# Perspective: The Clinical Use of Polygenic Risk Scores: Race, Ethnicity, and Health Disparities

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Polygenic risk scores (PRS) are an emerging precision medicine tool based on multiple gene variants that, taken alone, have weak associations with disease risks, but collectively may enhance disease predictive value in the population. However, the benefit of PRS may not be equal among non-European populations, as they are under-represented in genome-wide association studies (GWAS) that serve as the basis for PRS development. In this perspective, we discuss a path forward, which includes: 1) inclusion of underrepresented populations in PRS research; 2) global efforts to build capacity for genomic research; 3) equitable implementation of these tools in clinical practice; and 4) traditional public health approaches to reduce risk of adverse health outcomes as an important component to precision health. As precision medicine is implemented in clinical care, researchers must ensure that advances from PRS research will benefit all. *Ethn Dis*. 2019;29(3):513-516; doi:10.18865/ed.29.3.513

**Keywords:** Precision Medicine; Polygenic Risk Scores; Genome-Wide Association Studies

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## Introduction

A cornerstone of precision medicine is to target intervention efforts to those at highest risk of disease by accounting for individual-level risk factors derived from the combination of environmental, lifestyle and genetic factors. Polygenic risk scores (PRS) provide a rapidly emerging example of such efforts. PRS are based on multiple gene variants that, taken alone, have weak associations with disease risks, but collectively may enhance disease predictive value in the population.[1] To date, PRS have had largely undefined clinical utility; however, growing evidence suggests that PRS may add value to traditional risk factors for identifying individuals at increased risk of multiple conditions, including cardiovascular disease (CVD). For example, Khera and colleagues developed a genome-wide PRS that identified 2.5% of individuals with a 4-fold increased risk for coronary disease.[2] Thus, PRS presents an opportunity to improve health outcomes through precision medicine; however, this opportunity remains unequal and could exacerbate disparities in racial and ethnic minority populations due to under-representation of these populations in underlying PRS research.[3]

## Clinical Use of PRS and Implications for Health Disparities

The added value of PRS is unclear compared with or in addition to existing prevention and management approaches based on age, family history, and environmental risk factors.[4] This is especially true among populations that are underrepresented in genomic research. Indeed, a recent perspective by Martin and colleagues warns that the clinical use of current PRS may exacerbate health disparities.[3] Studies have consistently demonstrated that PRS do not predict risk among non-European populations to the degree that they do for European populations.[3] This is because populations in current genome-wide association studies (GWAS) are primarily of European descent, and therefore PRS do not account for genomic variation within and between underrepresented, non-European populations. This limits the validity and utility of PRS among African, Latin American, Asian, and other ancestry groups.[5] Unfortunately,

the inclusion of non-Europeans in GWAS has remained the same or even declined over the past five years.[3]

More broadly, issues of health disparities in racial and ethnic minority populations have been observed in other areas of genomic medicine. For example, non-Whites who received multigene sequencing have higher rates of variants of unknown significance (uninformative genetic results in which it is unknown if a gene variant is associated with a given health outcome or not) than Whites, since the classification of variants (as pathogenic or non-pathogenic) relies heavily on data from primarily European populations.[6] For a patient, the number of variants of unknown significance increases as the number of genes tested increases; thus, as sequencing costs continue to drop and gene panels expand, this issue will worsen and expose underrepresented populations to potential harms associated with uncertain results. Compounding resulting disparities, there is a paucity of research related to the clinical implementation of genomics in diverse settings and among diverse populations.[7]

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## A Path Forward

As the translation of genomic medicine, and PRS more specifically, gains momentum in clinical use, it is imperative to pause and consider the impact current PRS will have on health disparities among populations who are under-represented in GWAS. Clinical medicine must grapple with the ethics of promoting the translation of this promising precision medicine tool and preventing the exacerbation of disparities. At this critical juncture of clinical and precision medicine, we must define a path forward to address an urgent need for transdisciplinary research to improve the participation of underrepresented populations into genomic research in order to obtain diverse GWAS data to inform PRS research. Resulting PRS must then be evaluated for their clinical utility and appropriate implementation into diverse clinical settings and patient populations. Herein, we propose three areas that will achieve this appropriate implementation: 1) inclusivity in genomic research; 2) equitable implementation of PRS; 3) concurrent health interventions.

## Inclusivity in Genomic Research

Inclusion of underrepresented populations is critical for the clinical implementation of PRS. In the United States, disparities in participation persist due to a variety of factors including low trust in medical and research institutions resulting from personal, social and cultural experiences of discrimination and past research misconduct.[8] Given historical inequities, improving participation in genomic research will be challenging and will require building trust with community leaders, stakeholders and members.[9] Engaging underrepresented communities in a culturally aware manner, may allow for sustained collaboration with community partners in research. Invigorated efforts are needed to engage communities first, and then conduct inclusive genomic research. The NIH *All of Us Research* (https://go.usa.gov/xmUz4) and NHLBI's *Trans-Omics and Precision Medicine* (TOPMed) programs have embraced this concept. For example, the 144,000 current participants in TOPMed consist of approximately 60% with substantial non-European ancestry (https://www.nhlbiwgs.org).

In addition to domestic efforts to include racial and ethnic minority groups in genomic research, global efforts to build capacity for genomic research, such as The Human Heredity and Health in Africa initiative, are needed to build upon our understanding of global genetic diversity and health.[10] Building global connections that allow for secure data-sharing remains a challenge. These efforts will require

multisite, transdisciplinary research teams, including basic, translational, and public health researchers. Often disparate, these fields have complementary skills that would facilitate rigorous, inclusive genomic research.

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## Equitable Implementation of PRS

Once inclusive PRS are developed, research will be needed to ensure the evaluation and equitable implementation of these tools in clinical practice. Implementation science, the study of methods to promote the translation of evidence-based practices into routine health care and public health practice, may provide a useful toolbox for promoting implementation of PRS across diverse clinical settings and populations. A key tenet of implementation science acknowledges the importance of engaging multilevel key stakeholders (eg, community members, providers, payers) as a strategy to accelerate sustained adoption. Taken together, by including diverse populations in PRS research and promoting the equitable implementation of PRS, researchers and practitioners may see the promise of PRS for all.

## Concurrent Public Health Interventions

In the interim, we can learn from current PRS, and continue to intervene on health behaviors related to health outcomes. A recent study demonstrated that within all genetic risk subgroups (as defined by PRS), CVD outcomes were improved among those who adhered to a healthy lifestyle, suggesting that lifestyle modifications may improve CVD outcomes regardless of one's genetic risk score.[11] Such traditional public health approaches continue to be important in reducing risk of adverse health outcomes and an important component of precision public health.

## Conclusion

As precision medicine takes a foothold in clinical care, researchers must act to ensure that advances from PRS research will benefit all. If not, current PRS may exacerbate existing disparities in health outcomes among underrepresented populations. Through transdisciplinary and community-participatory research, opportunities for inclusive genomic research and medicine are possible.

Conflict of Interest

No conflicts of interest to report.

Author Contributions

Research concept and design: Roberts, Khoury; Manuscript draft: Roberts, Khoury, Mensah; Statistical expertise: Khoury; Administrative: Roberts, Mensah; Supervision: Khoury

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