Genetics in Medicine (2023) 25, 100804

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Genetics in Medicine
An Official Journal of the ACMG

www.journals.elsevier.com/genetics-in-medicine

ACMG STATEMENT

Laboratory perspectives in the development of polygenic risk scores for disease: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)

ARTICLE INFO

Article history:
Received 27 January 2023
Accepted 27 January 2023
Available online 27 March 2023

Keywords:
Ethnicities
Laboratory considerations
Polygenic risk scores

Introduction

Complex health related disorders, including some forms of cardiovascular disease, diabetes, asthma, autism, and cancer, arise through the relative contributions of genetic, environmental, and lifestyle factors over long periods of time. Unlike monogenic disorders, complex disorders develop via a cumulative effect across many genomic loci, each conferring small individual risks. Polygenic risk scores (PRSs)[1] combine these small individual variant effects to predict risk for developing complex disorders (Box 1) and may be combined with monogenic disease risk and nongenetic risk factors in an integrated risk model to predict disease risk more accurately. The predictive ability of a PRS is inherently limited by the heritability of each disease or trait within a specific population, and most current PRSs focus on providing personalized risk prediction to individuals for common, chronic diseases that have a *significant* degree of heritability.

The concept underlying PRSs, which are case-control studies used to estimate risk, has been used historically in clinical genetics limited to single or very small numbers of variants[1] (eg, *F5*, *APC*, and *CHEK2* risk alleles and pharmacogenomic diplotypes). PRSs differ in that they are constructed as weighted sums of hundreds to thousands or even millions of risk allele scores using effect sizes from genome-wide association studies (GWAS). From these associations, weights can then be assigned for how much the

The Board of Directors of the American College of Medical Genetics and Genomics approved this statement on January 23, 2023.
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doi: https://doi.org/10.1016/j.gim.2023.100804

Box 1. Definition of polygenic risk score

Polygenic risk score is an estimate of an individual's susceptibility to develop a specific disorder, based upon the weighted association of single-nucleotide variants (formerly single-nucleotide polymorphisms) or risk variants identified in genome-wide association studies.

presence of each variant in an individual contributes to the disease risk.

This Points to Consider document will (1) provide general consideration for PRS-based genetic tests, (2) outline considerations for the laboratory implementing such tests, (3) recommend appropriate criteria for reporting of PRS, and (4) define and disclose the scope and limitations of such tests. We do so by addressing questions critical to the appropriate development and implementation of PRS tests for clinical use in the risk assessment of complex diseases. The clinical application of PRSs will be addressed in an independent document.[2]

General Considerations

Conditions (purpose, methodology) under which PRS could be considered for clinical use

PRSs have unique measurement considerations in what they can and cannot reveal about an individual person's risk of disease. The following considerations describe scenarios in which PRSs may be helpful and some of their general limitations:

1. PRSs are not diagnostic tests. PRSs predict risk in healthy individuals and should not be used for the purpose of diagnosis of a genetic cause of disease. PRS have not been designed or tested for differential diagnosis in symptomatic individuals.
2. PRSs are distinct from monogenic tests. Single gene or panel tests focus on loci and variants with large effects, whereas PRSs evaluate a cumulative risk of multiple loci. Currently combining polygenic and monogenic risk is not always straightforward or appropriate. Some data indicate that PRS may modify an individual's likelihood for inherited disorders;[3-5] however, unless well-validated, test results from PRSs and tests of genes with large effects should be treated as distinct measures.
3. Use of PRSs to predict risk of a specific disease or trait. Individual PRS should not be used to predict risk for traits or diseases in which they have not been validated. For example, it may be tempting to assume that PRS for obesity may relate to development of type 2 diabetes. These phenotypes have a relationship,[1] yet PRSs are very specific, and knowledge of one trait's genetic risk may not be informative for another related trait. The factors considered when the PRS was validated also matters. In some validation studies, traits are derived from research interviews or are self-reported. In many instances, traits are abstracted or computed from billing or diagnostic codes in electronic health records (EHRs). These approaches have different levels of accuracy in determining case/control status and selection biases, which may affect clinical implementation of PRSs. Clinical reports about PRSs should accurately reflect the underlying trait measured.
4. PRSs are intended for heritable common diseases. Currently, PRSs are not as appropriately developed to provide risk for rare diseases. Owing to their typical lower relative risks, PRSs are more meaningful for common diseases with appreciable levels of absolute risk. PRSs for rare diseases may be misinterpreted or considered false positives (disproportionate action in the context of a low predicted relative risk). Even for common, but less prevalent diseases (eg, <1% population incidence), the positive predictive value of a high-risk PRS result may be very low. In addition, current PRSs are not as appropriately developed for common diseases with low heritability, wherein they may be misinterpreted as overstating the genetic component of a disease.[6] PRSs can be useful in cases in which family history is limited and cases in which individuals do not carry pathogenic variants in high-penetrance genes.
5. The harms and benefits of PRS should be considered at the population level and benchmarked against available risk-prediction tools. Although not everyone with high risk for a disorder will develop a given disease and because some individuals at low risk will develop the same disease, there will always be anecdotes of success and failure. Laboratories and health systems need to communicate PRS performance characteristics clearly and accurately, as is done for other clinical variables, such as the use of lipid panels to predict heart disease. Robust evaluation of the benefits of PRSs, cost of PRSs, and harm/benefit ratio should be done at the population scale with recommendations propagated to provider–patient encounters.

Measurement of a PRS

In contrast to monogenic diseases, multifactorial, complex diseases require non–family-based approaches, such as a PRS, because of the lack of population-level genetic segregation.[7,8] As PRS algorithms were being developed, their selection was informed by population genetics data, which typically did not include all ethnic populations, limiting their applicability across populations. The following recommendations describe the considerations in the measurement of PRSs:

1. PRSs generate likelihood ratios, and translation to absolute risk requires an accurate understanding of disease incidence in an individual's population. The likelihood ratios generated using PRSs may be

generated entirely from genomic information and do not communicate absolute risk. In practice, for some clinical applications, PRSs have been combined with other clinical risk scores to form integrated risk scores.[9,10] If an odds ratio is reported, we recommend it be translated to absolute risk for the individual using individual-specific population incidence measures, if available, because studies have shown that most individuals comprehend absolute risk more intuitively than relative risk.[11]

2. PRS methodology heavily rely on linkage disequilibrium (LD), which results in differential utility of PRS by ancestral haplotype. PRS as a concept is already well understood in genetic testing areas, such as pharmacogenomics, and uses common variation, many of which have different frequencies across population ancestries. Although the premise is that biologically relevant variants are in LD with these common variants, the most common biologically relevant variants and LD patterns may vary from population to population. As a result, PRSs validated in one population may not function as effectively in others. This should be considered on a test-by-test basis and adequately addressed before implementation. This is because of both underrepresentation of certain populations in genomic studies and inherent differences in haplotype structure. In addition, admixed individuals have often not been included in data sets used for PRS development. Inclusive community discussions to evaluate acceptability and demand for PRSs before making decisions on implementation are encouraged.

Key learning points

At this time, there is no PRS that has been shown to deliver equally informative and accurate results to individuals across genetic ancestries. The extent to which differences are clinically and ethically meaningful should be decided through inclusive community partnerships and context experts. Decisions may consider the availability, or lack thereof, of alternative risk tools, because this has the potential to exacerbate existing health disparities.

Implementation of PRS for Clinical Use—Considerations for the Laboratory Offering PRS

Implementation of an assay for clinical use includes test development, optimization, and validation. Like other types of genetic tests, assays used to generate clinically reported PRS must meet federal requirements for establishing performance specifications (accuracy, precision, analytical sensitivity and specificity, reportable range, reference intervals, and any other required performance characteristic). These specifications lead to an assignment of overall analytical validity (AV),[12] clinical validity (CV),[12] and clinical utility (CU),[12,13] as well as ethical considerations[14] (commonly referred to as ACCE[15]) of PRSs in specific disease risk prediction contexts (Box 2).

To demonstrate the AV and CV of PRSs for clinical use, genotypes, technology and platforms, imputation algorithms, and sample cohorts being used should be considered.

AV of a PRS for clinical use

To establish the AV of a PRS for clinical use, one needs to keep in mind the following considerations:

1. Genotypes: the source of the genotypes, including whether there are rarer variants driving the model, is of significant importance. Tissue input and analyte isolation procedures used need to be considered as well as the generalizability of the PRS from one assay or methodology to another.[16] One should also consider the type of variant to be evaluated. For instance, determining whether insertions/deletions (InDels) are to be included in the PRSs because they are known to have poor performance on a cytogenomics microarray and higher technical variability in short-read sequencing.
2. Robustness of calls: consistency needs to be observed in genotype calling (whichever method used) to limit variability of the PRS when run multiple times on the same specimen and/or individual.
3. Validation samples: sample cohorts should include multiple replicates of gold standard benchmarking data sets (eg, NA12878). In addition, samples representing

Box 2. Analytical validity, clinical validity, clinical utility, and ethical considerations definitions

Analytical validity refers to the accuracy with which a particular genetic characteristic, such as a DNA sequence variant, chromosomal deletion, or biochemical indicator, is identified in a given laboratory test.[11]
Clinical validity refers to the accuracy with which a genetic test identifies a particular clinical condition.[11]
Clinical utility refers to the risks and benefits resulting from genetic test use. The most important considerations in determining clinical utility are (1) whether the test and any subsequent interventions lead to an improved health outcome among individuals with a positive test result and (2) what risks occur as a result of testing.[11] Also refers to the use of test results to inform clinical decision-making.[12]
Ethical, legal and social implications (ELSI) is a broad category of bioethical benefits and harms of a test for individuals, families, and society.[13]

those to be used in the assay extracted with established in-house protocols should be used to show the ability of these samples to work with the chosen assay. Alternatively, one can obtain publicly available samples for which published PRSs for the condition of interest exist, with the understanding that performance needs to be established in-house.

4. Validation run setup: the laboratory should follow standard guidelines for genetic tests, enabling the evaluation of intrarun and inter-run variability, including multiple replicates of gold standard benchmarking data sets within and across runs.
5. Analytical performance metrics: similar to other genetic tests, the laboratory should establish genotyping accuracy (analytical sensitivity and specificity across required genotypes) and reproducibility (within a run and between runs). All metrics required per regulation can be expressed as a range across replicate samples (eg, analytical sensitivity). In addition, other sample quality metrics (quality scores, coverage, percentage of no-calls, etc) should also be evaluated. If imputed data are used, the analytical performance metrics should be calculated using these data.
6. Limitations of the assay: PRS variability (because of imputation and study cohorts) is expected and therefore the following metrics should be evaluated to establish assay limitations:
   - Reproducibility of the score: the same samples should be run multiple times for each PRS to establish a range of reporting.
   - Determining actionability: reproducibility studies should also document the degree to which PRS obtained from the same sample remained within a given actionability bin. PRSs are often translated into clinical "bins" of actionability based on CU and validity (eg, NCCN Clinical Practice Guidelines[17] suggest that increased screening and follow-up is recommended for individuals with an estimated lifetime breast cancer risk of 20% or higher—although PRSs are not yet endorsed). Laboratories may consider stating high risk vs not high risk or even tiers of risk (eg, low, average, and high).

Technology and platforms used for the development of PRSs

The technology used to measure genomic variation is important for PRSs. Precision and accuracy in variant calling both are important for PRSs when establishing AV, ie, the ability to reliably determine an individual's PRS. PRS calculations may be influenced in different ways if the platform changes. There are several major technology platforms that have been used for PRSs, which can be broadly split into genotype-based or sequencing-based sources.

1. Genotyping arrays: genotyping arrays are the oldest and most often used platform for developing PRSs,[18] targeting specific variants or sites chosen as representatives of blocks of the genome that tend to be inherited together. These representative sites are typically common variants and may show different minor allele frequencies in different ancestral populations. Current genotyping arrays typically target 500,000 to 2,000,000 sites, although specific platforms differ in density and configuration of included sites. Genotyping arrays have been shown to be more accurate for single-nucleotide variants than for InDels and for common than for rare variants.[16]
   Importantly, genotyping arrays do not target all variation and PRSs may rely on a method called imputation, which uses reference populations to statistically infer variation at millions of sites across the genome that were not directly measured.[19] Although imputation can increase the number of variants identified, this comes at the expense of accuracy, with a more substantial drop seen for InDels than for single-nucleotide variants. In addition, imputation typically cannot assess rare variation; although, rare variants are not typically included in PRS calculations. The completeness and accuracy of imputation depends both upon the reference population data set and the genetic ancestry of the individual. Common reference panels include the Haplotype Reference Consortium (http://www.haplotype-reference-consortium.org/) and the 1000 Genomes Project (https://www.genome.gov/27528684/1000-genomes-project). Each reference population differs in terms of the diversity and size of the reference population, affecting performance in different populations, with the accuracy of imputation being higher for more well-studied populations with larger reference samples.
2. Sequencing: sequencing-based assays range from amplicons to gene panels, exomes, and genomes. Genomes can detect the associated variants present within a PRS at high accuracy with few limitations, whereas the other techniques typically do not cover most variants included in PRS models. Although genome sequencing costs have been substantially reduced, it is still costly compared with other methods,[20,21] and therefore off-target exome sequencing[22] has been proposed as a possible strategy for obtaining data for PRS calculation. Various techniques measure an assortment of alleles randomly selected from the genome and use data from reference populations to determine the most likely haplotypes in the individual, a technique called imputation. However, low-pass genome and off-target exome sequencing methods require similar imputation techniques to identify genome-wide variations as genotyping arrays and therefore suffer from similar reductions in accuracy.

Table 1 High-level distinctions of the different categories of PRS and the algorithmic considerations underlying them

Categories	Algorithmic Considerations
Extended PRS	PRS that are extended to hundreds to thousands or even millions of sites with low individual effect scores. These PRS can generate larger likelihood ratios at the extremes of the distribution, although it may suffer from increased ancestry specific bias, including predictive power coming from measures of geographic effects[7,8] and fine-scale population stratification rather than genetic effects.
Stand-alone PRS	PRS that use only genetic data to generate likelihood ratios. This makes validation of the laboratory and bioinformatics processes more straightforward, although it may lead to less predictive power than integrated PRS.
Integrated PRS	PRS that incorporate other demographic or health data with genetic data, potentially including monogenic findings. Although integrated PRS generally have more predictive power than stand-alone PRS, they are more challenging to validate because of the sources of the additional data. The quality and sources of nongenetic information should be regularly checked to make sure an integrated PRS remains valid.
Ancestry specific PRS	PRS developed in and validated for specific population ancestries.[29]
Transethnic PRS	PRS using a diverse validation group or methods to cross-walk information from larger population groups to inform groups with smaller numbers of validation samples.[30]

PRS, polygenic risk score.

An additional component of platform evaluation is determining the need to identify rare variants that may be related to the phenotype of interest. Although most PRSs use common variations, some specifically use genotype high-impact variation at lower minor allele frequencies (ex. *APOL1* in chronic kidney disease).[23] In these instances, it would be critical for the laboratory to specifically validate the performance of these sites and to monitor the high-impact variations specifically during testing, which possibly fail the PRS if the site cannot be genotyped. In addition, recent work has shown potential for combining risk estimates from PRS with rare variation associated with Mendelian disease.[24] In this instance, it would be important for the laboratory to know the performance of common pathogenic variations in their assay to determine the applicability of implementing a method combining rare Mendelian variations with PRS. For reasons discussed above, genome data would be most complete for these scenarios, unless the genotyping array was specifically designed and validated to detect these variants.

Bioinformatic and statistical algorithms used for the calculation of PRS

As PRSs are an emerging field, there are an increasing number of approaches and models used to create disease-associated weights. The earliest models focused on sites whose disease association passed a threshold for genome-wide significance, often limiting the PRS inputs to few sites, which may be more easily and directly genotyped. More recently adopted models[25,26] incorporate information from hundreds of thousands to millions of sites across the genome, paring them down to informative sites based upon LD structure and other measures. These models therefore require either genome sequencing or imputation to determine variant status. High-level distinctions of the different categories of PRS including genetic risk scores and the algorithmic considerations underlying them are listed in Table 1. Considerations for the calculation of PRSs are outlined below:

1. Approaches to calculating PRSs in multiple ancestries can vary. The use of ancestry specific PRS may require a laboratory to validate multiple PRSs for the same disease, and there could be challenges in determining which PRS to apply to an individual, particularly for individuals with admixed ancestries. For transethnic PRSs, some studies have shown that they can be more predictive than PRSs based upon a single ancestry; however, challenges in designing appropriate validation and limitations into applicability beyond populations included in the PRSs still apply. Even with the use of ancestry specific or transethnic PRSs, the odds ratio for high-risk individuals may vary by ancestral or geographic stratification, and for ancestry, the clinical implementation of PRSs may require additional considerations, such as adjustment of raw scores or calculation of the true risk differences by genetic ancestry.[7,8] If appropriate PRSs are not available, choosing mismatched PRSs may lead to worse outcomes. Laboratories should clearly communicate limitations related to ancestry on their reports.
2. PRSs are dependent upon accurate and consistent phenotype data. The ability of a PRS to predict risk is only as accurate as the disease status information it is based upon. Although some phenotype data may come as discrete laboratory results, much of it comes from self-reported questionnaires or information extracted from the medical record, both of which may contain errors. In addition, use of International Classification of Disease, Logical Observation Identifiers Names and Codes (LOINC), or Current Procedural Terminology (CPT) codes alone may contain errors and may not accurately reflect disease status, particularly in cases in which office visits or testing are to rule-out a condition.

Fortunately, more sophisticated algorithms, including those developed by the eMERGE consortium, that combine coded data from the EHR with natural language processing of notes have proven accurate at predicting disease state.[27] It is important for the clinical laboratory to determine whether the disease association in the GWAS and PRS is the disease of interest for their assay and to detail these specifics in their reports.

3. The underlying GWAS data that feed into the models are constantly expanding. There are newer and more diverse data sets continuously available. Larger data sets can enable more refined estimates of disease risk per site, especially for less common variants, and may tease out tag sites from variants with true effect, thereby improving the accuracy of the PRS.[28]
4. Sex-specific PRS risk considerations: for phenotypes that have been validated in a sex-specific context (eg, breast and prostate cancer), the laboratory needs to choose how it determines the sex to use for the individual (self-reported sex at birth vs sex determined from the assay). If using metrics such as a count of X-chromosomes, discrepancies may occur for individuals with underlying genetic conditions, such as sex chromosome aneuploidies. Considerations should also be taken for transgender individuals, especially for those with hormonal or surgical interventions that likely have not been modeled in the PRS development.
5. Other GWAS considerations that underlie PRSs; because PRSs are statistical associations, there are many considerations for their development that can significantly change their interpretation or application, including adjustment for latent, or unobserved, population structures. Such adjustment is common, but how it is done often varies. In addition, adjustment for per-person factors such as age, sex at birth, etc, may also be included in the validation of the model. How such adjustments are done as part of the development and validation can alter the interpretation of the PRSs compared with that using published studies and should be carefully considered by the laboratory.

CV and CU of a specific PRS

A PRS with demonstrated CV cannot be assumed to have CU. The accompanying Points to Consider statement[2] goes into detail on how CV and CU are weighed in deciding the appropriateness of a PRS for testing in a specific disease and population context. We briefly summarize these key considerations.

1. CV parameters are established through PRS development and validation procedures. A comprehensive list of CV reporting steps in PRS development and validation are provided in the ClinGen Polygenic Risk Score Reporting Standard.[31] PRSs may be validated for stand-alone use or in an integrated risk model.
2. CV is a precursor to CU but should not be conflated as utility. CV simply describes the context in which a PRS has been demonstrated to reliably predict a disease or trait phenotype, eg, in what population (age, ancestry, etc) or within what timeframe (10-year risk vs lifetime risk). Improved prediction does not guarantee increased health benefits. Other types of evidence are needed to demonstrate the CU of a PRS or integrated risk model.
3. Studies establishing CU of a test must demonstrate health benefits via an intervention using PRS-based risk information. This requires prospective and carefully phenotyped studies that intervene using PRS risk information. Typical study designs to establish CU are randomized control trials or pragmatic clinical trials. The clinical relevance of risk thresholds should be validated in these trials.
4. CU depends on the health benefits of the associated intervention. It is important to consider the availability of treatments when proposing new polygenic score–based applications of risk assessment.

Ethical considerations for PRS

Many of the ethical, legal, and social issues considered in Mendelian testing apply to PRSs,[32] and implementation and reporting of PRSs should follow ethical standards used in genetic testing to protect individuals from possible harms.

1. Informed consent should cover the benefits, risks, and limitations of a specific PRS. Recommendations for clinicians consenting individuals for PRS testing are provided in the accompanying Professional Practice and Guidelines Committee document.[2]
2. Laboratories and health care institutions should have appropriate data protection procedures and policies. Institutional policies may cover topics such as the return of secondary findings (when results are actively sought but are not the primary reason for testing), incidental findings (when results are not being intentionally sought, although they may be anticipated because they are known to be potentially associated with the test), or unanticipated (not typically associated) and the potential for genetic discrimination.
3. With respect to potential discrimination, PRSs differ from Mendelian genetic information in that it is risk prediction information based on a statistical association and does not indicate a diagnosis or definitive probability of disease. This should be clearly conveyed in laboratory results to avoid misinterpretation from insurance and other third parties.
4. As a population health tool, PRS should be available for everyone in a target population (an at-risk group for which the PRS is identified as valuable) and therefore is recommended to be applied uniformly. At minimum, PRS offered by clinical laboratories and health care institutions should be validated for diverse

ancestries; ideally, PRS performance is also equally optimized for all ancestries.

Key learning points

Currently, there are no large-scale studies that have established the CU of PRS or integrated risk models. CU should be disease and individual population specific and must be established before broad implementation of PRSs.

Considerations for Reporting of PRSs

Integration of PRSs into clinical risk calculation has the potential to inform risk management strategies and improve disease prevention in different disease settings. A recently published prospective study on atherosclerotic cardiovascular disease risk estimation including PRSs of a cohort of 7342 individuals demonstrated positive effects of reporting PRSs, such as motivation of favorable health behavior change and propensity to seek medical attention.[33] Although PRS reporting is being rapidly implemented into clinical practice, the approaches taken by different groups have been highly variable. Brockman et al[34] reviewed the existing PRS reports from commercial and academic groups and highlighted the unmet need for additional efforts to standardize score disclosure. The key insights on reporting PRS from this study were (1) visual elements (eg, color, simple graphics) and numerical estimates in the form of percentiles can have significant effect on the study participants' understanding, recognition, and interpretation of their PRS and (2) owing to varying levels of interest in understanding complex medical and genomic information, study participants would benefit from resources adapted to their individual needs in real time. Static genomic test reports would limit one's ability to explore results and therefore are not desirable for PRS disclosure. Compared with single risk gene information, PRSs require a more personalized approach for risk communication. PRSs should be provided along with a discussion about the nature of PRSs and the individual's personalized level of risk. Special considerations should also be given to the limitations and uncertainties of PRSs in result interpretation and reporting.[35]

1. The intended purpose of the PRSs should be clearly stated on the report, including what trait or disease is being predicted and how results might inform care. The predicted outcome of the PRS should also be defined (eg, type 2 diabetes based on HbA1c $\geq$ 6.5% vs type 2 diabetes based on HbA1c and end stage renal disease). If clinical guidelines become available for specific PRS or integrated risk models, then they should be referenced in the report for clinicians to refer to when formulating a medical management plan.
2. It should be clearly stated that PRS is a risk prediction tool and not meant for diagnostic purposes. Language of the report should not be deterministic, rather it should convey the uncertainty of the predicted outcome and absolute risks may be influenced by other factors such as age or can be modified based on interventions. In addition, the report should clearly convey the predictive limitations of the model (missing heritability or limited understanding of nongenetic risk).
3. PRS can be presented as continuous or categorical risk. Some phenotypes are dichotomous, whereas others vary along a smooth spectrum. A PRS may provide a specific level of risk in either case, or be binned to compare, for example, tenth and 90th percentiles where individuals would be classified as within certain risk tiers. These performance and reporting specifications need to be addressed in the validation process.
4. Reports should optimize principles of numeracy and risk communication. The individual's risk in relation to the PRS distribution should be reported. This should include the individual's relative risk of a specific predicted outcome in comparison to the average risk, with outlined conditional parameters that were used to validate the PRS. Temporal conditions with the predicted risk, such as risk of outcome over the next 10 years, should be stated clearly. It would also be of benefit to report the absolute or lifetime risk when available, which is often confused with relative risk by individuals getting tested and clinicians alike.[36] Most individuals benefit from having risk presented in multiple ways (eg, stating both 90th percentile and top 10%) and in visual format.
5. In instances of using integrated risk models that combine genetic risk and nongenetic risk, the report should clearly present all variables contributing to an individual's overall risk estimate. Providers and patients should have a sense of how much the PRS contributes to the risk. It is therefore helpful to relate the relative effect sizes of variables influencing the positive predictive value of the risk model. If the lab result is the PRS alone, it is recommended that it be included in the EHR. If the lab result is the integrated score, then the integrated risk is what should be displayed in the EHR.
6. Technical limitations of the testing should also be clear and transparent on the report.[37] It may be of value to report if an individual's self-reported race (or another demographic variable) has been shown to have reduced predictive value or has not yet been validated by the specific PRS model. This is important in any instance when the individual differs from characteristics of the research study used to estimate the effect size of each genetic variant by genetic ancestry, age, environmental load, or disease definition or when there is a technical bias in data collection. A general

limitation statement detailing reduced performance in specific ethnicities or admixed populations may also suffice.
7. Negative or low risk results should have language to ensure that these results are not misunderstood as having no risk for disease. PRSs are intended to add precision to risk stratification in the population for conditions with anticipated actionability. Consistent with current preventive screening practices, individuals indicated as negative or low risk by a PRS or integrated risk score should still monitor their risk of developing that disease as nongenetic risk factors may increase risk with time.
8. Recommendations for post-test counseling are covered in the accompanying points to consider.[2] These counseling recommendations consider issues surrounding clinical management/actionability, familial risks, and personal utility/psychosocial considerations.

Key learning points

Integration of PRSs into clinical reporting has been implemented in multiple disease settings; however, the approaches of communicating PRS are highly variable. A more personalized way of risk communication is required for PRS reporting. The limitations and uncertainties of PRSs should be clearly indicated in the report.

Special Considerations

Testing in the context of Mendelian conditions

If the PRS is being used within a joint prediction model for Mendelian disease risk, there are additional challenges in validating the use of these combined tests.

1. The target populations for testing differ. Mendelian testing is usually done in high-risk populations with significant family history; the weight/penetrance of rare variants may be inaccurate or unknown in asymptomatic individuals. Challenges exist with testing of healthy populations and should be given careful consideration[38,39] keeping in mind the potential benefits and risks.[40]
2. The risk information conveyed by each test type differs. Mendelian variant curation frameworks rely on an understanding of disease mechanisms and rare variants classified as pathogenic speak to the underlying biology. PRS describes a statistical association, and high-risk does not indicate an underlying disease pathology. Similarly, rare variants curated in Mendelian variant curation frameworks can be considered for diagnostic criteria, whereas PRS is solely considered screening information. There is no clear guidance on how these different types of risk information can be accurately combined or related to one another.
3. The predicted phenotype of a PRS may not be appropriate for Mendelian diseases. PRSs predict complex conditions and can use other clinical risk markers in an integrated risk model when possible. These conditions may not correlate 1:1 with Mendelian phenotypes. For example, familial hypercholesterolemia is a primary low-density lipoprotein cholesterol disorder that can lead to coronary artery disease. PRSs that predict low-density lipoprotein[41] may be the most accurate counterpart for combined risk prediction in this population, yet most PRSs[3] will predict coronary artery disease and often with other clinical risk factors, such as glucose and blood pressure, that are typically not assessed in individuals at risk for familial hypercholesterolemia. This is related to the first issue of clearly defining the target population for testing and the purpose in risk prediction for that population.
4. When designing reports including both monogenic high-penetrance variants and PRS in a joint model, the potential effect on medical management must be considered. Many thresholds for prophylactic action or screening recommendations are dependent on lifetime or absolute risk of disease, which are traditionally dependent on well-established risks conferred by Mendelian conditions, such as hereditary breast and ovarian cancers, familial hypercholesterolemia, or predictive risk models based on other inputs such as family history (eg, BRCAPRO).[42] It is therefore important to consider the clinical impact of reporting results from a joint model evaluation.

Secondary findings in PRS analysis

The laboratory may detect moderate or high penetrant variants for a Mendelian disease or other similar genetic variants, some of which may be related to the disease risk being predicted by the PRS and others may relate to a separate disease or represent heterozygous pathogenic variants for autosomal recessive disease. The laboratory should have a clear policy on whether these variants will be included in result reporting.

Reanalysis of PRSs as improved polygenic risk or integrated risk models become available

Returning results at regular time intervals is not a precedent in genomic medicine in which current practices around revisiting genetic risk information are prompted by either new results or new symptoms. In preventive practice, a setting in which PRSs are likely to be used, risk information is revisited regularly (typically at annual exams or other set time frames of screening). Although the risk information obtained from a PRS is stable over time, new or updated PRS may be developed, and integrated risk values

will continue to change. Implementing a newer or improved algorithm would require the laboratory to revalidate and determine its unique performance, possibly necessitating an updated report if an individual's score is reanalyzed.

Future Considerations

Promoting health equity

PRSs are often more accurate in individuals of European ancestry than in others because of the biases in Eurocentric GWAS and their overgeneralized use, which may lead to worse outcomes for minority populations. To realize the full potential of PRSs, there needs to be greater diversity in genetic studies to ensure that health disparities are not further increased.[43,44]

Epigenomic risk modeling

PRSs are a DNA-based test and potential interactions between genetic susceptibility and epigenetic changes may not have been considered. Given the effect of environment on the epigenome, future work should consider adoption of new methods for including the epigenome in more precise and individualized types of PRS.[45]

Assisted reproductive technology

The use of PRSs as an adjunct to embryo selection through in vitro fertilization and preimplantation genetic testing is not recommended at this time because of the lack of CV and utility of this technology.[46,47] There are currently no data on its diagnostic effectiveness in embryos. Further research is indicated to understand its application in clinical care and to understand any potential application in reproductive medicine. Two independent American College of Medical Genetics and Genomics documents will address the ethical, social, and legal issues associated with PRS testing and embryo selection in greater detail.

Conflict of Interest

The authors declare no conflicts of interest.

Authors

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