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ACMG STATEMENT

The clinical application of polygenic risk scores: A points to consider statement of the American College of Medical Genetics and Genomics (ACMG)

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Introduction

Polygenic inheritance is a non-Mendelian form of inheritance in which the risk of a trait, disorder, or disease results from the combined contribution of variants from multiple genes. Most chronic illnesses and complex disorders are multifactorial and are associated with polygenic inheritance and environmental influences. Genome-wide association studies (GWAS) evaluate the association of specific loci with various complex disorders, such as cardiovascular disease, diabetes, cancer, neuropsychiatric conditions, or individual traits, such as height and blood pressure.[1-5]

A polygenic risk score (PRS) is generally derived from GWAS data and calculated as the weighted sum of estimated per-allele effect sizes of single-nucleotide variants, also called single-nucleotide polymorphisms.[6,7] The weight of the variant demonstrates the magnitude of the risk of those variant alleles associated with the phenotype or disease of interest.[8] PRS is an estimate of a genetic susceptibility to the condition of interest, calculated from the effect size of the risk variants of a trait.[9] PRS algorithms have been developed, validated, and published for numerous clinical conditions.[10] The resultant statistical associations appear valid, and they are widely believed to have the potential to

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drive early intervention or prevention measures.[9,11,12] Algorithms that incorporate both genetic and nongenetic factors (eg, age, sex, lifestyle and family history) that are integrated into PRS models are also being developed.[8]

A significant limitation of PRS is the historical use of European-based genetic data sets, which hinder both the application of and research using PRS. There are concerns about the potential for PRS to exacerbate health care disparities.[13] The American College of Medical Genetics and Genomics (ACMG) supports efforts that seek to both improve available data sets for populations with non-European ancestry and optimize analytic methods so that genomic risk can be accurately and equitably identified across all human populations.

Although being rapidly incorporated into health care, there are currently no clinical guidelines available for the use of this technology. PRSs are probabilities and do not directly provide an absolute risk for disease development. For example, having a specific *BRCA1* pathogenic variant in an individual is associated with a 60% to 80% absolute risk of developing breast cancer. In contrast, PRS provides the relative risk of developing a disease and should be used as an adjunct tool to determine the likelihood of developing a specific disorder. Prospective studies are needed to determine if a given PRS result paired with a specific preventative measure leads to better clinical outcomes.

This document offers guidance to the health care provider who seeks to understand the challenges and limitations of applying PRS testing in patient care. The ACMG has developed this Points to Consider document to address the potential value of PRS given the limited evidence-base for clinical utility. Table 1 outlines the general considerations for the clinical application of PRS. An accompanying ACMG Points to Consider document addresses considerations for the development, implementation, and reporting of PRS from a laboratory perspective.[15] A third ACMG document addresses the issues related to prenatal clinical applications of PRS testing.[16]

Table 1 Clinical application of polygenic risk score

Point number	Points to consider
1	PRS test results do not provide a diagnosis, instead they provide a statistical prediction of increased clinical risk.
2	A low PRS does not rule out significant risk for the disease or condition in question.
3	If the risk prediction of a PRS is derived from a population that is different from the patient being tested, then the results may have a poor predictive value for the patient.
4	Isolated PRS testing is not the appropriate test for clinical scenarios in which monogenic etiology is known or suspected.
5	Before testing, a patient and provider should discuss the indications for the PRS test, and the patient should be informed how the PRS results will be used to guide medical management.
6	PRS-based medical management should be evidence-based; however, there is currently limited evidence to support the use of PRS to guide medical management.
7	Clinical follow-up for PRS should be consistent with best practices outlined by professional societies with appropriate expertise in instances when and where evidence-based practice guidelines exist.
8	The ACMG's position is that preimplantation PRS testing is not yet appropriate for clinical use and should not be offered at this time.[14]

ACMG, American College of Medical Genetics and Genomics; *PRS*, polygenic risk score.

General Considerations for a Health Care Provider

PRS test results do not provide a diagnosis, instead they provide a statistical prediction of increased clinical risk

A clinician's strategy for obtaining and managing PRS results should incorporate the concept that even the individual with a high disease-risk prediction by PRS may never develop the disease in question, because the PRS percentile result represents the individual's ranking of odds ratio of the lifetime disease risk in a chosen population. Similarly, individuals with low PRS predicted risk can develop the disease.[17] PRS-related clinical risk should be understood both within an individual-specific clinical context (eg, the individual's age, medical and family history, and other clinical data) as well as within an understanding of the limitations of the test. Furthermore, healthy lifestyle could play a protective role in developing a certain condition, even for individuals with high PRS results.[18] PRS may be calculated for a specific individual using prediction models that were generated based on discovery GWAS summary statistics identifying allele-specific effect size per variant and validated on independent populations or can be determined from large studies independent from GWAS discovery before validation in independent cohorts. The performance of the PRS model should be validated on a comparable test population independent from the population in which the model was generated. PRS results only deliver a risk prediction for the trait, disorder, or disease for which the specific model was generated.[19-22] Monogenic etiologies for the trait, disorder, or disease addressed by the PRS are not evaluated through PRS calculations (eg, breast cancer PRS does not assess for monogenic *BRCA1*-associated breast cancer risk). However, PRS has been shown to be associated with a modified clinical risk level for features of monogenic conditions (eg, age of disease onset).[23]

A low PRS does not rule out significant risk for the disease or condition in question

Potential sources of unidentified risk in PRS come from unmeasured risks (ie, environmental and genomic) as well as limitations related to data, methodology, and reporting conventions. It is important to understand that PRS results are typically given in the unit of the effect size used in the calculation (such as beta coefficient or the natural logarithm of the odds ratio). The calculations can be adjusted for linkage disequilibrium (LD) and then be transformed to *z*-scores based on the relevant GWAS population (assuming normal distribution). They can also be converted to a score between the first to 99th percentiles for ease of interpretation, if preferred. The result in percentile represents the individual's ranking of odds ratio of the lifetime disease risk in a chosen population. A low percentile score can be interpreted as a low prediction of the disease compared with a reference population and does not typically report the absolute lifetime risk of the disease.[6,24] The absolute risk derived from the original GWAS or reference population is not always available. Moreover, the area under the curve, even applied on the same population as the model, may not be as high as lifestyle-based prediction models,[25] although some studies have shown that PRS may be at least comparable or stronger risk predictors than traditional risk tools.[9,26]

If the risk prediction of a PRS is derived from a population that is different from the patient being tested, then the results may have a poor predictive value for the patient

One of the most important challenges of widespread use of PRS is optimization of the appropriate data set for individual ancestries including admixed populations.[15] PRS models are based on the specific population studied in the relevant GWAS cohort. Most GWAS have been performed primarily using populations of European descent, which leads to decreased predictive accuracy of PRS scores in other populations owing, in part, to differences in the LD patterns and allele frequencies.[27,28] In addition, to promote applicability across populations and health care equity and limit health disparities, PRS statistical prediction capacity should ideally be optimized for all ancestries.[29,30] Currently, more GWAS are being conducted on various populations, which is expected to increase the applicability of PRS to individuals from their respective backgrounds, which is addressed in detail in the accompanying Laboratory Quality Assurance Committee document.[15,28,30] In addition, methods to infer admixture in the genotype data and adjust for the LD differences are being developed and validated to improve the accuracy of PRS for diverse populations.[31] These efforts are predicted to increase the applicability of PRS tests to various populations, ultimately hoping to increase access to PRS testing among a variety of genetic ancestries and promote health equities.[32] Although the need for development of sex-specific polygenic scores has been proposed,[33] most GWAS do not include sex-specific data.[11] There is currently not enough evidence for the application of sex-specific PRS, although some studies found different PRS results depending on sex, when looking at PRS in cardiovascular disease events or psychiatric conditions.[34,35]

Isolated PRS testing is not the appropriate test for clinical scenarios in which monogenic etiology is known or suspected

Clinicians could misattribute a polygenic etiology to individuals with monogenic forms of common disease.[36] When attempting to ascertain the genetic basis of disease risk for an individual, health care practitioners should be aware of the identifiable patterns of clinical features for the monogenic forms of the trait, disorder, or disease for which they are attempting to assess the individual risk. If an individual's clinical presentation (phenotype) and/or family history fits a pattern that is consistent with a monogenic etiology for the trait, disorder, or disease and specific testing is available, then monogenic testing should be performed instead of, or in addition to, PRS. It is therefore important to clearly define the target population for testing and the purpose of risk prediction for that population.[15] For example, if multiple affected family members are identified with malignancies suggestive of a hereditary cancer syndrome, this important family history finding may be overlooked by PRS testing alone and could result in missed opportunities for disease prediction and targeted evidenced-based risk management.[36] Clinical genetic specialists (eg, medical geneticists or genetic counselors) can facilitate optimal clinical evaluations and genetic testing strategies.

Before testing, a patient and provider should discuss the indications for the PRS test, and the patient should be informed how the PRS results will be used to guide medical management

Appropriate genetic counseling and informed consent is crucial before PRS testing. It is important to highlight critical differences between testing for monogenic disorders and PRS testing. For example, the clinical utility including accuracy of PRS in various clinical conditions is not very well established.[11,12] In addition, the PRS results cannot be used to predict the relative disease risk for other family members,[37] although some correlation may be observed depending on the degree of relatedness between family members.[37] Furthermore, the uncertainty surrounding future interpretations of PRS should also be a component of pretest counseling.

PRS-based medical management should be evidence-based; however, there is currently limited evidence to support the use of PRSs to guide medical management

Currently, the direct evidence of improved clinical outcomes associated with the prospective use of PRS to guide medical management is limited. In addition, there is a need for cost-effectiveness data studies for PRS assessment, which are currently lacking. The extrapolation of evidence from established non-PRS risk management to PRS-related risk management may be prudent in some scenarios (eg, checking fasting glucose in the setting of diabetes risk) and may not be in others (eg, prophylactic surgery in the setting of cancer risk). PRS may demonstrate relative risk predictions of a specific disease in question compared with the model population for which an intervention may be desired. Until robust outcome research findings are available that build evidence relating to effective interventions, clinicians using PRS should make efforts to standardize their management approach and when possible, contribute to efforts that analyze clinical outcomes of prospective PRS-based management. Currently, there are no clinical guidelines available for the use of PRS.

Clinical follow-up for PRS should be consistent with best practices outlined by professional societies with appropriate expertise in instances when and where evidence-based–practice guidelines exist

An increasing number of studies are being conducted to investigate potential intervention strategies, screening recommendations, prognostic implications, and other aspects of clinical decision-making strategies. Long-term clinical follow-up of individuals obtaining a PRS score, and determining the presence or absence of the condition, in addition to looking into other aspects of clinical outcomes should be aligning practice guidelines generated by professional societies.

The ACMG's position is that preimplantation PRS testing is not yet appropriate for clinical use and should not be offered at this time

Owing to the complexity of PRS testing and the interpretation and applicability of its results, the ACMG considers preimplantation genetic testing for disorders that exhibit multigenic or polygenic inheritance is not appropriate for clinical use and should not be offered as direct-to-consumer testing at this time.[14] Two independent ACMG documents will be addressing this topic in more detail, including the ethical, social, and legal considerations associated with PRS testing for embryos.

As PRS tests are being developed for implementation in the clinical settings, it is important to continue to monitor progress and to focus on key considerations including main advantages and limitations of PRS testing, such as its clinical utility, the inclusion of multiple ethnicities, and the advances in technology as new evidence is generated.

Key Learning Points

At this time, the ACMG advocates against clinical implementation of PRS testing unless the provider and patient have a clear understanding of the limitations of the testing and applicability to the specific patient, including how the results will be used to guide evidence-based clinical care.

Conflict of Interest

The authors declare no conflicts of interest.

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