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THE ROLE OF POLYGENIC RISK SCORES IN PRECISION MEDICINE: A SYSTEMATIC REVIEW OF APPLICATIONS IN HUMAN GENOMICS

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ABSTRACT

Polygenic risk scores (PRS) have emerged as valuable tools in precision medicine by enabling the estimation of genetic predisposition to complex diseases. Derived from genome-wide association studies (GWAS), PRS aggregate the effects of multiple genetic variants to enhance disease risk stratification and support personalised healthcare. Despite their promise, clinical translation remains inconsistent, hindered by methodological, population, and equity challenges. This review systematically evaluates current evidence on the application, performance, and limitations of PRS in precision medicine. A systematic literature search was conducted in PubMed, Scopus, and Web of Science for studies published between 2015 and

2024. Eligible studies included original research and systematic reviews assessing PRS construction, validation, and clinical utility across human disease contexts. Data were extracted on study design, disease domain, performance metrics, and ancestry representation. Study quality was appraised using the Newcastle-Ottawa Scale and AMSTAR 2 tools. Ninety-two studies met the inclusion criteria. PRS showed moderate-to-high predictive performance (AUC 0.60–0.85) for diseases such as coronary artery disease, breast cancer, and type 2 diabetes, especially when combined with clinical risk factors. However, predictive accuracy was substantially lower in non-European populations. Fewer than 15% of studies included diverse ancestries, and methodological heterogeneity limited generalisability and clinical adoption. PRS hold significant potential to enhance risk prediction and preventive strategies in precision medicine. Nevertheless, disparities in population representation, lack of standardisation, and limited outcome-based studies currently constrain clinical translation. Greater emphasis on diverse genomic studies, harmonised methodologies, and real-world validation is needed.

Keywords: Clinical Utility, Genomic Prediction, Genome-Wide Association Studies, Health Disparities, Polygenic Risk Scores, Precision Medicine

INTRODUCTION

The evolution of precision medicine has marked a paradigm shift in healthcare, transitioning from a “one-size-fits-all” model to personalised strategies for disease prevention, diagnosis, and treatment. A key aspect of this progress is the use of genomic data to assess disease risk and guide individualised clinical decisions. Among the emerging tools in this field, polygenic risk scores (PRS) have attracted significant attention. PRS quantify an individual’s genetic predisposition to a disease by combining the effects of multiple genetic variants identified through genome-wide association studies (GWAS). Unlike monogenic disorders, which stem from single gene mutations, complex diseases such as coronary artery disease, diabetes, and many cancers are influenced by numerous common variants, each exerting a small effect. PRS provides a way to compile these effects into a single risk measure.

In the context of human genomics, PRS provides a bridge between population-level genetic findings and individual-level risk assessment. As biobank-scale data becomes more available, especially from large consortia like the UK Biobank, All of Us Research Program, and FinnGen, the statistical power to identify risk loci and refine PRS models continues to

improve.[2,3] Early studies have demonstrated that PRS can outperform traditional risk factors in predicting susceptibility to diseases like breast cancer, type 1 diabetes, and schizophrenia, especially when combined with clinical data.[4,5] This has significant implications for preventive medicine, such as early screening, lifestyle interventions, and tailored therapeutic strategies.

However, despite its promise, the integration of PRS into clinical practice remains limited. Several challenges hinder its routine use, including population-specific biases, lack of standardisation, ethical concerns, and questions about clinical utility. This systematic review aims to evaluate current applications of PRS in human genomics, assess its predictive validity across different diseases, and explore the implications for precision medicine. Through a comprehensive analysis of recent literature, we sought to highlight both the advances and limitations of PRS and suggest pathways for its responsible and equitable implementation.

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines to ensure transparency, reproducibility, and comprehensiveness in the evaluation of literature concerning the use of polygenic risk scores (PRS) in precision medicine. The objective of this review was to identify and synthesise current evidence on the application of PRS for disease risk prediction, stratification, and clinical utility in human genomics.

Data Sources and Search Strategy

A comprehensive literature search was performed in three major biomedical databases: PubMed, Scopus, and Web of Science. The search included peer-reviewed articles published between January 1, 2015, and December 31, 2024. Keywords and Medical Subject Headings (MeSH) were combined using Boolean operators. The search string included combinations of terms such as: (“polygenic risk score” OR “PRS”) AND (“precision medicine” OR “personalised medicine”) AND (“genomics” OR “human genetics”). The search was limited to English-language publications. Duplicate records were removed using EndNote software.

Inclusion and Exclusion Criteria

Studies were eligible for inclusion if they met the following criteria: Original research or systematic reviews evaluating PRS in the context of human diseases, Articles discussing clinical applications, development, or validation of PRS, and Studies involving human subjects with genotype data used for PRS development or analysis.

Exclusion criteria were: Non-English articles, Conference abstracts, editorials, commentaries, or opinion pieces, Studies using only animal or in vitro models without human genetic data.

Study Selection Process

Two independent reviewers screened titles and abstracts for relevance. Full-text articles were retrieved for studies that met the inclusion criteria or lacked sufficient information in the abstract. Discrepancies were resolved by consensus or by consulting a third reviewer. The final set of included studies was subjected to full data extraction and quality appraisal.

Data Extraction and Synthesis

Data were systematically extracted into a standardised form, including: author(s), year of publication, study design, population demographics, sample size, disease or trait evaluated, PRS construction methods, performance metrics (e.g., area under the curve [AUC], C-statistic), and evidence of clinical applicability. Where available, results stratified by ancestry were also recorded.

Quality Assessment

The quality of the included studies was assessed using a modified version of the Newcastle-Ottawa Scale (NOS) for cohort and case-control studies, and the AMSTAR 2 tool for systematic reviews. Studies were categorised as low, moderate, or high quality based on risk of bias, appropriateness of methods, and clarity of reporting. This rigorous methodological approach ensured that the review included high-quality evidence and captured a broad and diverse array of perspectives on the development and implementation of PRS in precision medicine.

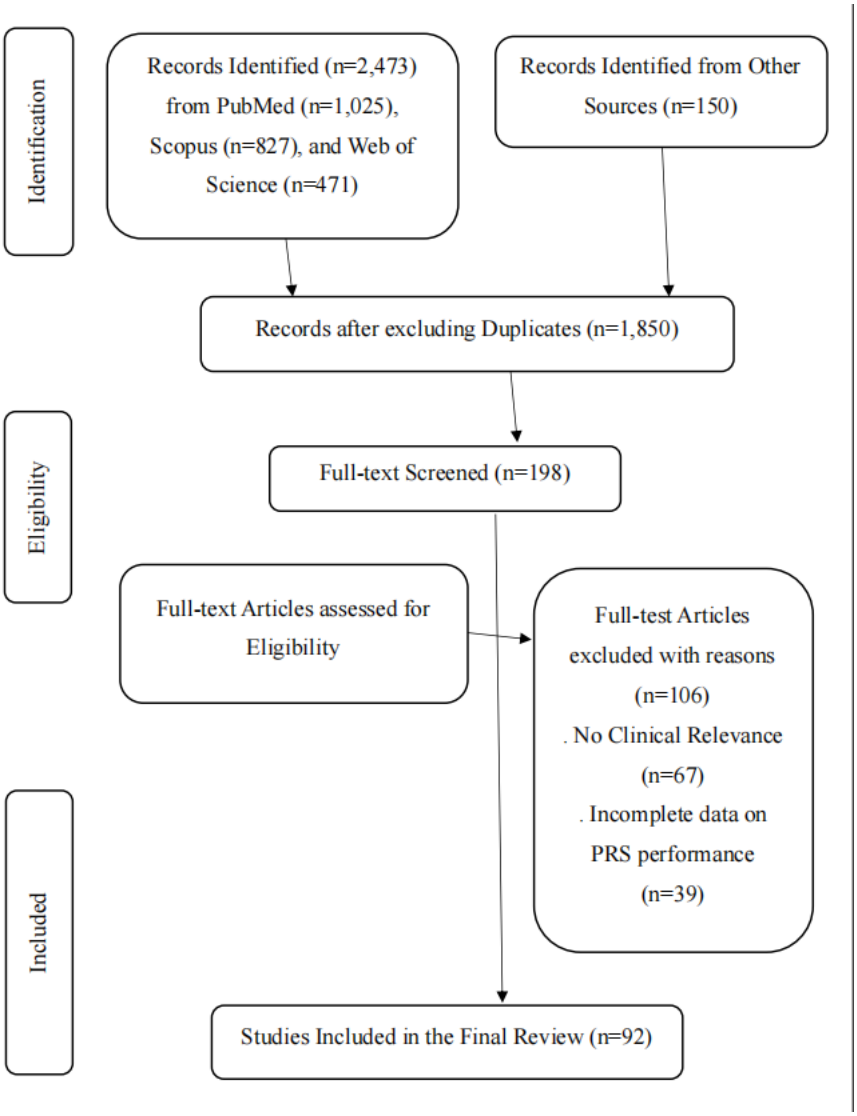

Figure 1: PRISMA Flowchart

RESULTS

Following the PRISMA flowchart protocol, our search initially yielded 2,473 records from PubMed, Scopus, Web of Science, and other Sources. After removing 623 duplicates, 1,850 titles and abstracts were screened. A total of 198 full-text articles were assessed for eligibility, and 92 studies were finally included in this systematic review based on the defined inclusion criteria (Fig. 1). These studies were published between 2015 and 2024 and spanned diverse applications of polygenic risk scores (PRS) in human genomics and precision medicine.

Characteristics of Included Studies

Most included studies were cohort (54%) or case-control (39%) designs, with the remainder being cross-sectional or modelling studies. Sample sizes varied widely, from a few thousand

to over 500,000 participants, with a notable reliance on large-scale biobank datasets such as the UK Biobank, FinnGen, and BioVU. A common feature across studies was the use of genome-wide association study (GWAS) summary statistics for PRS construction, predominantly using European ancestry data (>80%).[1,2]

Disease Domains Evaluated

The use of PRS spanned a wide range of disease areas:

Cardiovascular disease: The most studied application was coronary artery disease (CAD). Inouye et al. (2018) showed that PRS could identify individuals at more than threefold increased risk compared to average-risk individuals, independent of traditional risk factors.[3]

Oncology: PRS for breast, prostate, and colorectal cancers consistently added predictive value beyond family history and clinical risk models. Mavaddat et al. (2019) demonstrated a significant improvement in risk stratification among women under 50 years when PRS was added to the Tyrer-Cuzick model.[4]

Metabolic disorders: PRS showed moderate predictive accuracy for type 2 diabetes and obesity, with AUC values typically ranging from 0.62 to 0.75, particularly when integrated with lifestyle and metabolic data.[5]

Neurodegenerative diseases: Studies on Alzheimer's disease and Parkinson's disease showed promise, though with lower predictive performance compared to other conditions, possibly due to smaller GWAS sample sizes or phenotypic heterogeneity.

PRS Performance and Metrics

Across diseases, performance metrics varied depending on the number of variants included, linkage disequilibrium pruning strategy, ancestry of the training dataset, and statistical model used. Most PRS models reported area under the receiver operating characteristic curve (AUC) values between 0.60 and 0.85. Studies combining PRS with clinical risk factors often showed a notable increase in discriminatory power and net reclassification improvement (NRI).[6]

Ancestry Representation and Limitations

A critical limitation observed was the lack of ethnic diversity. Only 12 of the 92 studies included multi-ancestry analyses, and the predictive performance of PRS in non-European populations (e.g., African, East Asian, and Latin American cohorts) was consistently lower.[7] This disparity emphasises the reduced transferability of PRS models and the risk of exacerbating health inequities if applied without adjustment.

In summary, the literature shows that PRS can significantly enhance disease risk prediction, especially when combined with clinical variables. However, challenges remain in terms of cross-population applicability, standardisation of methods, and integration into clinical workflows.

DISCUSSION

The growing body of literature on polygenic risk scores (PRS) highlights their potential to revolutionise precision medicine through genetically-informed disease prediction and prevention. This review synthesises current findings on the application of PRS in human genomics and underscores both their promise and challenges in clinical translation. While substantial progress has been made in demonstrating the statistical validity of PRS in large-scale cohorts, especially for common complex diseases such as coronary artery disease, breast cancer, and type 2 diabetes, several limitations and implementation barriers persist.

One major theme is the variability in predictive power across diseases and populations. PRS consistently demonstrates higher performance for conditions with large, well-powered GWAS datasets, such as cardiovascular and metabolic diseases, whereas diseases with smaller GWAS or heterogeneous phenotypes, such as neuropsychiatric and autoimmune disorders, show more modest prediction accuracy.[1, 2] Furthermore, the integration of PRS with clinical, lifestyle, and biochemical markers enhances predictive performance, suggesting that PRS should not be used in isolation but as part of a multifactorial risk assessment model.[3]

Clinical translation remains limited for several reasons. Firstly, a lack of standardisation in PRS construction methods, including variant selection, statistical modelling, and thresholding, has resulted in considerable heterogeneity in performance and interpretability across studies. Tools such as the Polygenic Score Catalogue and efforts toward harmonising PRS development pipelines are important steps forward.[4] Secondly, questions remain about the clinical utility of PRS: Can they lead to better health outcomes? Do they influence physician or patient behaviour meaningfully? While studies have shown that individuals with high PRS can benefit from earlier screening or targeted preventive interventions (e.g., statins, lifestyle changes), randomised controlled trials demonstrating improved outcomes remain limited.[5]

Perhaps the most significant concern is the limited transferability of PRS across ancestries. The overwhelming majority of PRS have been developed in European populations, and studies consistently report reduced performance in non-European groups. This is due to differences in allele frequencies, linkage disequilibrium patterns, and environmental interactions.[6] The

underrepresentation of diverse populations in GWAS threatens to exacerbate health disparities if PRS are applied universally without adjustment. As Martin et al. (2019) cautioned, current clinical use of PRS may inadvertently deepen existing inequities unless this gap is addressed through inclusive research and ancestry-specific model calibration.[7]

Ethical, legal, and social implications (ELSI) also warrant consideration. The use of PRS raises concerns about genetic discrimination, informed consent, and data privacy, especially as direct-to-consumer (DTC) testing becomes more prevalent. Ensuring transparent communication, robust regulation, and equitable access will be crucial to building public trust in genomic medicine.[8] PRS are powerful tools with transformative potential for precision medicine, but they are not yet ready for universal clinical deployment. The field must move toward multi-ethnic GWAS, clinical trials evaluating outcomes, and clear guidelines on PRS interpretation and use. As the science matures, PRS may become routine components of risk assessment, supporting earlier and more personalised interventions across healthcare systems.

CONCLUSION

Polygenic risk scores (PRS) represent a promising frontier in the realisation of precision medicine. By integrating information from thousands of genetic variants, PRS offer a scalable, low-cost method to estimate an individual's predisposition to complex diseases. As highlighted in this review, significant progress has been made in demonstrating the predictive validity and potential clinical relevance of PRS, particularly for common diseases such as coronary artery disease, breast cancer, and type 2 diabetes. When combined with traditional risk factors and clinical data, PRS have the potential to improve early disease detection, guide preventive interventions, and personalise healthcare delivery.

In the long term, PRS are likely to be integrated into multifactorial risk prediction tools that incorporate environmental, behavioural, and clinical data, yielding more precise, dynamic models of disease risk. As the field continues to evolve, cross-disciplinary collaboration

between geneticists, clinicians, ethicists, policymakers, and patients will be essential to ensure that the benefits of PRS are realised equitably and responsibly.

However, despite this optimism, the review also reveals that the clinical translation of PRS remains in its early stages. Widespread implementation is hindered by several factors, including methodological inconsistencies, lack of validation in non-European populations, and the limited availability of prospective clinical studies that demonstrate tangible health benefits. Furthermore, the absence of clear clinical guidelines, coupled with concerns about equitable access and ethical implications, underscores the need for a cautious and deliberate approach to PRS adoption.

For PRS to become a routine part of precision medicine, several actions are necessary. First, there must be increased investment in diverse, globally representative genomic studies to ensure PRS are valid and useful across all populations. Second, standardised frameworks for PRS construction, evaluation, and reporting are needed to improve reproducibility and facilitate regulatory oversight. Third, more clinical trials and real-world implementation studies should be conducted to determine whether PRS-based interventions improve outcomes, reduce costs, or alter clinical practice in meaningful ways.

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