on the analysis of phenotypes among related individuals, primarily in the context of animal or plant breeding programmes, without knowledge of genotypes. Traits such as milk yield in cattle or oil content in maize became the focus of selection experiments, which provided further insights into quantitative genetics[6].

In the mid-twentieth century, population geneticists including Fisher, JBS Haldane and Sewall Wright advanced theoretical models to describe how genetic variation is shaped by forces such as drift, mutation, migration and selection[7] (see Fig. 1 for a population genetics background for PRSs). However, it was not until later in the twentieth century — when genetic markers across the genome became available — that the field of disease genetics emerged[8]. Although linkage analysis had been successful in identifying loci for rare Mendelian diseases, it was largely ineffective for complex traits characterized by polygenicity and small effect sizes[9]. In a 1996 commentary, Neil Risch and Kathleen Merikangas[10] proposed a shift in strategy: the genotyping of common single-nucleotide variants (SNVs) across the genome to identify associations with complex traits. This vision came to fruition with the advent of GWAS, catalysed by the availability of the human genome sequence, Haplotype Map (HapMap) data and genotyping arrays. Subsequent GWAS, including the landmark study by the Wellcome Trust Case Control Consortium[2], validated this approach, leading to the discovery of thousands of loci associated with a wide range of diseases and traits, often implicating many variants for a single condition[11]. A logical next step was to aggregate the effects of multiple trait-associated variants into a single PRS for that trait — that is, quantifying an individual's inherited susceptibility to disease based on the cumulative contribution of many common variants[1,2,12].

Background

Mathematically, a PRS is the sum of risk alleles at disease-associated loci weighted by the strength of association of each risk allele with the trait or disease (which can, for example, be expressed as the log odds ratio for binary traits or as the slope of the linear regression between allele count and trait for continuous traits)[13] (Box 1). Initial PRSs were constructed from loci identified in GWAS that met the threshold of statistical significance. However, for many highly polygenic traits, PRSs perform better when they also include a much larger number of variants below the threshold[14–16]. The source GWAS data (either individual level or summary statistics) are called the training dataset, and the parameters (for example, the *P*-value threshold for statistical significance below which SNVs are included) are selected in an independent tuning dataset. The final step of testing is performed in an independent, out-of-sample cohort to avoid generating inflated prediction metrics[13].

The assessment of polygenic disease risk in this manner is the focus of intense research, with increasing reports of the clinical validation and implementation of PRSs. For example, PRSs for CHD, type 2 diabetes, Alzheimer disease and breast and prostate cancers are available for clinical application and are being used in clinical settings in several countries including the USA. In addition, PRSs for immune-mediated inflammatory diseases (such as type 1 diabetes and ankylosing spondylitis)[17], eye disorders such as glaucoma[18] and respiratory diseases (such as chronic obstructive pulmonary disease)[19] are being evaluated for clinical use. Although no guidelines have yet been established for the clinical use of PRSs, as the field awaits additional studies demonstrating their clinical utility, there is recognition of the potential to improve health outcomes and the need for further research.

Research consortia studying PRSs include Electronic Medical Records and Genomics (eMERGE)[20] and Polygenic Risk Methods in Diverse Populations (PRIMED)[21] in the USA, the former focusing on clinical implementation of PRSs and the latter on reducing the performance gap in PRSs between population groups. The All of Us[22] cohort, established in the USA with an emphasis on diversity, and the FinnGen[23] and UK Biobank[24] cohorts from Europe are valuable resources for validating PRSs. Several additional global genomic data sharing initiatives are attempting to develop PRSs for diverse groups[25,26]. The ClinGen consortium in the USA includes PRS working groups that have developed a PRS reporting standard[27] and are establishing a framework for curating evidence for the clinical utility of PRSs. Several speciality societies, such as the American Heart Association[28], European Society of Cardiology[29] and American College of Medical Genetics and Genomics (ACMG)[30], as well as a Task Force of the International Common Disease Alliance[17], have commented on the clinical use of PRSs.

Although enthusiasm for using PRSs is increasing — as reflected in the emergence of PRS-focused companies, direct-to-consumer (DTC) genetic testing services[31] and academic centre-based genomic initiatives — the transition to routine clinical use faces several hurdles. These include the limited familiarity of patients and clinical service providers with the probabilistic nature of polygenic risk, the lack of integration of PRSs into electronic health record (EHR) systems and the paucity of clinical decision support (CDS) tools to guide the interpretation of PRSs and the clinical management of patients. There is a need to establish clinical standards for PRSs and regulatory and policy guidelines, given the different methods for constructing PRSs and their application to different diseases. Moreover, outcome studies are needed to establish whether the return of a PRS to an individual improves clinical decision-making and health outcomes, thereby informing practice guidelines and supporting the cost–effectiveness of PRS testing.

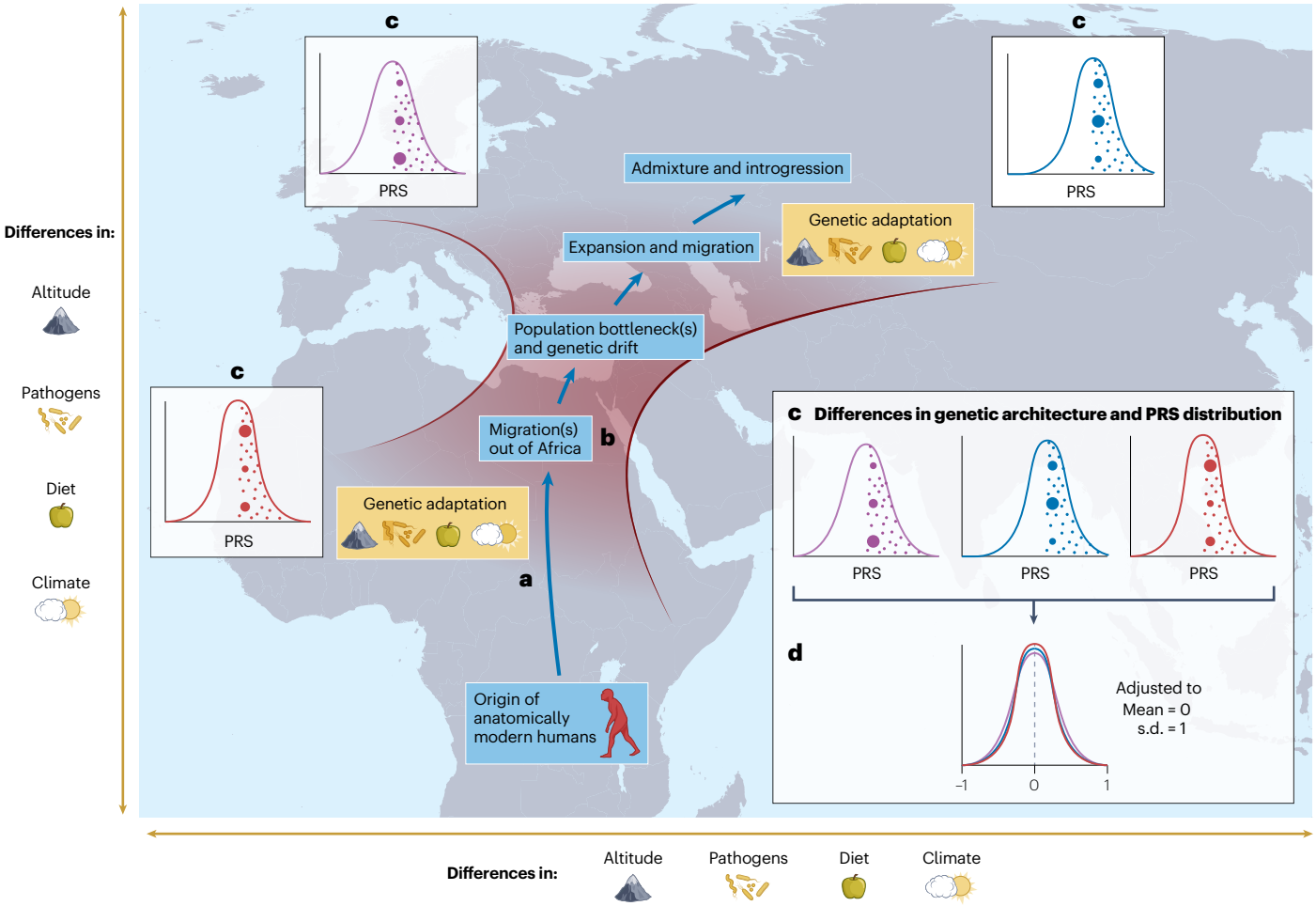


Fig. 1 | The influence of population and evolutionary genetics on polygenic risk scores. A simplified depiction of how human population genetics and evolutionary history underly differences in polygenic risk score (PRS) distributions across continental groups. Both neutral and non-neutral phenomena influence allele frequencies in such groups. The former includes genetic drift and gene flow facilitated by population migration, and the latter includes forces of natural selection[172]. **a**, After their origin in Africa around 300,000 years ago, anatomically modern humans were exposed to diverse environments, pathogens and nutrients, resulting in their genetic adaptation through natural selection. **b**, The subsequent migration(s) of humans out of Africa 50,000 years ago was characterized by a population bottleneck, which increased the effect of genetic drift, followed by explosive population growth and migration[173]. Again, exposure to diverse environments, pathogens and nutrients led to the selection of certain genetic variants in different populations[172]. **c**, Differences in allele frequencies and linkage disequilibrium between populations that have been geographically and culturally separated lead to differences in genetic architecture and in the distribution of PRSs. Although causal variants (represented by larger dots within the PRS distributions) may be shared, the frequency and effect sizes differ between groups. This leads to variable transferability of a PRS that is based on data from one genetic ancestry group to other groups. **d**, To compare effect sizes across different PRSs, traits, cohorts or studies, when the raw score ranges differ, PRSs from different groups are standardized to a mean of zero and a standard deviation (s.d.) of 1.

This Review focuses on the translational aspects of polygenic risk assessment; it summarizes the potential use of PRSs in the clinic, with an emphasis on practical challenges and the evidence that is needed for their responsible implementation. Although other recent reviews have covered PRS methodology and reporting standards[14,27,32], the author focuses here on the next steps required for their clinical adoption, particularly in the context of improving risk prediction for common diseases (see Table 1 for potential clinical applications of PRSs). The current status of PRS testing is discussed within the four domains — analytical validity, clinical validity, clinical utility and ethical, legal and social implications — of the ACCE framework[33], which is a standard analytical process adopted by various entities worldwide for evaluating scientific data on emerging clinical genetic tests. Barriers to PRS use, including scientific and infrastructure gaps, are highlighted. Future directions in data harmonization and regulatory frameworks to bridge the translational divide between genetic discovery and personalized medicine and to promote the successful clinical implementation of PRSs are discussed.

Analytical validity of PRSs

Polygenic risk assessment can be considered an 'omic' technology that uses genome-wide genetic variation to construct a PRS. Here, the author

Box 1 | Calculating a polygenic risk score

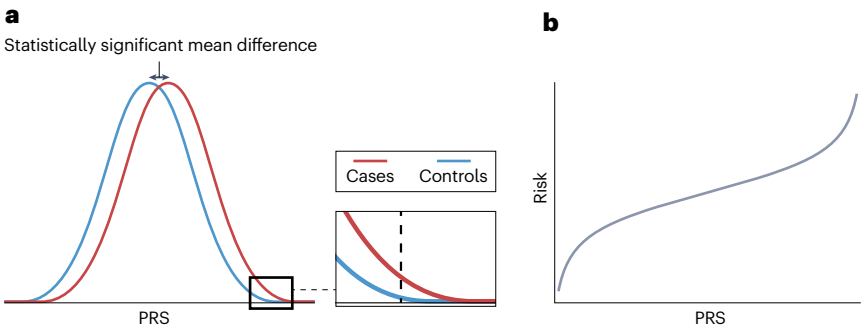
A polygenic risk score (PRS) for a disease or trait in an individual is the numeric value calculated from a PRS model and may be presented as a raw score or as an adjusted score in the context of a population distribution (in other words, as a percentile or standard deviation from the population mean). The PRS for an individual *j* is calculated as follows:

$$PRS_j = \sum_i \beta_i \times G_j^i$$

where β_i is the effect size (or β) of the *i*th genetic variant and G_j^i is the genotype of individual *j* at the *i*th variant.

A PRS scoring file is a list of genetic variants with their associated weights (effect sizes) for a particular trait and is typically included in the Polygenic Score (PGS) Catalog, an open database of polygenic scores and the relevant metadata. The metadata typically include additional details such as the studies and populations used to develop and/or validate the PRS; the method used to calculate the PRS; the number of genetic variants included in the PRS and the genome build.

The overlap between PRS distributions in cases and controls (see the figure) — despite the difference in mean PRSs being highly statistically significant — means that PRSs cannot be used as standalone screening tests. The relationship between a PRS and risk for disease is not linear but rather follows a probit function with flared tails (see the figure, part **b**). As a result, cases are enriched among those with very high PRS scores (as shown by the dashed black line in the inset of figure, part **a**)[174].



discusses aspects related to the analytic validity of PRSs, including identifying genetic variants by genotyping arrays or whole-genome sequencing (WGS), imputation of non-genotyped variants and methods for constructing PRSs and adjusting for genetic ancestry and admixture.

Measuring genetic variation

An initial step in calculating a PRS is the accurate capture of commonly occurring genetic variation across the genome of the individual. Genotyping on arrays, followed by statistical imputation of non-genotyped variants using patterns of linkage disequilibrium, is a cost-effective way to calculate PRSs. For example, the Global Diversity Array[34] includes more than 1.8 million SNVs and is optimized for understudied groups, such as those of African ancestries or Latino ethnicities. Array-based genotyping is highly reproducible for common variants, especially when using the same genotyping platform, rigorous quality control pipelines and high-quality reference panels for imputation[35]. Reproducibility is lower for rare variants, when different genotyping arrays are used, and in cohorts of diverse genetic ancestries. By contrast, WGS can capture both common and rare variants without reliance on imputation, which could potentially provide more robust input data for calculating a PRS. However, the analytical validity of WGS data used in PRS calculations is sensitive to coverage depth, variant calling algorithms and sequencing error rates[36,37]. Insufficient coverage or suboptimal variant calling pipelines can lead to the misclassification of genotypes, which in turn may reduce the performance of PRSs that are calculated from WGS data. At present, genotyping arrays remain the pragmatic standard in most research settings owing to their scalability and affordability whereas, for clinical use, low-pass WGS is emerging as an alternative.

Imputing non-genotyped variants

Genotype imputation — and, by extension, PRS accuracy — is influenced by both genotyping array design and the choice of reference panel[38]. The differences in genotype imputation quality across different reference panels can be substantial and can affect PRS calculation. The quality of imputation depends on several factors, including reference panel size, sequencing coverage of the reference panel, minor allele frequency (in the reference panel) of the variant being imputed, haplotype accuracy in reference and study samples, density of genotyping array, match between the study and reference populations and the imputation algorithm used[39]. Although the 1000 Genomes Project reference panel has been widely used for genotype imputation, larger and more diverse panels such as the Trans-Omics for Precision Medicine (TOPMed) reference panel[40] identify a greater number of variants. However, linear reference panels derived from short-read sequences will miss a proportion of the genomic variation in understudied populations, which could reduce the performance of PRSs in these groups[41]. Recognizing this limitation, the Human Pangenome Project[42] has completed telomere-to-telomere sequencing of 350 individuals from diverse groups to develop comprehensive reference panels that capture most of the genetic variation worldwide. This will enable a more complete ascertainment of genetic variation in non-European genetic ancestry groups, such as individuals of African

ancestries or Latino ethnicities, in turn improving the performance of PRSs for these groups.

Constructing PRSs

PRSs are constructed using two broad categories of method that differ in variant selection strategy: pruning and thresholding or genome-wide methods (for example, LDpred, PRS-CS or SBayesR)[13]. The pruning and thresholding method chooses a *P*-value threshold for disease-associated variants that produces the highest prediction accuracy in a tuning cohort. Correlated SNVs within an arbitrarily chosen window size for linkage disequilibrium are removed to select those SNVs that are nearly independent from each other and thus can be fit additively. By contrast, genome-wide methods include all SNVs simultaneously, accounting for linkage disequilibrium between SNVs, using a reference panel to reduce the risk of overfitting[43]. Statistical techniques are used to apply shrinkage or regularization to the GWAS effect sizes, such as penalized regression (for example, LASSO regression using Lassosum, an R package that adapts penalized regression to GWAS summary statistics[44]) as well as Bayesian approaches (for example, SbayesR or PRS-CS) that implement shrinkage by specifying a prior distribution of SNV effect sizes[45,46]. An independent validation dataset is typically used to assess the predictive power and generalizability of SNV weights. The optimal method (pruning and thresholding or genome-wide) depends on the genetic architecture of a trait[47,48]. Genome-wide methods can adapt to different genetic architectures and tend to perform better than pruning and thresholding[49] but are computationally burdensome, motivating efforts to develop methods that improve both prediction accuracy and computational efficiency, particularly in large biobank-scale datasets[50,51].

Adjusting for genetic ancestry

For clinical application, PRSs must be adjusted to the ancestral background of the tested individual[52]. This requires both inference of the genetic ancestry of the test subject and alignment to appropriate reference distributions. One strategy uses principal component analysis (PCA) to place an individual within a global ancestry space[52,53]. The adjustment of PRSs based on PCA should ideally model both the variance and means of PRSs in an ancestry-dependent manner[52,53]. Alternative methods to adjust for ancestry quantify genetic distance — for example, using Euclidean metrics — to identify reference individuals with similar ancestry, such as by a *k*-nearest-neighbour algorithm[54] or interpolation weights that are based on the Euclidean distance from ancestry groups in the global PCA space[55]. These approaches can improve PRS adjustment to avoid systematic misclassification of risk, particularly in individuals of admixed or under-represented backgrounds.

Clinical validity of PRSs

The clinical validity of a PRS depends on how strongly it is associated with the trait of interest. Metrics for reporting the clinical validity of a PRS[27] include the hazard ratio associated with a 1 standard deviation increase in PRS or with having a high PRS (for example, in the top 5th percentile), the proportion of disease liability[56] explained by a PRS and discrimination as assessed by the area under the receiver operating curve, which is a composite metric of sensitivity and specificity[57]. Additional metrics include reclassification indices and net benefit[58]. Being in the highest range of the distribution of a PRS for certain diseases may be associated with risk equivalent to that posed by the

Table 1 | Potential clinical applications of polygenic risk scores

Application	Detail	Disease-specific example
Refine risk prediction for common disease	As one of the inputs into multivariable risk prediction algorithms[3]	Inclusion of a PRS in clinical risk algorithms to predict absolute risk of CHD or breast cancer[79,160]
Refine risk estimates for disease in the presence of pathogenic or likely pathogenic variants implicated in monogenic disorders	Polygenic background may influence the penetrance and expressivity of monogenic disease[161]	Among carriers of a monogenic risk variant, the probability of disease by age 75 years ranged from 17% to 78% for CHD, 13% to 76% for breast cancer, and 11% to 80% for colon cancer, dependent on polygenic background[161]
Understand the genetic basis of conditions that resemble monogenic disorders but where no pathogenic variants are identified	Examples include heritable cancer syndromes, severe hypercholesterolaemia, prolonged QT syndrome and cardiac hypertrophy[162]	In a UK Biobank study of individuals with a prolonged QT interval (>480 ms) on an ECG, 3.4% carried a monogenic variant, whereas 21% were in the top decile for a PRS[163]
Pharmacogenomics, therapeutic targeting	Assess response to drugs or predisposition to adverse reactions; identify groups who would benefit the most from drug therapy[164,165]	Participants with a higher PRS for type 2 diabetes had greater reductions in haemoglobin A1c in response to sulfonylurea therapy[166]
Targeted recruitment into clinical trials	Enrich clinical trials for higher risk patients to reduce sample size and cost[167,168]	In clinical trials of monoclonal antibodies to PCSK9 that lower LDL-cholesterol, the risk reduction was greater in those with a high PRS for CHD[169]. An a priori prediction and corresponding trial design could have led to a roughly fivefold reduction in trial size by targeting a higher risk subset of patients[169]
Interpretation of laboratory tests in diverse groups	Establish new ranges for laboratory tests in diverse groups after regressing out polygenic influence on such measures[170]	A polygenic predisposition to lower white blood cell counts was associated with a lower risk of identifying pathology on a bone marrow biopsy performed for a low white blood cell count and a higher risk of discontinuing azathioprine treatment[170]
Predict disease trajectory or prognosis	PRSs for disease severity and prognosis have not yet been widely validated given relatively small study cohorts[18]	A PRS for glaucoma predicted glaucoma progression and need for surgical intervention in prospectively monitored individuals with early-onset glaucoma[18]
Identify aetiological pathways activated in an individual	In theory, enrichment in certain aetiological pathways could be detected in a PRS for an individual, with implications for drug therapy[171]	A pathway PRS could distinguish subtypes of inflammatory bowel disease and bipolar disorder[171]

CHD, coronary heart disease; ECG, electrocardiogram; LDL, low-density lipoprotein; PRS, polygenic risk score.

monogenic form of the disease[53]. For example, a PRS for CHD in the top 5th percentile is associated with a twofold to threefold higher risk of CHD than a PRS below this threshold, which is similar to the risk of CHD from a monogenic disease such as familial hypercholesterolaemia[53]. The clinical validity of PRSs in certain settings may be reduced by the modest performance and variable transferability across genetic ancestry groups. Additional aspects relevant to the clinical validity of PRSs include how to calculate absolute risk estimates after incorporating a PRS; how to combine PRSs with other genetic risk factors (family history and monogenic risk), non-genetic risk factors (social, environmental and lifestyle factors) and known clinical risk factors; and how to assess the clinical impact of PRSs in different contexts such as age and sex.

Improving performance

The performance of a PRS improves with increasing size and diversity of the GWAS training datasets[56]. The ceiling for such improvement is set by SNV heritability[59,60] and it is possible that with very large sample sizes of source GWAS, fine mapping of causal variants and functional annotation of genetic variants, a PRS could eventually explain most of the narrow-sense heritability in a trait[61]. In parallel, innovations in methodology could also improve PRS performance, such as the inclusion of genome-wide SNVs to calculate a PRS, using linkage disequilibrium score regression to account for correlation between SNVs. This approach led to better performing PRSs for diseases with high polygenicity, such as CHD, but not for breast and prostate cancers, possibly owing to differing genetic architectures. Additional approaches to improve PRS performance include: the use of multi-ancestry data with ancestry-specific linkage disequilibrium information to provide a more accurate estimate of effect sizes and to identify causal variants[62,63]; jointly modelling multiple correlated traits to leverage pleiotropy across traits[64–67]; incorporating rare and structural variants[68,69]; and the use of functional annotation to weight GWAS variants[14,70].

Transferability across ancestry groups

The performance of PRSs across genetic ancestry groups varies. Methodological innovations can reduce but not eliminate the gap in performance of PRSs in non-European genetic ancestry groups, and there is a need to increase the size of training datasets for such individuals. Recognizing this, the PRIMED Consortium[21] aims to reduce disparities in polygenic risk assessment by both methods development and increasing the size of GWAS datasets for individuals of non-European ancestries. The gap in PRS performance is widest between individuals of European genetic ancestries and African genetic ancestries, owing to the marked imbalance in the size of available GWAS datasets to train PRSs for these two groups. Hence, there is a need to establish infrastructure and biobanks for genotyping on the African continent[25,26] and to increase enrolment of African diaspora populations in biobanks and GWAS. These efforts could also lead to novel insights into human disease genetics, given the greater genetic variation and lower linkage disequilibrium in African populations. Another group for which there are limited GWAS data is South Asians, who comprise nearly a quarter of the world's population. Initial efforts to increase the representation of this group in GWAS include the Pakistani Genome Resource[71] and the Genes & Health study, which includes 40,000 individuals of Pakistani and Bangladeshi origin living in East London, UK[72]. Biobanking projects that are already established or underway across the world[25,26,73], as well as diverse reference panels for genotype imputation and multi-ancestry GWAS, should eventually lead to improvement in the transferability of PRSs[21,63,74].

Use in admixed individuals

In individuals from admixed populations (for example, Uighurs in China and Latinos and African Americans in the USA[75]), PRSs are challenging to calculate and their clinical validity may be reduced as admixture proportions can vary widely from person to person. For example, in Latinos, the average proportion of European genetic ancestries ranges from 45% in Mexican Americans to 80% in Puerto Ricans[76]. Approaches to calculating PRSs in admixed individuals include estimating overall proportions of genetic ancestries and adjusting the PRS accordingly[14]. An alternative approach is to map local genetic ancestry along the genome[77] and then aggregate the PRS from each segment. However, this approach may be limited by the lack of adequate training datasets as well as reference panels for one or more of the source populations. Furthermore, as admixture is pervasive and nearly every human is 'admixed' to some degree, individuals may not always discretely map onto distinct continental ancestry groups used as references. Therefore, methods that incorporate continuous representations of genetic ancestry may prove useful in calculating PRSs[54,55,78].

Joint modelling with other genetic risk factors

Family history and PRSs provide complementary information on genetic risk, which can be modelled jointly for a more complete assessment of disease susceptibility, as demonstrated in analyses of UK Biobank[79] and FinnGen[80] datasets. Both common and rare variants contribute to complex traits[81], and accounting for any linkage disequilibrium between rare and common variants may allow for their joint inclusion in a PRS. An example of jointly modelling a PRS using both common and rare genetic variants (as well as non-genetic risk factors) is the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) model and the corresponding CanRisk tool, which is widely used for breast cancer risk assessment[82]. However, additional work is needed to determine optimal methods for integrating rare variants into a PRS[83]. Prospective cohorts in which family history and rare variants were assessed at the outset and incident disease ascertained at follow-up (for example, as assessed for UK Biobank and All of Us cohorts) are necessary to generate weights for multivariable integrated risk models. In addition, most PRSs comprise genetic variation in the form of SNVs and may capture only a fraction of the total heritable risk for complex traits. Inclusion of genetic variation beyond SNVs, such as structural variants, as well as gene expression, methylation and somatic mosaicism, is likely to improve risk prediction (Box 2).

Joint modelling with environmental, social and lifestyle factors

In addition to genetic factors, the risk of common diseases is strongly influenced by environmental, social and lifestyle factors, and these should be included when assessing risk[58,84] (Box 2). However, such variables have often been inconsistently ascertained in epidemiological studies and appropriate weights for statistical modelling in risk prediction equations may not be available. In a subset of All of Us participants[84] who completed a social determinants of health (SDOH) survey, CHD risk was higher in African Americans than in other self-identified race/ethnicity (SIRE) groups but not after adjustment for the higher SDOH burden in African Americans. In the UK Biobank[58], a polysocial score that included SDOH and psychosocial factors was as strongly predictive for incident CHD as a PRS. In both studies, non-white individuals were at higher risk of CHD and this risk appeared to be mediated by social–environmental factors and SDOH, which supports the concept of race as a social construct. In addition, the PRS for CHD was not

Box 2 | Multiple inputs for assessing risk of a common disease

A polygenic risk score (PRS) is an important input for risk assessment of common diseases for several reasons. First, a PRS is often comparable to or a stronger predictor of disease than individual risk factors. For example, in one study[175], a PRS had greater discriminatory power for incident CHD than any of six conventional factors (smoking, diabetes, hypertension, body mass index, self-reported high cholesterol and family history). Second, for most diseases, the PRS is orthogonal to conventional risk factors and adding a PRS to such factors increases the accuracy of prediction[175]. Third, a PRS in the highest percentile may confer a risk similar to that of a monogenic aetiology[53]. Finally, a PRS can be informative relatively early in life, before other risk factors have manifested[93,175].

Given the complex multifactorial aetiology of common diseases, multiple inputs, in addition to a PRS, are necessary to assess disease risk, disease subtypes and temporal profiles[176–178]. These include:

- Conventional risk factors such as age, sex, adiposity and smoking;
- Genetic factors other than a PRS: family history, rare variants, acquired somatic variants (somatic mosaicism), epigenetic features, structural variants and gene expression;
- Circulating proteomic and/or metabolomic markers;
- Lifestyle, social and environmental factors, including social determinants of health and the exposome;
- Electronic health record data, including results of imaging or other laboratory studies;
- Self-reported or objective measures of physical activity, sleep and other physiological parameters.

Additional factors to consider in assessing disease risk include: (1) risk factors can change over the life course and therefore risk estimates are dynamic; (2) risk factors may vary across different disease subtypes; and (3) single, very strongly predictive biomarkers (for example, having odds ratios of 20-fold or higher) are rare. It is more likely that progress in risk prediction will be made by the continued accretion of low-to-moderate strength biomarkers that are minimally correlated with established risk factors.

The use of complex, multiple inputs for assessing disease risk may require machine-learning approaches as well as model calibration, as described subsequently.

High-dimensional models

Multivariable risk prediction models that include a PRS and clinical, demographic, lifestyle and 'omic' variables can be affected by potential correlations and interactions between these predictors. In this context, machine-learning approaches may offer advantages over traditional regression methods. One such method is elastic net regression, which enables both variable selection and coefficient shrinkage, thereby accommodating correlated predictors and enhancing model stability[179]. Predictor weights can be derived in a training dataset and then validated in an independent test set. By penalizing model complexity, elastic net regression reduces the risk of overfitting and may improve the generalizability of PRS-enhanced models to external populations.

Model calibration

Regardless of the modelling strategy, risk prediction models can be affected by sources of error such as exposure measurement error (inaccuracy in assessing an individual's exposure to a particular lifestyle or environmental factor) and unmeasured confounders (which may account for the observed association between exposure and outcome). Consequently, model calibration (the extent to which predicted probabilities correspond to observed outcome frequencies) is a crucial and often underappreciated aspect of model evaluation[180]. For example, among individuals assigned a 10% predicted risk of developing disease over a 10-year period, calibration would be reflected in 10% of them developing the outcome over this period. Calibration should be assessed using independent and, ideally, population-representative cohorts. Importantly, models that are well calibrated in one population may exhibit poor calibration in another owing to differences in PRS performance, baseline disease risk and covariate distributions. When miscalibration is detected, recalibration techniques — such as updating the baseline hazard or model intercept — may be necessary. Stratified calibration assessments can also help to identify and address disparities in model performance across subgroups, supporting equitable clinical implementation of such models.

correlated with SDOH and thus these factors could be jointly modelled to provide additive risk information.

Clinical utility of PRSs

The clinical utility of a genetic test depends on the adoption of effective evaluation and treatment conditioned on the results and is influenced by factors such as the target population (for example, adults of a certain age range), the prevalence and public health burden of the disease or trait of interest and the potential for mitigating high risk if detected[85–87]. It is important to note that data from a genotyping array for an individual can be used to calculate a range of PRSs to assess susceptibility to multiple conditions, which raises the question of which PRSs should be calculated at what time, and when and how these should be reported to the individual. In phase IV of the eMERGE Network, 20 PRSs that were considered clinically relevant were proposed by the participating sites[52]; 10 of these PRSs were chosen for clinical implementation based on potential actionability as well as the availability of validated multi-ancestry PRSs.

Definitions of clinical utility vary: a narrow definition includes improved health outcomes in an individual, whereas a broader definition also includes personal utility and utility to the family and society. The broad definition of clinical utility of a genetic test adopted by the ACMG is the "effect on diagnosis, therapeutic management, and prognosis, as well as health and psychological well-being for patients and their relatives, and economic impacts on health-care systems"[88]. These aspects are further discussed subsequently.

Medical decision-making and health outcomes

The narrow definition of clinical utility focuses on whether the use of a genetic test improves health outcomes (such as by decreasing morbidity and mortality) as these end points inform practice guidelines and decisions about funding for genetic tests by public health systems

and private insurers[89,90]. However, given the likely long latency between disclosure of a PRS and health outcomes, surrogate or intermediate outcomes are often assessed[91]. These include the influence of PRSs on screening strategies, risk stratification, therapeutic decisions and changes in patient behaviour. An illustrative example is a prospective screening study for prostate cancer[92]: men in the top decile of a PRS for prostate cancer were found to have a higher detection rate of clinically relevant tumours compared with screening of men guided solely by prostate-specific antigen levels or MRI[92]. Supplementary Table 1 lists examples of diseases that pose a substantial public health burden and for which a PRS, combined with traditional risk algorithms and family history, could inform risk-based screening and preventive care. Of these conditions, PRSs for CHD, type 2 diabetes, Alzheimer disease and breast and prostate cancers are already available for use in clinical practice, although not yet routinely implemented[92–95].

Personal utility and societal considerations

Beyond traditional clinical outcomes, the calculation of an individual's PRS may have personal utility through perceived benefits in psychological preparedness, informed life planning and satisfaction from accessing personal genomic information[87,96,97]. Patients may value information for its own sake, even in the absence of clinical actionability, and report impacts on lifestyle, long-term care planning and family communication. At the societal level, PRSs intended for stratifying disease risk must aim for a population-level health benefit and not solely clinical or personal utility for individual patients. An important consideration for policymakers and funders is cost–effectiveness when testing PRSs at scale. Initial reports based on simulation and modelling indicate that the use of PRSs for diverse conditions such as cardiovascular disease[98], type 2 diabetes[99], open-angle glaucoma[100] and various cancers[101–104] is modestly cost-effective. Cost savings could result from targeted versus uniform screening, offering screening to those at higher risk and avoiding screening in those at lower risk.

Evidence base for clinical utility

Despite growing interest in the use of PRSs in the clinic, empirical evidence supporting the clinical utility of PRSs remains limited[92,105,106]. Only a small number of randomized controlled trials have been completed to date[107]. One such study, the myocardial infarction genes (MI-GENES) trial (ClinicalTrials.gov: NCT01936675), randomized participants to receive either conventional or PRS-integrated risk assessments for CHD[95]. Those who received the PRS-integrated score had significantly lower LDL-cholesterol levels at 6 months after risk assessment and, in a post hoc analysis, lower rate of major cardiovascular events at 10 years, likely on the basis of earlier and longer statin use[108]. Other, ongoing, initiatives are expanding the evidence base for clinical utility of PRSs[109,110]. The Genomic Medicine at Veterans Affairs (GenoVA) study (ClinicalTrials.gov: NCT04331535) is a randomized clinical trial looking at whether PRSs for six common diseases (CHD, type 2 diabetes, atrial fibrillation and breast, colorectal and prostate cancers) alter time to diagnosis[110]. PRS-guided mammographic screening for breast cancer is being tested in the Women Informed to Screen Depending on Measures of Risk (WISDOM) (ClinicalTrials.gov: NCT02620852) and Personalized Risk Assessment for Prevention and Early Detection of Breast Cancer: Integration and Implementation (PERSPECTIVE I&I) studies[111,112]. In the USA, the eMERGE Network (ClinicalTrials.gov: NCT05277116) is evaluating near-term outcomes related to medical decision-making following the clinical deployment of PRSs for 10 common conditions[113]. In the UK, the Our Future Health initiative is incorporating PRSs for several chronic diseases, such as cancer, cardiovascular disease, Alzheimer disease and diabetes, within a large (5 million individuals) population-based cohort to examine implementation at scale[114,115]. Implementation of PRSs in national human genomics programmes outside the USA and the UK, such as Genome Canada, Precision Health Research, Singapore (PRECISE), the Danish National Genome Center (DNGC), the Qatar Genome Program (QGP) and Australian Genomics, will provide valuable insights into the utility of PRSs in diverse settings[116].

Although randomized clinical trials remain the gold standard to assess the clinical implementation of PRSs, their feasibility is limited by cost, complexity and long timelines. A diverse array of study designs is therefore essential to evaluate the utility of PRSs in real-world settings. These include prospective and retrospective cohort studies, health economics modelling, simulation-based analyses, implementation science studies, case series and observational designs. As evidence accumulates, standardized reporting will be crucial to compare PRSs and synthesize the data. Assessment frameworks that evolve with new technologies and methodological refinements will be necessary to evaluate the utility of PRSs across diverse healthcare settings. Structured reporting of outcomes and harmonized metrics will be essential to ensure that emerging evidence can guide the responsible clinical use of PRSs. The ClinGen PRS Clinical Utility Working Group is curating evidence for the clinical utility of selected PRSs — beginning with those for breast cancer and CHD — with the intention of developing a systematic framework for assessing clinical utility.

Ethical, legal and social implications

Deploying PRSs in clinical practice has ethical, legal and social implications not only for individuals but also their family members and communities[117]. It is crucial to gather diverse perspectives on the potential benefits and harms of polygenic risk assessment, particularly from populations historically marginalized by genetic research. In addition, engaging legal experts, ethicists and policymakers can help to establish an ethical framework for implementing PRSs.

Equity at the population level

Differential performance of PRSs between groups. The predictive power of PRSs varies widely between and even within demographic groups[118,119] and is lower in individuals of non-European ancestries than in those of European genetic ancestries[17,118]. For example, the odds ratio for CHD for a 1-standard-deviation increase in PRS was twice as high in individuals of European ancestries than in individuals of African ancestries (1.53 versus 1.27)[118]. This raises an ethical dilemma — should PRSs be deployed for routine clinical use for all individuals regardless of genetic ancestry in the face of such disparate performance? It is important to note that despite their lower predictive power in individuals of non-European ancestries, PRSs could still provide useful risk reclassification in certain settings, such as for CHD in African Americans[118]. Strategies to enable equitable polygenic risk assessment across the globe are discussed in more detail in other reviews[25,26].

Race, genetic ancestry and population descriptors. The debate about whether and how to incorporate SIRE in risk algorithms for common diseases is ongoing, despite the consensus that race and ethnicity are not biological constructs but reflect a multitude of factors, mostly social and environmental[120]. Although there is a push to replace race and ethnicity in clinical risk algorithms with SDOH[121], it is worth noting that race and ethnicity capture additional important exposures

that may not be easily quantifiable, such as experiences of racism and discrimination and exposure to unique environmental factors. Incorporating genetic ancestry into risk algorithms is also challenging as individuals are often divided into discrete continental ancestry groups, despite the complex and continuous nature of genetic ancestries. Overall, the addition of SIRE to PRS models could be useful in specific groups with sufficient data (for example, African Americans in the USA) and in certain clinical contexts such as cardiometabolic disease and cancers[122,123].

Implications for public health and screening programmes. The potential application of PRSs at the population level has important public health implications related to equity in disease prevention and management. Widespread implementation of a PRS must be accompanied by efforts to ensure equitable access to testing and follow-up care, to avoid worsening of health disparities[124,125] and to maximize population-level benefit by reducing the burden of disease. There are concerns that increased healthcare expenditures incurred by those with access to PRS testing might divert resources from disadvantaged individuals[126]. In addition, the emergence of private companies offering polygenic risk assessments for embryos raises concerns regarding selecting embryos based on low PRSs for various diseases[127], such as the promotion of eugenics, the imprecision in polygenic risk prediction and the possibility of unwanted pleiotropic effects.

Implications for individuals and families

Implications for individuals. At the individual level, relying solely on a PRS for risk stratification could lead to misclassification — that is, labelling a person as low risk when they are actually at high risk and vice versa[128] — although it should be noted that risk misclassification is inherent to all biomarkers and not unique to PRSs. This could lead to false reassurance or anxiety, contribute to overdiagnosis as part of a multivariable risk model or result in unnecessary interventions[97]. Patients with a family history of disease who receive a PRS that is not high may be falsely reassured. Genetic determinism — the belief that genes define destiny — could distract from the importance of lifestyle and environmental factors in modulating health outcomes. Individuals with a high PRS for conditions such as psychiatric disorders might perceive a sense of inevitability of developing the condition[129] and face social stigma, which could impact their relationships and employment opportunities. For diseases with no known intervention, the potential benefits (in terms of family planning or altered life plans) should be weighed against the stresses of receiving the result.

Implications for family members. The PRSs of first-degree family members are correlated, and in one study, high PRSs for four cardiometabolic diseases were concordant among siblings[130]. However, unlike for single-gene disorders, it is difficult to determine exact probabilities for a high PRS in relatives, as polygenic burden may not segregate predictably within families owing to meiotic recombination and independent assortment. It is therefore unclear when cascade testing for relatives of an index case is necessary or whether a clinician should inform the relatives of an individual with high polygenic risk[131].

Testing children of index cases for PRSs is controversial, and the American Academy of Pediatrics (AAP) and the ACMG recommend postponing genetic testing for conditions that manifest later in life unless immediate actions are necessary[132]. The AAP and the ACMG consider the age of the child — whether they are an older child or a mature adolescent — as influencing the decision whether to disclose results of a PRS. To further explore some of these issues, the eMERGE IV study returned PRSs for four conditions (type 1 and 2 diabetes, obesity and asthma) to children and their guardians[113].

Insurance coverage and genetic discrimination. Individuals and, potentially, their family members must also be made aware of the possible implications for employment and insurance coverage before undergoing PRS testing. Measures for protection against genetic discrimination are in place in countries including Australia, Canada, the USA and UK[133] but the effectiveness of such protections can differ from country to country. For example, in the USA, the Genetic Information Nondiscrimination Act protects individuals from discrimination by employers and health insurers; however, additional protections are necessary for life, disability and long-term care insurance, which are not as yet legally protected in the USA. Despite genetic discrimination being relatively uncommon, the fear of it may deter individuals from pursuing polygenic risk assessment[134,135]. Consideration should be given by policymakers and lawmakers to prohibiting the use of PRSs in underwriting for different types of insurance[133].

Availability of PRS testing. Although reports of the clinical validity and potential utility of PRSs for predicting common disease risk have generated enthusiasm for their use in clinical practice, such testing is not readily available outside the DTC setting[29]. The commercialization of PRSs has been relatively slow for several reasons, including the complex quality control, bioinformatics and statistical pipelines needed to calculate a PRS from genotype data, which may not be familiar to clinical laboratory staff. Genotyping arrays are used widely for research GWAS but not routinely in the clinical setting. Close collaboration among molecular geneticists, bioinformaticians and statistical geneticists is necessary to develop and update PRSs for clinical use. For example, a report from the eMERGE Network highlights the considerable effort needed to develop and calculate clinical-grade PRSs for a range of conditions using genotyping array data[52].

Owing to the limited availability of PRSs in traditional hospital or clinic settings, individuals may turn to DTC genetic testing to learn about their genetic predisposition to disease[31]. DTC genetic testing is relatively easy to obtain and may also include access to a genetic counsellor or a clinician, although follow-up with a clinician is less likely to occur than when results are returned in a clinical setting[31]. Other drawbacks include a lack of transparency as to how genetic risk is calculated, lack of access to clinical data and concerns about how companies handle, store and potentially share genetic data with third parties (for example, researchers or insurance companies), including risks of data breaches and commercialization of patient data without benefit sharing. DTC genetic testing is in a state of flux and it is unclear which models will survive going forward[31].

Barriers to the clinical use of PRSs

There are several barriers to the widespread clinical use of PRSs. As discussed earlier, the major barrier is their limited transferability across diverse ancestry groups, which compromises both accuracy and equity; ongoing efforts aim to increase the diversity of the genotyping data used to construct PRSs, as has been reviewed elsewhere[25,26]. In addition, there is currently a low level of awareness and understanding of PRSs among patients and healthcare providers, although this would be the case initially for any novel medical application. Other obstacles include challenges in communicating probabilistic risk, lack of familiarity among providers in the use of PRSs, the inherent imprecision of

Box 3 | Communicating polygenic risk

When communicating a polygenic risk score (PRS)-informed disease risk to an individual, several factors should be considered. (1) Ideally, the risk estimate should be linked to a clinical action to improve health outcome. (2) Risk estimates may give a false sense of precision; the uncertainty around such estimates should be communicated to the patient to facilitate informed and shared decision-making. (3) Use of visuals such as colour-coded icon arrays and risk percentile ranks can improve the understanding of both clinicians and patients (see the figure, for some examples). Dashboards within a patient's electronic health record could be used to display the PRS alongside traditional risk factors (such as family history, smoking and laboratory test results)[181]. (4) The variation in levels of understanding among patients, as well as their selective engagement with the report, should also be considered when designing PRS reports, to avoid misinterpretation[140]. (5) Patients (as well as care providers) may need guidance on how clinical variables, family history and monogenic variants were combined with PRS results.

The risk information in a PRS can be conveyed using three approaches that are not mutually exclusive[182]: absolute risk over a given period of time, relative risk or odds ratio, or percentile rank within a given population (see the figure; note that the figure does not depict uncertainty around estimates).

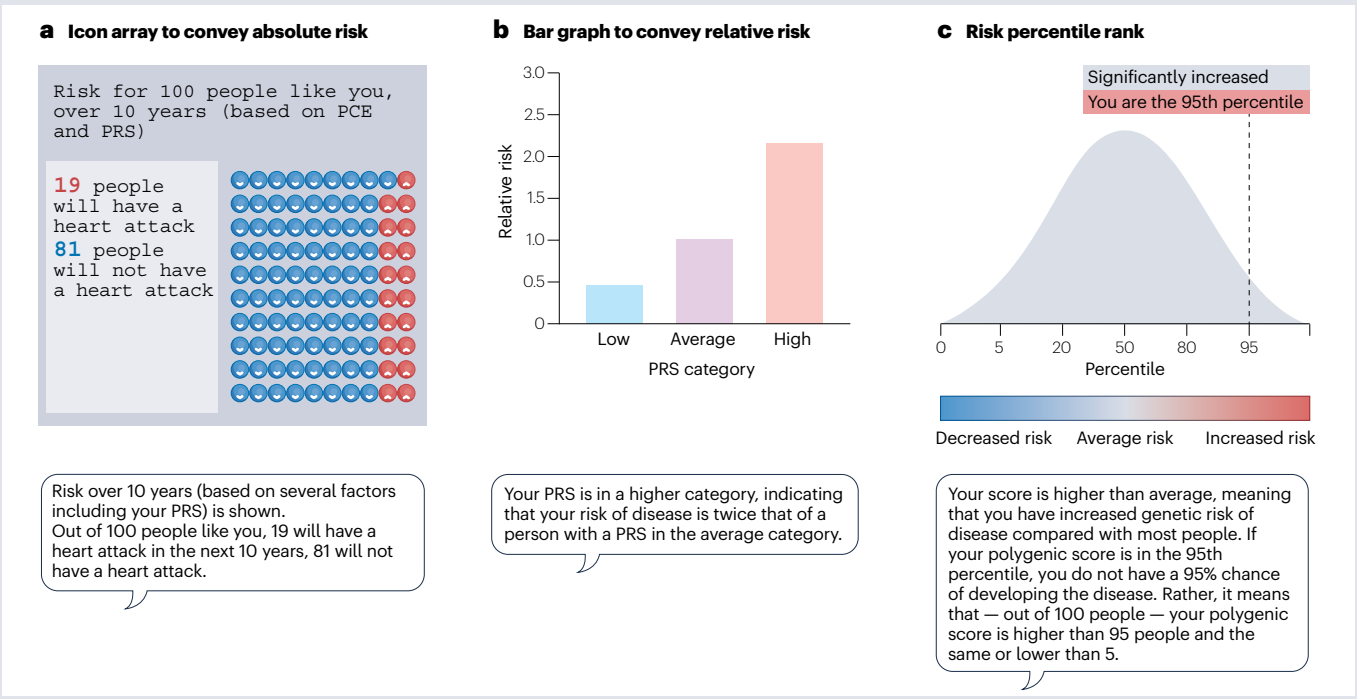
Absolute risk

PRSs are most useful when integrated into existing clinical equations, such as those for breast cancer and coronary heart disease (CHD), that estimate absolute risk over a defined period. The Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) equation for breast cancer risk is the only clinically used equation that can accommodate a PRS, family history and rare genetic variants together with clinical risk variables[160]. The pooled cohort equations (PCEs) for CHD have not yet been modified to include genetic risk factors but as the CHD PRS is orthogonal to PCE, it can be incorporated in a log additive manner into the equations[79]. For most common conditions, such as atrial fibrillation, abdominal aortic aneurysm, diabetes, colorectal cancer or neurological diseases, validated algorithms to estimate absolute risk are typically not in routine clinical use. Here, absolute risk can be estimated using epidemiological indices of disease incidence, mortality and prevalence[183]. It is worth noting that in many countries, the lack or paucity of epidemiological data means that absolute risk estimates may not be available.

Absolute risk estimates are especially useful when linked to management guidelines from speciality societies. For example, a 5-year risk of breast cancer of 25% or higher, as calculated by BOADICEA, would be an indication for regular breast imaging such that any abnormalities on imaging could lead to decisions about chemoprevention or surgery to reduce risk. A 10-year risk of CHD 10% or higher, as calculated by PCEs for CHD, would be an indication to start a statin medication to lower disease risk (see the figure, part **a**).

Relative risk

Alternatively, relative risk can be used if absolute risk cannot be estimated — for example, a twofold higher relative risk of disease for individuals with a PRS in the top 10th percentile (see the figure, part **b**) can be used to translate that information into action. Clinicians might be able to contextualize this information by



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comparing the magnitude of effect with other risk factors for which there are already established guidelines (such as family history).

Percentile rank
A percentile rank compares an individual's PRS with the distribution of PRSs within a chosen population (see the figure, part **c**). However, the percentile rank alone does not enable sufficient clinical risk contextualization, because it gives no indication of how much of the overall disease risk is explained by the PRS.

individual-level estimates and the evolving nature of risk prediction as methods improve.

Challenges in communicating probabilistic risk

Patients often hold deterministic views of genetic risk, underestimating the ability to modify such risk through behavioural or medical interventions. Cultural beliefs — including concepts of fate, heredity and kinship — further shape interpretations of risk information[136]. Therefore, the effective communication of PRSs must emphasize that polygenic risk is probabilistic and that disease risk is dynamic, influenced by modifiable factors such as environment, behaviour and social determinants. Risk communication should be neutral and contextual, highlighting how interventions such as lifestyle changes or medication can modify risk trajectories (Box 3). This approach was successfully implemented in the MI-GENES trial, where a genetic counsellor framed the risk of cardiovascular disease as being mutable[95]. However, risk disclosure by genetic counsellors trained in probabilistic risk communication is impractical at scale. Digital communication tools — including pictograms, animations and videos — tailored according to genomic literacy, educational attainment and sociocultural background may improve understanding[137,138].

Lack of familiarity among providers

The implementation of PRSs could initially be centralized in preventive genomics clinics but as PRS testing is increasingly considered for routine use in preventive medicine, it will likely be introduced in primary care — a setting in which many providers lack specialized training in genomics and may be unfamiliar with probabilistic risk communication[128,131]. Furthermore, the simultaneous calculation of multiple PRSs across a range of common diseases will likely result in a high proportion of patients being flagged as at increased risk for at least one condition[139]. Without dedicated time, reimbursement and clear guidelines, healthcare providers may struggle to interpret and convey such information. CDS tools offering guidance on interpretation and follow-up may facilitate the use of PRSs in primary care, especially when algorithms for estimating absolute risk and relevant specialty guidelines are unavailable[17,95]. For example, the eMERGE Network created a genome informed risk assessment (GIRA) tool to help both patients and providers better understand comprehensive disease risk profiles that include a PRS[113]. In addition, a 'champion user' trained in genetic risk communication could serve as a resource and guide for PRS testing and interpretation in a primary care practice[140]. To equip future clinicians for managing PRS results, polygenic risk assessment should be included as a topic in medical school curricula, in sections that deal with epidemiology, public health and prevention.

Imprecision of individual-level risk estimates

PRSs developed for the major continental groups may have variable performance within these groups owing to factors other than direct genetic effects, including population structure[119,141,142], differing environmental factors[143,144] and assortative mating[145,146]. The impact of such factors can be assessed by comparing a PRS based on standard GWAS with a PRS based on sibling GWAS[145], and potentially mitigated using novel statistical methods. Alternately, multiple cohorts in different regions within a continent could be studied to address this heterogeneity. However, the development of PRSs for every geographic region may not be feasible, and some degree of imprecision is unavoidable when extrapolating a PRS derived from a group to an individual (this problem is not unique to PRSs; most assays in clinical use have a range of intra-assay and inter-assay variation).

Figure 2 illustrates the steps in the PRS development process at which 'noise' could be introduced and propagated, thereby leading to imprecision of risk estimates. A factor contributing to imprecision is the varying performance of a PRS in the context of factors such as age, sex and smoking history[147]. For example, the association between a PRS and disease risk often differs by age group, owing to biological, environmental and other epidemiological factors. These differences can affect the interpretation and clinical application of PRSs across the life course. PRS performance typically decreases with increasing age and the predictive utility of a PRS is greater in younger individuals than in older individuals[148].

These sources of heterogeneity can lead to variability in individual risk classifications, even when the population-level performance of a PRS is robust. As a result, PRSs for a given disease that perform similarly in overall discrimination may diverge in identifying the same individual as high risk[149,150], necessitating caution in clinical use. One strategy could be to use consensus risk thresholds — in other words, instead of using high-risk classification from one score, define high-risk individuals as those ranked in the top tier across more than one PRS. Another approach could be to aggregate multiple PRSs for the same trait into a composite score, reducing sensitivity to the assumptions of any one method[151].

Changes in risk estimates over time

PRS-based risk predictions may change over time owing to age-related factors, the emergence of comorbidities or shifts in environmental exposures, often in a nonlinear manner[152]. In addition, methods to construct PRSs are constantly evolving, and risk estimates could change as PRS performance improves. Mechanisms should be in place to periodically review PRS performance and to estimate risk in a dynamic manner. For such re-analysis of risk, the original genotype or sequencing data for an individual must be available to use the most up-to-date PRS methodology. This problem is somewhat akin to the re-interpretation of rare variants of uncertain significance as new information becomes available. As yet, there is no standard infrastructure for clinical recontact or re-interpretation of genetic tests[128], although some genetic testing companies provide an option for a patient to create a portal through which updates in the interpretation of a genetic test could be communicated. Establishing policies and technical systems to support

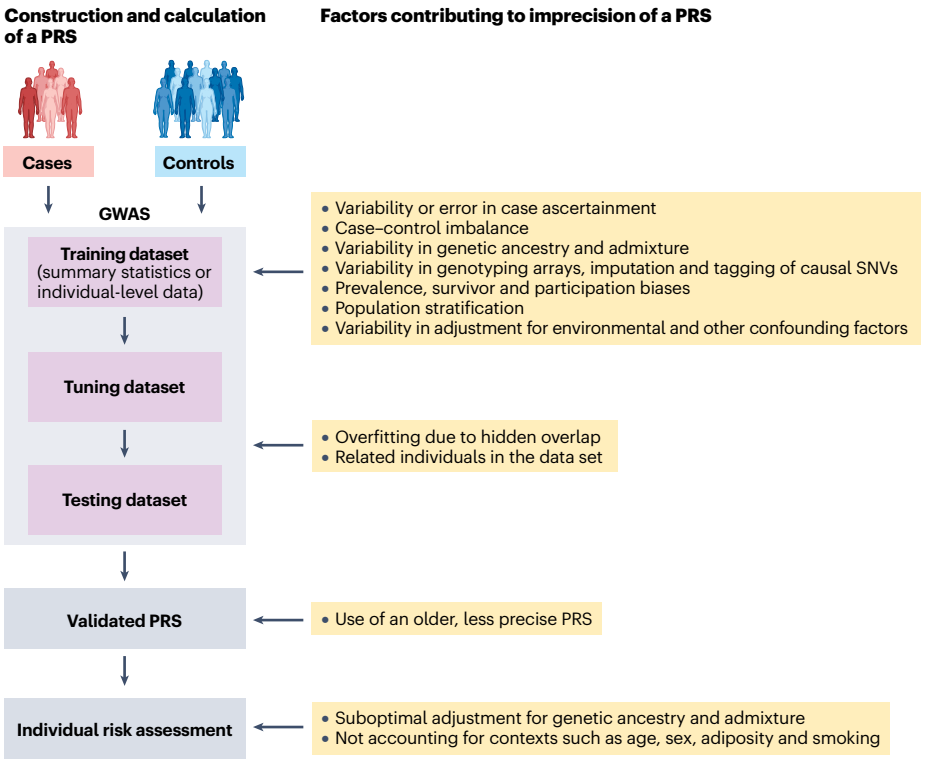

Fig. 2 | Potential sources of imprecision in a polygenic risk score for an individual. Shown are the steps — from genome-wide association study (GWAS)-based training data to the construction of a polygenic risk score (PRS) and the calculation of an individual PRS — at which 'noise' could be introduced, leading to imprecision of risk estimates. SNV, single-nucleotide variant.

dynamic risk assessment will be essential to fully realizing the clinical utility of PRSs in the long term.

Infrastructure and regulatory challenges

Expanding the clinical use of PRSs will require not only overcoming technical and operational barriers but also fostering collaboration across domains to develop robust infrastructures, harmonized data standards and adaptable regulatory frameworks. Crucial components include the integration of genomic data into EHRs, interoperable CDS tools and standardized methods for PRS development, storage and interpretation[153] (Fig. 3).

Storing PRS data in the medical record

Currently, there is no uniform strategy for integrating PRS data — or genomic data more broadly — into EHR systems. An ideal infrastructure would consist of a centralized, secure genomics data ecosystem that includes accredited laboratories linked to cloud-based genomic repositories where validated PRS calculations are performed; an EHR data warehouse for aggregating clinical risk factors; and a CDS system that draws from a frequently updated knowledge base (Fig. 3). These components can be connected through application programming interfaces, enabling modular system upgrades independently of the EHR. The Fast Healthcare Interoperability Resources, which is the global standard for passing healthcare data between systems, provides a framework for encoding genomic data in a structured, machine-readable format, facilitating interoperability between laboratories and EHR platforms[154]. A PRS could be calculated on-demand using validated quality control and informatics pipelines that adapt to new data or evidence. Structured PRS outputs could then trigger CDS system alerts, to enable risk stratification and support communication between providers[154]. Metadata accompanying each PRS should document the version of the algorithm used and its ancestry-specific performance characteristics to ensure interpretability and traceability.

Data standards and harmonization

Unlike single-gene tests, PRSs are derived from genome-wide variant data using a wide range of statistical models and assumptions. Although genotyping and sequencing would be carried out in certified laboratories, standardization is also needed for downstream processes — such as data storage, PRS calculation and clinical reporting — to ensure transparency, reproducibility and comparability across settings. The Polygenic Score (PGS) Catalog (PGS Catalog) is a centralized, open-access repository for published PRSs, providing score files (alleles and weights), phenotype definitions and metadata[155]. However, the completeness and quality of submitted data can vary, and adoption of standardized reporting metrics remains uneven[155]. The Social Science Genetic Association Consortium has published a curated collection of PRSs for 47 predominantly behavioural traits, developed using consistent and rigorous methodologies[156]. The PGS-Calc tool complements the PGS Catalog by allowing users to estimate individual risk using the most appropriate available PRS for a given trait[155,157]. Continued development of such infrastructures will be essential for the independent evaluation and scaling needed for the clinical implementation of PRSs.

Regulatory and policy aspects

Regulatory oversight of PRS testing will have a pivotal role in determining its pace and extent of clinical adoption. Regulatory frameworks vary across regions and countries and must balance innovation with public trust and health equity. A key distinction lies in whether a PRS is classified

as a CDS tool or a medical device. Classification as a CDS tool offers greater flexibility as the PRS would typically be subject to software validation and quality assurance standards, permitting updates to PRS algorithms without requiring repeated regulatory review[112]. By contrast, designating a PRS as a medical device would trigger more rigorous oversight, potentially slowing implementation and innovation[17,112,117]. Given the dynamic nature of PRS methodologies and evidence for their use, regulatory frameworks should incorporate mechanisms for the periodic reassessment of clinical validity and utility of a PRS. Such adaptability will be essential to ensure that the PRSs used in practice reflect the most current knowledge, while maintaining standards for safety and efficacy. In the USA, agencies such as the FDA and Central Laboratory Improvement Amendments (CLIA) aim to ensure that genetic tests are analytically valid, clinically meaningful and safe[158]. The FDA has, to date, generally deferred regulation of laboratory developed tests (such as PRSs) to the CLIA process.

Conclusions

The advent of GWAS ushered in an era of remarkable productivity and discovery in the field of disease genetics and led to collaborative contributions to large meta-analyses[159]. However, this momentum often came at the expense of methodological rigour. Case and control definitions were inconsistently applied, convenience sampling (choosing participants who are readily available and easy to access) was common, most participants were of European genetic ancestries, and population stratification and environmental factors were not fully accounted for (Fig. 2). Consequently, the precision of PRSs at the individual level and their transferability across populations are variable. Although recent efforts aim to address these issues through innovative statistical methods and the inclusion of under-represented populations, PRSs — even in their optimal form — cannot be regarded as standalone predictors of disease onset. Instead, they are one component in a multifactorial framework for risk stratification that incorporates clinical variables, family history, lifestyle and environmental exposures and other omics data (Box 2). The complex aetiology of common diseases requires integrative risk models that reflect both genetic predisposition and environmental context.

Integrating PRSs into routine healthcare delivery presents additional infrastructure and policy challenges. These include the need for secure data storage, computational tools for on-demand PRS calculation and interoperable frameworks for integrating PRSs into

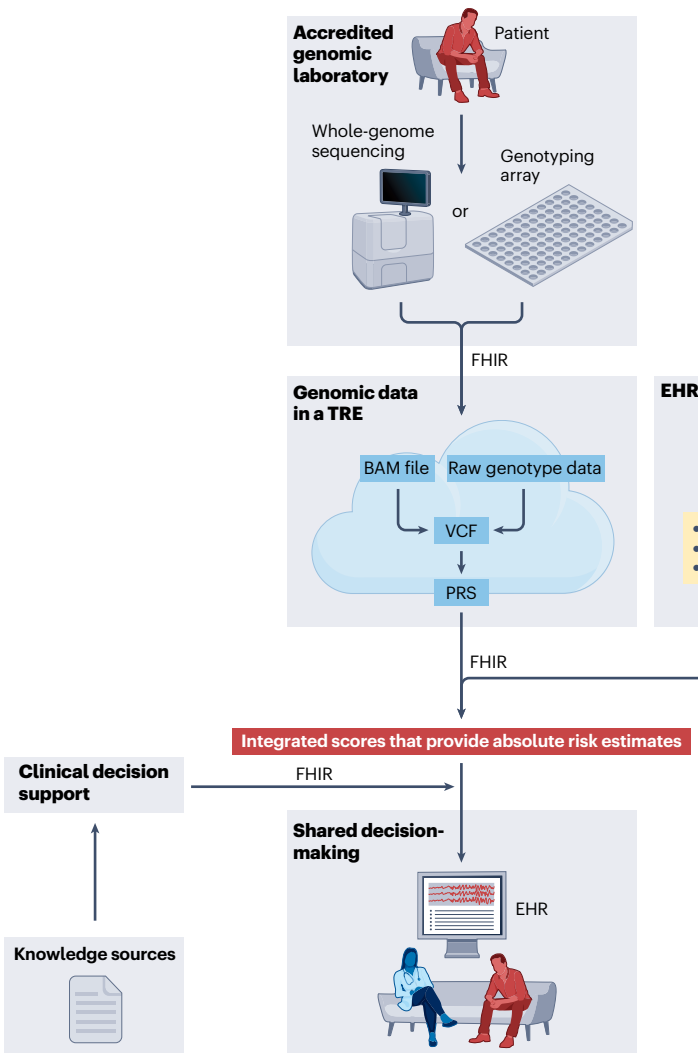

Fig. 3 | A framework for integrating polygenic risk scores into the electronic health record. Genomic data (from whole-genome sequencing or genotyping array) obtained from an accredited laboratory are transmitted to a trusted research environment (TRE or 'cloud'), where polygenic risk scores (PRSs) are calculated. Integrated disease risk scores are calculated using PRSs plus clinical variables, family history and social determinants of health (SDOH) obtained from the electronic health record (EHR) data warehouse. Absolute risk estimates are made available to the clinician with linkage to a clinical decision support (CDS) tool and relevant knowledge sources. Fast Healthcare Interoperability Resources (FHIR) specifications facilitate the exchange of genomic data between different domains[154]. BAM, binary alignment map; VCF, variant call file.

Glossary

Absolute risk
Refers to the actual probability or likelihood of an event occurring in a specific population over a defined time period. It is often expressed as a percentage or a proportion. By contrast, relative risk compares the risk of an event or outcome occurring in two different groups, typically those exposed to a certain factor versus those who are not exposed.

Clinical decision support
(CDS). Refers to various tools and systems designed to enhance the decision-making capabilities of healthcare professionals at the point of care. These tools provide clinicians with knowledge and patient-specific information to help them make informed decisions about patient care.

Disease liability
The unobserved, continuous measure of an individual's predisposition to disease owing to both genetic and environmental factors, with disease manifesting only if liability exceeds a certain threshold.

Genetic ancestry groups
A set of individuals who share similar genetic ancestries based on quantitative measure(s) of genetic resemblance between individuals.

Genetic architecture
The genetic architecture of a quantitative trait or phenotype refers to the number of genetic variants affecting the trait or phenotype, the magnitude of the variants' effects, allele frequencies of the variants and interactions of variants with each other and with the environment, all of which contribute to heritability. Most common diseases are highly polygenic or even 'omnigenic', whereby many thousands of genetic variants of modest effect sizes could have a cumulative effect on disease predisposition.

Heritability
A statistic that estimates the degree of the variation in a trait that is owing to genetic variation in a population. Broad-sense heritability represents the fraction of phenotypic variation explained by both additive and dominance effects; narrow-sense heritability considers additive effects only and is the proportion of phenotypic variation owing to additive effects of multiple genetic variants.

Linkage disequilibrium
The nonrandom association of alleles at two or more loci on the same chromosome.

Polygenic risk
Refers to the cumulative contribution of many genetic variants across the genome to an individual's risk of developing a complex trait or disease. A polygenic risk score quantifies polygenic risk for an individual.

SNV heritability
A subset of narrow-sense heritability that refers to the proportion of the phenotypic variability that is explained by all single-nucleotide variants (SNVs) used in a genome-wide association study. SNV heritability sets a limit on the predictive accuracy of a polygenic risk score based on common variants.

Social Determinants of Health
(SDOH). These are environmental conditions in which people are born, grow, live, work and age. They include economic stability, education access and quality, healthcare access and quality, neighbourhood and built environment and social and community context.

EHRs[128]. Standards must be established for how PRSs are constructed, validated, reported and applied across different clinical contexts. To support the development of clinical practice guidelines, a robust evidence base is needed to show that PRS testing informs medical decision-making and improves health outcomes in a cost-effective manner[128]. Regulatory frameworks must evolve to accommodate the complexity of PRS-guided care, and endorsement from multiple oversight bodies will be essential for the broader adoption of a PRS. Equally important are the ethical considerations related to the use of race, ethnicity and genetic ancestry in the development and interpretation of PRSs[120]. Ensuring equitable access to PRS testing, risk communication and follow-up care, while minimizing the potential for misuse — such as insurance discrimination or the reinforcement of health disparities — is paramount. Achieving this balance will require careful coordination among researchers, clinicians, policymakers and patient advocacy groups.

Despite these challenges, the emergence of PRSs has reshaped the landscape of complex trait genetics and represents an important advance in personalized disease risk prediction. As training datasets grow in size and diversity, and as analytical methods evolve, the predictive accuracy, precision and cross-population transferability of PRSs will continue to improve[25]. Broader implementation of PRSs in clinical research and practice will generate the evidence required to guide policy and funding decisions. When combined with other modalities — such as proteomics, metabolomics, imaging and longitudinal EHR data — PRSs have the potential to markedly improve disease risk prediction, inform screening strategies and support earlier interventions to reduce risk. Such integrative approaches will have a crucial role in reducing the global burden of common complex diseases.

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References

1. Purcell, S. M. et al. Common polygenic variation contributes to risk of schizophrenia and bipolar disorder. *Nature* **460**, 748–752 (2009).
2. Wellcome Trust Case Control Consortium. Genome-wide association study of 14,000 cases of seven common diseases and 3,000 shared controls. *Nature* **447**, 661–678 (2007).
A landmark study in human genetics, demonstrating the power of GWAS by identifying multiple novel genetic variants associated with seven common diseases. The study was an important step forward in understanding the genetic basis of common diseases and led to a subsequent surge in GWAS.
3. Kullo, I. J. et al. Polygenic scores in biomedical research. *Nat. Rev. Genet.* **23**, 524–532 (2022).
4. Wray, N. R., Kemper, K. E., Hayes, B. J., Goddard, M. E. & Visscher, P. M. Complex trait prediction from genome data: contrasting EBV in livestock to PRS in humans: genomic prediction. *Genetics* **211**, 1131–1141 (2019).
This report provides a framework for understanding the similarities and differences between genomic prediction in livestock and humans. Livestock typically have large family sizes and a greater degree of relatedness within a breed, whereas humans have smaller family sizes and there is a focus on unrelated individuals for genetic analysis.
5. Fisher, R. A. The correlation between relatives on the supposition of Mendelian inheritance. *Trans. R. Soc. Edinb.* **52**, 339–433 (1918).
6. Hill, W. G. Can more be learned from selection experiments of value in animal breeding programmes? Or is it time for an obituary? *J. Anim. Breed. Genet.* **128**, 87–94 (2011).
7. Okazaki, A., Yamazaki, S., Inoue, I. & Ott, J. Population genetics: past, present, and future. *Hum. Genet.* **140**, 231–240 (2021).
8. Donis-Keller, H. et al. A genetic linkage map of the human genome. *Cell* **51**, 319–337 (1987).
9. Kullo, I. J. & Ding, K. Mechanisms of disease: the genetic basis of coronary heart disease. *Nat. Clin. Pract. Cardiovasc. Med.* **4**, 558–569 (2007).
10. Risch, N. & Merikangas, K. The future of genetic studies of complex human diseases. *Science* **273**, 1516–1517 (1996).
A commentary that was pivotal in shifting the focus from linkage studies to association studies for uncovering the genetics of complex diseases. The authors argued that association studies, given sufficient sample sizes, would have far greater power to detect common variants influencing disease risk, which laid the conceptual groundwork for GWAS.
11. Manolio, T. A., Brooks, L. D. & Collins, F. S. A HapMap harvest of insights into the genetics of common disease. *J. Clin. Invest.* **118**, 1590–1605 (2008).
12. Wray, N. R., Goddard, M. E. & Visscher, P. M. Prediction of individual genetic risk to disease from genome-wide association studies. *Genome Res.* **17**, 1520–1528 (2007).
13. Choi, S. W., Mak, T. S. & O'Reilly, P. F. Tutorial: a guide to performing polygenic risk score analyses. *Nat. Protoc.* **15**, 2759–2772 (2020).
A comprehensive and practical guide for researchers to carry out PRS analyses, offering detailed protocols and best practices.

14. Kachuri, L. et al. Principles and methods for transferring polygenic risk scores across global populations. *Nat. Rev. Genet.* **25**, 8–25 (2024).
15. Boyle, E. A., Li, Y. I. & Pritchard, J. K. An expanded view of complex traits: from polygenic to omnigenic. *Cell* **169**, 1177–1186 (2017).
16. Visscher, P. M., Yengo, L., Cox, N. J. & Wray, N. R. Discovery and implications of polygenicity of common diseases. *Science* **373**, 1468–1473 (2021).
17. Adeyemo, A. et al. Responsible use of polygenic risk scores in the clinic: potential benefits, risks and gaps. *Nat. Med.* **27**, 1876–1884 (2021).
18. Craig, J. E. et al. Multitrait analysis of glaucoma identifies new risk loci and enables polygenic prediction of disease susceptibility and progression. *Nat. Genet.* **52**, 160–166 (2020).
19. Zhang, J. et al. Polygenic risk score added to conventional case finding to identify undiagnosed chronic obstructive pulmonary disease. *JAMA* **333**, 784–792 (2025).
20. Linder, J. E. et al. Prospective, multi-site study of healthcare utilization after actionable monogenic findings from clinical sequencing. *Am. J. Hum. Genet.* **110**, 1950–1958 (2023).
21. Kullo, I. J. et al. The PRIMED consortium: reducing disparities in polygenic risk assessment. *Am. J. Hum. Genet.* **111**, 2594–2606 (2024).
A perspective on the PRIMED consortium, an initiative aimed at improving the accuracy and equity of polygenic risk assessment across diverse populations to address disparities in genomic medicine and make polygenic risk prediction more inclusive and clinically relevant for global populations.
22. Denny, J. C. et al. The 'All of Us' research program. *N. Engl. J. Med.* **381**, 668–676 (2019).
23. Kurki, M. I. et al. FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* **613**, 508–518 (2023).
24. Bycroft, C. et al. The UK Biobank resource with deep phenotyping and genomic data. *Nature* **562**, 203–209 (2018).
25. Kullo, I. J. Promoting equity in polygenic risk assessment through global collaboration. *Nat. Genet.* **56**, 1780–1787 (2024).
26. Fatumo, S. et al. A roadmap to increase diversity in genomic studies. *Nat. Med.* **28**, 243–250 (2022).
27. Wand, H. et al. Improving reporting standards for polygenic scores in risk prediction studies. *Nature* **591**, 211–219 (2021).
28. O'Sullivan, J. W. et al. Polygenic risk scores for cardiovascular disease: a scientific statement from the American heart association. *Circulation* **146**, e93–e118 (2022).
29. Schunkert, H. et al. Clinical utility and implementation of polygenic risk scores for predicting cardiovascular disease: a clinical consensus statement of the ESC Council on Cardiovascular Genomics, the ESC Cardiovascular Risk Collaboration, and the European Association of Preventive Cardiology. *Eur. Heart J.* **46**, 1372–1383 (2025).
30. Abu-El-Haija, A. et al. The clinical application of polygenic risk scores: a points to consider statement of the American College of Medical Genetics and Genomics (ACMG). *Genet. Med.* **25**, 100803 (2023).
31. Majumder, M. A., Guerrini, C. J. & McGuire, A. L. Direct-to-consumer genetic testing: value and risk. *Annu. Rev. Med.* **72**, 151–166 (2021).
32. Ndong Sima, C. A. A. et al. Methodologies underpinning polygenic risk scores estimation: a comprehensive overview. *Hum. Genet.* **143**, 1265–1280 (2024).
33. Haddow, J. E. & Palomaki, G. E. in *Human Genome Epidemiology: A Scientific Foundation for Using Genetic Information to Improve Health and Prevent Disease* (eds Khoury, M. J., Little, J. & Burke, W.) 217–233 (Oxford Press, 2003).
34. Nguyen, D. T. et al. A comprehensive evaluation of polygenic score and genotype imputation performances of human SNP arrays in diverse populations. *Sci. Rep.* **12**, 17556 (2022).
35. Laurie, C. C. et al. Quality control and quality assurance in genotypic data for genome-wide association studies. *Genet. Epidemiol.* **34**, 591–602 (2010).
36. Goldfeder, R. L. et al. Medical implications of technical accuracy in genome sequencing. *Genome Med.* **8**, 24 (2016).
37. Zook, J. M. et al. An open resource for accurately benchmarking small variant and reference calls. *Nat. Biotechnol.* **37**, 561–566 (2019).
38. Chen, S. F. et al. Genotype imputation and variability in polygenic risk score estimation. *Genome Med.* **12**, 100 (2020).
39. Das, S., Abecasis, G. R. & Browning, B. L. Genotype imputation from large reference panels. *Annu. Rev. Genomics Hum. Genet.* **19**, 73–96 (2018).
40. Kowalski, M. H. et al. Use of >100,000 NHLBI Trans-Omics for Precision Medicine (TOPMed) Consortium whole genome sequences improves imputation quality and detection of rare variant associations in admixed African and Hispanic/Latino populations. *PLoS Genet.* **15**, e1008500 (2019).
41. Sherman, R. M. et al. Assembly of a pan-genome from deep sequencing of 910 humans of African descent. *Nat. Genet.* **51**, 30–35 (2019).
42. Wang, T. et al. The Human Pangenome Project: a global resource to map genomic diversity. *Nature* **604**, 437–446 (2022).
43. Ma, Y. & Zhou, X. Genetic prediction of complex traits with polygenic scores: a statistical review. *Trends Genet.* **37**, 995–1011 (2021).
44. Mak, T. S. H., Porsch, R. M., Choi, S. W., Zhou, X. & Sham, P. C. Polygenic scores via penalized regression on summary statistics. *Genet. Epidemiol.* **41**, 469–480 (2017).
45. Ge, T., Chen, C. Y., Ni, Y., Feng, Y. A. & Smoller, J. W. Polygenic prediction via Bayesian regression and continuous shrinkage priors. *Nat. Commun.* **10**, 1776 (2019).
46. Lloyd-Jones, L. R. et al. Improved polygenic prediction by Bayesian multiple regression on summary statistics. *Nat. Commun.* **10**, 5086 (2019).
47. Mackay, T. F. The genetic architecture of quantitative traits. *Annu. Rev. Genet.* **35**, 303–339 (2001).
48. Timpson, N. J., Greenwood, C. M. T., Soranzo, N., Lawson, D. J. & Richards, J. B. Genetic architecture: the shape of the genetic contribution to human traits and disease. *Nat. Rev. Genet.* **19**, 110–124 (2018).
49. Pain, O. et al. Evaluation of polygenic prediction methodology within a reference-standardized framework. *PLoS Genet.* **17**, e1009021 (2021).
50. Wang, Y., Tsuo, K., Kanai, M., Neale, B. M. & Martin, A. R. Challenges and opportunities for developing more generalizable polygenic risk scores. *Annu. Rev. Biomed. Data Sci.* **5**, 293–320 (2022).
51. Yang, S. & Zhou, X. Accurate and scalable construction of polygenic scores in large Biobank data sets. *Am. J. Hum. Genet.* **106**, 679–693 (2020).
52. Lennon, N. J. et al. Selection, optimization and validation of ten chronic disease polygenic risk scores for clinical implementation in diverse US populations. *Nat. Med.* **30**, 480–487 (2024).
This paper from the eMERGE Network describes the process to optimize and validate PRSs for clinical implementation for 10 common chronic diseases across diverse populations in the USA.
53. Khera, A. V. et al. Genome-wide polygenic scores for common diseases identify individuals with risk equivalent to monogenic mutations. *Nat. Genet.* **50**, 1219–1224 (2018).
This study shows that genome-wide PRSs can identify individuals whose disease risk is comparable to that conferred by rare monogenic mutations, highlighting PRSs as tools for stratifying risk in the general population and catalysing broader clinical interest in the clinical use of PRSs.
54. Zhang, D., Dey, R. & Lee, S. Fast and robust ancestry prediction using principal component analysis. *Bioinformatics* **36**, 3439–3446 (2020).
55. Ruan, Y. et al. Leveraging genetic ancestry continuum information to interpolate PRS for admixed populations. Preprint at *medRxiv* https://doi.org/10.1101/2024.11.09.24316996 (2025).
56. Dudbridge, F. Power and predictive accuracy of polygenic risk scores. *PLoS Genet.* **9**, e1003348 (2013).
57. Chatterjee, N., Shi, J. & García-Closas, M. Developing and evaluating polygenic risk prediction models for stratified disease prevention. *Nat. Rev. Genet.* **17**, 392–406 (2016).
58. Naderian, M., Norland, K., Schaid, D. J. & Kullo, I. J. Development and evaluation of a comprehensive prediction model for incident coronary heart disease using genetic, social, and lifestyle-psychological factors: a prospective analysis of the UK Biobank. *Ann. Intern. Med.* **178**, 1–10 (2025).
59. Yang, J., Zeng, J., Goddard, M. E., Wray, N. R. & Visscher, P. M. Concepts, estimation and interpretation of SNP-based heritability. *Nat. Genet.* **49**, 1304–1310 (2017).
60. Manolio, T. A. et al. Finding the missing heritability of complex diseases. *Nature* **461**, 747–753 (2009).
61. Yengo, L. et al. A saturated map of common genetic variants associated with human height from 5.4 million individuals of diverse ancestries. *Nature* **610**, 704–712 (2022).
62. Koyama, S. et al. Population-specific and trans-ancestry genome-wide analyses identify distinct and shared genetic risk loci for coronary artery disease. *Nat. Genet.* **52**, 1169–1177 (2020).
63. Ruan, Y. et al. Improving polygenic prediction in ancestrally diverse populations. *Nat. Genet.* **54**, 573–580 (2022).
64. Norland, K., Schaid, D. J. & Kullo, I. J. A linear weighted combination of polygenic scores for a broad range of traits improves prediction of coronary heart disease. *Eur. J. Hum. Genet.* **32**, 209–214 (2024).
65. Truong, B. et al. Integrative polygenic risk score improves the prediction accuracy of complex traits and diseases. *Cell Genom.* **4**, 100523 (2024).
66. Krapohl, E. et al. Multi-polygenic score approach to trait prediction. *Mol. Psychiatry* **23**, 1368–1374 (2018).
67. Abraham, G. et al. Genomic risk score offers predictive performance comparable to clinical risk factors for ischaemic stroke. *Nat. Commun.* **10**, 5819 (2019).
68. Barnes, D. R. et al. Polygenic risk scores and breast and epithelial ovarian cancer risks for carriers of BRCA1 and BRCA2 pathogenic variants. *Genet. Med.* **22**, 1653–1666 (2020).
69. Harris, L. et al. Genome-wide association testing beyond SNPs. *Nat. Rev. Genet.* **26**, 156–170 (2025).
70. Norland, K., Schaid, D. J. & Kullo, I. J. Enhancing polygenic scores for cardiometabolic traits through tissue- and cell type-specific functional annotations. *HGG Adv.* **6**, 100427 (2025).
71. Saleheen, D. et al. Human knockouts and phenotypic analysis in a cohort with a high rate of consanguinity. *Nature* **544**, 235–239 (2017).
72. Finer, S. et al. Cohort profile: East London Genes & Health (ELGH), a community-based population genomics and health study in British Bangladeshi and British Pakistani people. *Int. J. Epidemiol.* **49**, 20–21 (2020).
73. Gallagher, C. S., Ginsburg, G. S. & Musick, A. Biobanking with genetics shapes precision medicine and global health. *Nat. Rev. Genet.* **26**, 191–202 (2025).
74. Weissbrod, O. et al. Functionally informed fine-mapping and polygenic localization of complex trait heritability. *Nat. Genet.* **52**, 1355–1363 (2020).
75. Tan, T. & Atkinson, E. G. Strategies for the genomic analysis of admixed populations. *Annu. Rev. Biomed. Data Sci.* **6**, 105–127 (2023).

76. Medina-Muñoz, S. G. et al. Demographic modeling of admixed Latin American populations from whole genomes. *Am. J. Hum. Genet.* **110**, 1804–1816 (2023).
77. Marnetto, D. et al. Ancestry deconvolution and partial polygenic score can improve susceptibility predictions in recently admixed individuals. *Nat. Commun.* **11**, 1628 (2020).
78. Ding, Y. et al. Polygenic scoring accuracy varies across the genetic ancestry continuum. *Nature* **618**, 774–781 (2023).
79. Saadatagah, S. et al. Polygenic risk, rare variants, and family history: independent and additive effects on coronary heart disease. *JACC Adv.* **2**, 100567 (2023).
80. Mars, N. et al. Systematic comparison of family history and polygenic risk across 24 common diseases. *Am. J. Hum. Genet.* **109**, 2152–2162 (2022).
81. Gibson, G. Rare and common variants: twenty arguments. *Nat. Rev. Genet.* **13**, 135–145 (2012).
82. Tsoulaki, O. et al. Joint ABS–UKCGG–CanGene–CanVar consensus regarding the use of CanRisk in clinical practice. *Br. J. Cancer* **130**, 2027–2036 (2024).
83. Smail, C. et al. Integration of rare expression outlier-associated variants improves polygenic risk prediction. *Am. J. Hum. Genet.* **109**, 1055–1064 (2022).
84. Norland, K., Schaid, D. J., Naderian, M., Na, J. & Kullo, I. J. Associations of self-reported race, social determinants of health, and polygenic risk with coronary heart disease. *J. Am. Coll. Cardiol.* **84**, 2157–2166 (2024).
This analysis of the All of Us dataset highlights that increased cardiovascular disease risk in African Americans is owing to higher burden of adverse SDOH. Joint modelling of a SDOH score and PRS improved the prediction of adverse cardiovascular events.
85. Torkamani, A., Wineinger, N. E. & Topol, E. J. The personal and clinical utility of polygenic risk scores. *Nat. Rev. Genet.* **19**, 581–590 (2018).
86. Burke, W. et al. Genetic test evaluation: information needs of clinicians, policy makers, and the public. *Am. J. Epidemiol.* **156**, 311–318 (2002).
87. National Academies of Sciences, Engineering, and Medicine; Health and Medicine Division; Board on Health Care Services; Board on the Health of Select Populations; Committee on the Evidence Base for Genetic Testing. *An Evidence Framework for Genetic Testing* (National Academies Press, 2017).
88. ACMG Board of Directors. Clinical utility of genetic and genomic services: a position statement of the American College of Medical Genetics and Genomics. *Genet. Med.* **17**, 505–507 (2015).
89. Pitini, E. et al. How is genetic testing evaluated? A systematic review of the literature. *Eur. J. Hum. Genet.* **26**, 605–615 (2018).
90. Walcott, S. E. et al. Measuring clinical utility in the context of genetic testing: a scoping review. *Eur. J. Hum. Genet.* **29**, 378–386 (2021).
91. Peterson, J. F. et al. Building evidence and measuring clinical outcomes for genomic medicine. *Lancet* **394**, 604–610 (2019).
92. McHugh, J. K. et al. Assessment of a polygenic risk score in screening for prostate cancer. *N. Engl. J. Med.* **392**, 1406–1417 (2025).
The study shows that incorporating a PRS can more effectively stratify men for prostate cancer risk, improving the detection of clinically relevant cancers while potentially reducing unnecessary screening and overdiagnosis. This work underscores the clinical utility of PRSs in tailoring cancer screening efforts for better outcomes.
93. Mars, N. et al. The role of polygenic risk and susceptibility genes in breast cancer over the course of life. *Nat. Commun.* **11**, 6383 (2020).
94. Mavaddat, N. et al. Polygenic risk scores for prediction of breast cancer and breast cancer subtypes. *Am. J. Hum. Genet.* **104**, 21–34 (2019).
95. Kullo, I. J. et al. Incorporating a genetic risk score into coronary heart disease risk estimates: effect on low-density lipoprotein cholesterol levels (the MI-GENES Clinical Trial). *Circulation* **133**, 1181–1188 (2016).
96. Broadstock, M., Michie, S. & Marteau, T. Psychological consequences of predictive genetic testing: a systematic review. *Eur. J. Hum. Genet.* **8**, 731–738 (2000).
97. Sanderson, S. C. & Inouye, M. Psychological and behavioural considerations for integrating polygenic risk scores for disease into clinical practice. *Nat. Hum. Behav.* **9**, 1098–1106 (2025).
98. Kiflen, M. et al. Cost-effectiveness of polygenic risk scores to guide statin therapy for cardiovascular disease prevention. *Circ. Genom. Precis. Med.* **15**, e003423 (2022).
99. Martikainen, J. et al. Economic evaluation of using polygenic risk score to guide risk screening and interventions for the prevention of type 2 diabetes in individuals with high overall baseline risk. *Front. Genet.* **13**, 880799 (2022).
100. Liu, Q. et al. Cost-effectiveness of polygenic risk profiling for primary open-angle glaucoma in the United Kingdom and Australia. *Eye* **37**, 2335–2343 (2022).
101. Cenin, D. R. et al. Cost-effectiveness of personalized screening for colorectal cancer based on polygenic risk and family history. *Cancer Epidemiol. Biomark. Prev.* **29**, 10–21 (2020).
102. Pashayan, N., Morris, S., Gilbert, F. J. & Pharoah, P. D. P. Cost-effectiveness and benefit-to-harm ratio of risk-stratified screening for breast cancer: a life-table model. *JAMA Oncol.* **4**, 1504–1510 (2018).
103. Callender, T. et al. Polygenic risk-tailored screening for prostate cancer: a benefit–harm and cost-effectiveness modelling study. *PLoS Med.* **16**, e1002998 (2019).
104. Xia, C., Xu, Y., Li, H., He, S. & Chen, W. Benefits and harms of polygenic risk scores in organised cancer screening programmes: a cost-effectiveness analysis. *Lancet Regional Health West. Pac.* **44**, 101012 (2024).
105. Koch, S., Schmidtke, J., Krawczak, M. & Caliebe, A. Clinical utility of polygenic risk scores: a critical 2023 appraisal. *J. Community Genet.* **14**, 471–487 (2023).
106. Kumuthini, J. et al. The clinical utility of polygenic risk scores in genomic medicine practices: a systematic review. *Hum. Genet.* **141**, 1697–1704 (2022).
107. Eklund, M. et al. The WISDOM personalized breast cancer screening trial: simulation study to assess potential bias and analytic approaches. *JNCI Cancer Spectr.* **2**, pky067 (2018).
108. Naderian, M. et al. Effect of disclosing a polygenic risk score for coronary heart disease on adverse cardiovascular events: 10-year follow-up of the MI-GENES randomized clinical trial. *Circ. Genom. Precis. Med.* **18**, e004968 (2025).
In a 10-year follow-up of the MI-GENES trial, disclosing a PRS for CHD alongside a standard Framingham risk score was associated with a lower incidence of major adverse cardiovascular events. This positive effect was likely driven by earlier and longer statin use, leading to lower LDL-cholesterol levels in the group receiving the PRS.
109. Fuat, A. et al. A polygenic risk score added to a QRISK®2 cardiovascular disease risk calculator demonstrated robust clinical acceptance and clinical utility in the primary care setting. *Eur. J. Prev. Cardiol.* **31**, 716–722 (2024).
110. Vassy, J. L. et al. The GenoVA study: equitable implementation of a pragmatic randomized trial of polygenic-risk scoring in primary care. *Am. J. Hum. Genet.* **110**, 1841–1852 (2023).
111. Esserman, L. J. et al. The WISDOM study: breaking the deadlock in the breast cancer screening debate. *npj Breast Cancer* **3**, 34 (2017).
112. Knoppers, B. M., Bernier, A., Granados Moreno, P. & Pashayan, N. Of screening, stratification, and scores. *J. Pers. Med.* **11**, 736 (2021).
113. Linder, J. E. et al. Returning integrated genomic risk and clinical recommendations: the eMERGE study. *Genet. Med.* **25**, 100006 (2023).
This paper describes how integrated genomic risk information that includes a PRS can be returned, alongside clinical recommendations, to patients in real-world healthcare settings, to guide prevention strategies. The study highlights challenges in implementation, providing crucial insights for integrating genomic risk assessment into routine clinical care.
114. Turnbull, C. et al. Population screening requires robust evidence — genomics is no exception. *Lancet* **403**, 583–586 (2024).
115. Cook, M. B. et al. Our future health: a unique global resource for discovery and translational research. *Nat. Med.* **31**, 728–730 (2025).
116. Howley, C. et al. The expanding global genomics landscape: converging priorities from national genomics programs. *Am. J. Hum. Genet.* **112**, 751–763 (2025).
117. Chapman, C. R. Ethical, legal, and social implications of genetic risk prediction for multifactorial disease: a narrative review identifying concerns about interpretation and use of polygenic scores. *J. Community Genet.* **14**, 441–452 (2023).
118. Dikilitas, O. et al. Predictive utility of polygenic risk scores for coronary heart disease in three major racial and ethnic groups. *Am. J. Hum. Genet.* **106**, 707–716 (2020).
119. Mostafavi, H. et al. Variable prediction accuracy of polygenic scores within an ancestry group. *eLife* **9**, e48376 (2020).
This study shows that PRSs can have variable prediction accuracy even among individuals within the same genetic ancestry group, owing to subtle differences in population structure and environmental exposures.
120. National Academies of Sciences, Engineering, and Medicine et al. *Using Population Descriptors in Genetics and Genomics Research: A New Framework for an Evolving Field* (National Academies Press, 2023).
121. Khan, S. S. et al. Development and validation of the American Heart Association's PREVENT equations. *Circulation* **149**, 430–449 (2024).
122. Borrell, L. N. et al. Race and genetic ancestry in medicine — a time for reckoning with racism. *N. Engl. J. Med.* **384**, 474–480 (2021).
123. Lewis, A. C. F. et al. Getting genetic ancestry right for science and society. *Science* **376**, 250–252 (2022).
124. Burke, W. Genetic tests: clinical validity and clinical utility. *Curr. Protoc. Hum. Genet.* **81**, 9.15.11–19.15.18 (2014).
125. Botkin, J. R. et al. Outcomes of interest in evidence-based evaluations of genetic tests. *Genet. Med.* **12**, 228–235 (2010).
126. Clarke, A. J. & van El, C. G. Genomics and justice: mitigating the potential harms and inequities that arise from the implementation of genomics in medicine. *Hum. Genet.* **141**, 1099–1107 (2022).
127. Turley, P. et al. Problems with using polygenic scores to select embryos. *N. Engl. J. Med.* **385**, 78–86 (2021).
128. Slunecka, J. L. et al. Implementation and implications for polygenic risk scores in healthcare. *Hum. Genom.* **15**, 46 (2021).
129. Dar-Nimrod, I. & Heine, S. J. Genetic essentialism: on the deceptive determinism of DNA. *Psychol. Bull.* **137**, 800–818 (2011).
130. Reid, N. J., Brockman, D. G., Elisabeth Leonard, C., Pelletier, R. & Khera, A. V. Concordance of a high polygenic score among relatives: implications for genetic counseling and cascade screening. *Circ. Genom. Precis. Med.* **14**, e003262 (2021).
131. Lewis, A. C. F. & Green, R. C. Polygenic risk scores in the clinic: new perspectives needed on familiar ethical issues. *Genome Med.* **13**, 14 (2021).
132. Ross, L. F. et al. Technical report: ethical and policy issues in genetic testing and screening of children. *Genet. Med.* **15**, 234–245 (2013).

133. Yanes, T. et al. Future implications of polygenic risk scores for life insurance underwriting. *npj Genom. Med.* **9**, 25 (2024).
This paper examines the potential impact of incorporating PRSs into life insurance underwriting processes. The paper also addresses ethical and regulatory concerns related to genetic discrimination and privacy that may arise from the use of genetic data in insurance settings.
134. Green, R. C., Lautenbach, D. & McGuire, A. L. GINA, genetic discrimination, and genomic medicine. *N. Engl. J. Med.* **372**, 397–399 (2015).
135. Amendola, L. M. et al. Why patients decline genomic sequencing studies: experiences from the CSER Consortium. *J. Genet. Couns.* **27**, 1220–1227 (2018).
136. Andreoli, L., Peeters, H., Van Steen, K. & Dierickx, K. Taking the risk. A systematic review of ethical reasons and moral arguments in the clinical use of polygenic risk scores. *Am. J. Med. Genet. A* **194**, e63584 (2024).
137. Wand, H. et al. Clinical genetic counseling and translation considerations for polygenic scores in personalized risk assessments: a practice resource from the National Society of Genetic Counselors. *J. Genet. Couns.* **32**, 558–575 (2023).
138. Widén, E. et al. How communicating polygenic and clinical risk for atherosclerotic cardiovascular disease impacts health behavior: an observational follow-up study. *Circ. Genom. Precis. Med.* **15**, e003459 (2022).
139. Hao, L. et al. Development of a clinical polygenic risk score assay and reporting workflow. *Nat. Med.* **28**, 1006–1013 (2022).
140. Lewis, A. C. F. et al. Patient and provider perspectives on polygenic risk scores: implications for clinical reporting and utilization. *Genome Med.* **14**, 114 (2022).
141. Kerminen, S. et al. Geographic variation and bias in the polygenic scores of complex diseases and traits in Finland. *Am. J. Hum. Genet.* **104**, 1169–1181 (2019).
142. Sohail, M. et al. Polygenic adaptation on height is overestimated due to uncorrected stratification in genome-wide association studies. *eLife* **8**, e39702 (2019).
143. Kamiza, A. B. et al. Transferability of genetic risk scores in African populations. *Nat. Med.* **28**, 1163–1166 (2022).
This study found significant variability in PRS performance within sub-Saharan Africa, noting differences between the South African Zulu and Ugandan cohorts, likely owing to genetic and environmental differences. The findings emphasize the need for increasing GWAS data sets in various regions of Africa to optimize polygenic risk prediction in African populations.
144. Abdellaoui, A., Dolan, C. V., Verweij, K. J. H. & Nivard, M. G. Gene–environment correlations across geographic regions affect genome-wide association studies. *Nat. Genet.* **54**, 1345–1354 (2022).
145. Smith, S. P. et al. A litmus test for confounding in polygenic scores. Preprint at *bioRxiv* https://doi.org/10.1101/2025.02.01.635985 (2025).
146. Plomin, R. & von Stumm, S. Polygenic scores: prediction versus explanation. *Mol. Psychiatry* **27**, 49–52 (2022).
147. Hou, K. et al. Calibrated prediction intervals for polygenic scores across diverse contexts. *Nat. Genet.* **56**, 1386–1396 (2024).
148. Jiang, X., Holmes, C. & McVean, G. The impact of age on genetic risk for common diseases. *PLoS Genet.* **17**, e1009723 (2021).
149. Abramowitz, S. A. et al. Evaluating performance and agreement of coronary heart disease polygenic risk scores. *JAMA* **333**, 60–70 (2025).
150. Ding, Y. et al. Large uncertainty in individual polygenic risk score estimation impacts PRS-based risk stratification. *Nat. Genet.* **54**, 30–39 (2022).
151. Misra, A. et al. Instability of high polygenic risk classification and mitigation by integrative scoring. *Nat. Commun.* **16**, 1584 (2025).
This paper examines the variability in classifying individuals as having high polygenic risk for complex diseases using different PRSs. The researchers propose an integrative scoring approach that combines multiple PRSs for a more robust and reliable risk classification.
152. Urbut, S. M. et al. MSGene: a multistate model using genetic risk and the electronic health record applied to lifetime risk of coronary artery disease. *Nat. Commun.* **15**, 4884 (2024).
153. Kullo, I. J., Jarvik, G. P., Manolio, T. A., Williams, M. S. & Roden, D. M. Leveraging the electronic health record to implement genomic medicine. *Genet. Med.* **15**, 270–271 (2013).
154. Dolin, R. H. et al. Introducing HL7 FHIR genomics operations: a developer-friendly approach to genomics-EHR integration. *J. Am. Med. Inf. Assoc.* **30**, 485–493 (2022).
155. Lambert, S. A. et al. The Polygenic Score Catalog as an open database for reproducibility and systematic evaluation. *Nat. Genet.* **53**, 420–425 (2021).
The paper introduces the PGS Catalog, a comprehensive open-access database to improve the reproducibility and systematic evaluation of PRSs. This resource provides standardized metadata and performance metrics for a wide range of PRSs, facilitating their comparison and application in diverse research and clinical settings.
156. Becker, J. et al. Resource profile and user guide of the polygenic index repository. *Nat. Hum. Behav.* **5**, 1744–1758 (2021).
157. Lambert, S. A. et al. Enhancing the polygenic score catalog with tools for score calculation and ancestry normalization. *Nat. Genet.* **56**, 1989–1994 (2024).
158. Park, J. & Cohen, I. G. The regulation of polygenic risk scores. *Harv. J. Law Technol.* **38**, 377–400 (2024).
159. Abdellaoui, A., Yengo, L., Verweij, K. J. H. & Visscher, P. M. 15 years of GWAS discovery: realizing the promise. *Am. J. Hum. Genet.* **110**, 179–194 (2023).
160. Lee, A. et al. BOADICEA: a comprehensive breast cancer risk prediction model incorporating genetic and nongenetic risk factors. *Genet. Med.* **21**, 1708–1718 (2019).
161. Fahed, A. C. et al. Polygenic background modifies penetrance of monogenic variants for tier 1 genomic conditions. *Nat. Commun.* **11**, 3635 (2020).
162. Saadatagah, S. et al. Genetic basis of hypercholesterolemia in adults. *npj Genom. Med.* **6**, 28 (2021).
163. Nauffal, V. et al. Monogenic and polygenic contributions to QTc prolongation in the population. *Circulation* **145**, 1524–1533 (2022).
164. Johnson, D. et al. A systematic review and analysis of the use of polygenic scores in pharmacogenomics. *Clin. Pharmacol. Ther.* **111**, 919–930 (2022).
165. Gibson, G. On the utilization of polygenic risk scores for therapeutic targeting. *PLoS Genet.* **15**, e1008060 (2019).
166. Li, J. H. et al. A polygenic score for type 2 diabetes risk is associated with both the acute and sustained response to sulfonylureas. *Diabetes* **70**, 293–300 (2021).
167. Klarin, D. & Natarajan, P. Clinical utility of polygenic risk scores for coronary artery disease. *Nat. Rev. Cardiol.* **19**, 291–301 (2022).
168. Fahed, A. C., Philippakis, A. A. & Khera, A. V. The potential of polygenic scores to improve cost and efficiency of clinical trials. *Nat. Commun.* **13**, 2922 (2022).
169. Damask, A. et al. Patients with high genome-wide polygenic risk scores for coronary artery disease may receive greater clinical benefit from alirocumab treatment in the ODYSSEY OUTCOMES trial. *Circulation* **141**, 624–636 (2020).
170. Mosley, J. D. et al. Clinical associations with a polygenic predisposition to benign lower white blood cell counts. *Nat. Commun.* **15**, 3384 (2024).
171. Choi, S. W. et al. PRSet: pathway-based polygenic risk score analyses and software. *PLoS Genet.* **19**, e1010624 (2023).
172. Benton, M. L. et al. The influence of evolutionary history on human health and disease. *Nat. Rev. Genet.* **22**, 269–283 (2021).
173. Pereira, L., Mutesa, L., Tindana, P. & Ramsay, M. African genetic diversity and adaptation inform a precision medicine agenda. *Nat. Rev. Genet.* **22**, 284–306 (2021).
174. Lencz, T. *Reference Module in Life Sciences* (Elsevier, 2024).
175. Inouye, M. et al. Genomic risk prediction of coronary artery disease in 480,000 adults: implications for primary prevention. *J. Am. Coll. Cardiol.* **72**, 1883–1893 (2018).
176. Hasin, Y., Seldin, M. & Lusis, A. Multi-omics approaches to disease. *Genome Biol.* **18**, 83 (2017).
177. Tahir, U. A. & Gerszten, R. E. Omics and cardiometabolic disease risk prediction. *Annu. Rev. Med.* **71**, 163–175 (2020).
178. Joshi, A., Rienks, M., Theofilatos, K. & Mayr, M. Systems biology in cardiovascular disease: a multiomics approach. *Nat. Rev. Cardiol.* **18**, 313–330 (2021).
179. Zou, H. & Hastie, T. Regularization and variable selection via the elastic net. *J. R. Stat. Soc. Ser. B Stat. Methodol.* **67**, 301–320 (2005).
180. Van Calster, B. et al. Calibration: the Achilles heel of predictive analytics. *BMC Med.* **17**, 230 (2019).
181. Brockman, D. G. et al. Design and user experience testing of a polygenic score report: a qualitative study of prospective users. *BMC Med. Genom.* **14**, 238 (2021).
182. Lewis, A. C. F., Green, R. C. & Vassy, J. L. Polygenic risk scores in the clinic: translating risk into action. *HGG Adv.* **2**, 100047 (2021).
183. Pal Choudhury, P. et al. iCARE: an R package to build, validate and apply absolute risk models. *PLoS ONE* **15**, e0228198 (2020).

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