Ancestry-Related Disparities in Polygenic Risk Score Performance for Type 2 Diabetes

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Abstract

Polygenic risk scores (PRSs) have emerged as a promising tool for predicting genetic risk of type 2 diabetes (T2D), with potential to support early intervention and personalized medicine. However, their clinical utility remains uneven across populations. This review examines how methodological approaches and population-specific genetic diversity drive differences in PRS performance across ancestral groups.

Performance disparities are driven largely by the predominance of European ancestry cohorts in genome-wide association studies (GWAS), reflecting broader systemic inequities in genomic research infrastructure and data collection, as well as a historical legacy of distrust toward biological research in some communities. These factors shape the composition of foundational datasets and the predictive models derived from them. In addition, genetic variation contributes to uneven PRS performance, as differences in allele frequencies and linkage disequilibrium patterns across populations influence how genetic risk is captured. Although advanced statistical and machine learning methods have improved predictive performance, they remain constrained by imbalanced training data and often fail to generalize across diverse populations.

As a result, PRS provide limited and uneven clinical value, often offering only modest improvements over traditional risk factors. Ongoing efforts to expand diverse genomic datasets and develop more inclusive modeling approaches represent important progress. Nevertheless, improving PRS equity will depend on expanding representation in genomic datasets, strengthening research infrastructure, and developing methods that better capture population-specific genetic variation.

Introduction

Fueled by advances in genome-wide association studies (GWAS), precision medicine incorporates genetic, clinical, and environmental data to improve disease diagnosis and risk prediction (Ju et al., 2022). GWAS analyzes large-scale genomic datasets to identify associations between genetic variants and complex traits or diseases. Building on these findings, polygenic risk scores (PRS) aggregate the effects of thousands to millions of genetic variants across the genome to estimate an individual's inherited susceptibility to disease (Chapman, 2023). By

stratifying individuals according to genetic risk, PRS have shown promise for enabling earlier detection, targeted prevention strategies, and more personalized clinical decision-making.

A significant limitation is that over 90% of participants included in GWAS across many traits and diseases are of European ancestry (Zhu et al., 2025). Consequently, most derived polygenic risk scores are constructed predominantly from European ancestry cohorts, with limited representation from Asian, Hispanic, African, and admixed groups. PRS developed from European ancestry datasets often demonstrate reduced predictive performance in non-European populations. This increases the risk of false positives and false negatives that may lead to inappropriate treatment decisions or missed opportunities for early intervention (Machado Reyes et al., 2022). Notably, African and African American populations harbor the most significant levels of genetic diversity and exhibit shorter linkage disequilibrium blocks. These features could enhance fine mapping resolution and improve risk prediction across all populations. The limited inclusion of these groups in GWAS restricts the fair application of PRS in clinical settings (Majara et al., 2023).

The greater the ancestral difference between the GWAS discovery cohort and the population in which a PRS is applied, the lower its predictive accuracy across many complex traits (Majara et al., 2023). This reduction reflects differences in linkage disequilibrium structure, allele frequencies, and effect size estimates across populations (Ng et al., 2013). For Type 2 Diabetes (T2D), PRS derived from European ancestry datasets achieve an Area Under the Curve (AUC) of 0.66 in European populations but decline to 0.63 in Hispanic populations and 0.58 in African populations, with variance explained dropping from 9.2% to 2.8% (Ge et al., 2022).

Because African ancestry populations have a disproportionate burden of T2D, reduced predictive performance in these groups has direct clinical consequences, increasing the risk of misclassification and limiting the utility of early risk stratification. These disparities highlight the structural limitations of GWAS datasets skewed by ancestry.

Addressing ancestry-related disparities in PRS performance requires both increased diversity in GWAS discovery cohorts and methodological innovation in cross-population modeling. One

approach involves constructing PRS from multi-ancestry GWAS that integrate data from diverse populations. Multiethnic PRS derived from multi-ancestry studies have been shown to outperform European-only or ancestry-specific scores (Irvin et al., 2024), highlighting the power of diverse large-scale data. Additional efforts focus on refining statistical methods, such as PRS-CSx, which jointly model ancestry-specific linkage disequilibrium patterns and effect size differences to improve cross-population predictions (Ruan et al., 2022).

Regardless of the methodological approach, ensuring equitable implementation of PRS in clinical practice requires careful evaluation of predictive performance across populations to prevent misclassification, unnecessary treatment, or psychological distress among underrepresented groups (Cronjé et al., 2023; Zhang et al., 2024). **Using Type 2 Diabetes as a case study, this review synthesizes evidence on ancestry-related differences in PRS performance, evaluates how traditional statistical approaches and emerging machine learning methods seek to improve predictive equity across diverse populations, and examines how reliance on broad ancestry categories may obscure substantial intra-continental genetic diversity and limit equitable implementation.**

Theme 1: Population Genetic Structure and Data Imbalance

Due to differences in population genetic architecture, PRSs derived from European GWAS often perform poorly when applied to other ancestral groups. Both Adeyemo et al. (2015) and Kamiza et al. (2022) evaluated the transferability of polygenic risk scores across African populations, but their approaches differed in scale and methodology. By assessing previously established Type 2 diabetes loci in Sub-Saharan African cohorts, Adeyemo et al. (2015) found that many loci identified in European GWAS either failed to replicate or showed reduced effect sizes. In contrast to this locus-level evaluation, Kamiza et al. (2022) evaluated full polygenic risk scores across multiple African populations and found that PRS developed in one African population often performed poorly in another, highlighting that genetic diversity within Africa itself can limit PRS transferability. Similarly, research in British Pakistani and Bangladeshi populations shows that many loci identified in European populations either fail to replicate or involve different causal variants (Chikowore et al., 2022; S et al., 2022). Transferability studies across African, South Asian, and admixed populations consistently report reduced predictive

performance when models developed in European cohorts are applied to other populations. Research by Furukawa et al. (2025) reinforces this observation, demonstrating that the effectiveness of a PRS is maximized when there is strong ancestral alignment between the discovery cohort and the target population. Although ancestry-matched PRS models may improve prediction accuracy, ancestry-specific approaches are complicated by the fact that self-reported ancestry may be inaccurate and that admixed individuals do not fit neatly into single-ancestry categories (Ge et al., 2022). As a result, researchers have explored multi-ancestry GWAS to improve PRS performance across populations; however, smaller sample sizes in underrepresented populations can introduce statistical noise and reduce predictive power (Majara et al., 2023). These findings indicate that transferability issues are not solely due to sample-size imbalance but also to fundamental differences in population genetic architecture, meaning that increasing diversity alone may improve PRS performance but will not fully eliminate cross-population prediction disparities (Adeyemo et al., 2015; Ramirez et al., 2022).

Beyond the systemic biases inherent in GWAS discovery cohorts and dataset underrepresentation, disparities in polygenic risk score performance across populations are also shaped by population-specific biological pathways, admixture, and the fact that individuals grouped under the same ancestry label are not environmentally homogeneous. Hispanic/Latino populations, which contain varying proportions of African, European, and Native American ancestry, demonstrate that polygenic risk prediction depends more on individual ancestry proportions than on broad population categories. European-derived PRS performed better in the Antioquia population, which has predominantly European ancestry, whereas prediction accuracy was substantially lower in the Chocó population, which has predominantly African ancestry (Chande et al., 2020). Multi-ethnic GWAS approaches generally improved prediction accuracy across admixed populations compared to single-ancestry GWAS, although performance disparities still remained (Chande et al., 2020). Notably, researchers observed that the Chocó population exhibited a higher predicted prevalence of T2D than was actually observed in reality. (Chande et al., 2020) attributed this variation to the protective effects of the population's specific lifestyle and dietary habits, which mitigated their overall risk. Genetic ancestry alone does not determine disease risk, as environmental and lifestyle factors also play important roles. For instance, moderate physical activity has been shown to reduce the predicted risk of Type 2

diabetes by approximately 7%–9% (Wu et al., 2021). Additionally, population-specific biological pathways may influence disease risk. (S. Liu et al., 2024) identified proteins associated with T2D risk across multiple racial and ethnic populations and found that some proteins were associated with diabetes risk in all populations, while others were population-specific. This suggests that the biological mechanisms contributing to T2D risk may differ across populations, further complicating the transferability of polygenic risk scores. Collectively, these findings demonstrate that disparities in polygenic risk score performance across populations arise from a combination of factors. While ancestry bias in GWAS is a primary driver, the impact is compounded by population-specific biological risk mechanisms, environmental influences, admixture, and complex genetic structures.

Polygenic risk scores rely on effect sizes derived from genome-wide association studies (GWAS), which in turn require large genomic datasets supported by biobanks, sequencing facilities, and long-term research programs. Genomic research infrastructure and large-scale biobanks are unevenly distributed globally, with major resources concentrated primarily in countries such as the United Kingdom, Canada, and the United States. Although African populations possess immense genetic diversity, national biobanks and sequencing facilities have only been established in the last decade, and many regions continue to face financial and logistical challenges in maintaining large-scale genomic research programs (Sengupta et al., 2025). Initiatives such as the All of Us Research Program aim to address this imbalance by building more diverse genomic datasets (Ramirez et al., 2022). The disproportionate concentration of genomic infrastructure and research resources within specific regions contributes significantly to the persistent overrepresentation of European ancestry in GWAS datasets, serving as a primary structural driver of disparities in polygenic risk score performance across diverse global populations.

The underrepresentation of certain populations in genomic research is not only due to infrastructure limitations and genetic or environmental differences, but also to historical unethical research practices that have created mistrust in medical and genetic research institutions. Persistent gaps in research participation are often rooted in historical ethical breaches. For instance, the widely documented case of Henrietta Lacks, whose cancer cells were

harvested without consent and utilized in biomedical studies for decades, triggered significant concerns regarding privacy, informed consent, and the ownership of biological materials (Greely & Cho, 2013). Similarly, the Tuskegee Syphilis Study serves as a stark example of misconduct, where treatment for syphilis was intentionally withheld from African American sharecroppers to study the disease's natural progression (Shukla et al., 2025). These historical transgressions remain widely recognized within African American communities and continue to influence trust in medical research and participation in contemporary genomic research, ultimately affecting the diversification of biobanks and genomic datasets. Social and communication factors also play a critical role in participation in genomic research and access to genetic testing. (C. L. Smith et al., 2025) found that many African American participants reported that honest communication about treatments was a key factor in building trust, followed by provider reputation, empathy, and active listening. Fostering accountability, transparency, and trust within underrepresented communities is therefore essential, as the absence of such trust reduces participation in research, leading to less diverse datasets, non-diverse GWAS, inequitable polygenic risk scores (PRS), ultimately preventing precision medicine from serving all populations equally.

Theme 2: Modeling Approaches and Optimization in PRS

PRS performance depends on how models handle linkage disequilibrium (LD), effect size estimation, and population-specific genetic architecture. Early approaches such as clumping and thresholding (C+T) reduce redundancy by selecting independent SNPs, improving interpretability. However, this filtering oversimplifies highly polygenic traits like Type 2 diabetes, where risk arises from many small, correlated effects (Prasad et al., 2025; Privé et al., 2019). This limitation is amplified across populations, as LD patterns vary by ancestry, meaning SNPs selected in one group may not tag the same causal variants in another.

In contrast, LDpred2 models LD across all variants within a Bayesian framework, retaining correlated signals rather than removing them, unlike selection-based approaches such as C+T (Privé et al., 2019, 2021). This improves prediction and better captures population-specific LD structure, although performance remains dependent on ancestry-matched reference panels, which are predominantly European (Elgart et al., 2022; Privé et al., 2021). Extending this approach, PRS-CSx integrates multi-ancestry GWAS data to improve effect size estimation across

populations by leveraging shared genetic effects across ancestries (Ruan et al., 2022). However, these gains may reflect improved statistical fitting rather than better representation of underlying biology, underscoring the dependence of PRS performance on equitable data representation (L. A. Smith et al., 2025).

A key limitation of traditional PRS models is their reliance on linear assumptions, which fail to capture complex genotype–phenotype relationships. Machine learning approaches address this by modeling nonlinear interactions, improving predictive accuracy in some contexts (Elgart et al., 2022; Hahn et al., 2022). For example, Elgart et al. (2022) reported substantial performance gains by combining standard PRS models, which capture linear additive effects, with XGBoost models that capture nonlinear interactions via gradient-boosted trees. However, these improvements introduce trade-offs, as models like XGBoost are prone to overfitting, particularly when data is imbalanced. While some performance gains likely reflect improved capture of nonlinear biological interactions, they may also result from more flexible fitting to complex patterns in the training data, making it difficult to distinguish true biological signal from overfitting (Elgart et al., 2022).

Other approaches target different dimensions of bias. PhyloFrame reduces overfitting in European-dominated datasets by integrating biological networks and applying regularization, capturing biologically meaningful relationships but potentially reducing signal (L. A. Smith et al., 2025). However, it addresses ancestry confounding only indirectly through regularization. In contrast, FairPRS explicitly targets ancestry confounding using invariant risk minimization to reduce ancestry-specific effects, improving equity across populations while potentially reducing accuracy in well-represented groups (Reyes et al., 2023). Together, these methodologies illustrate that "bias" in PRS models is multifaceted, encompassing statistical overfitting, ancestry confounding, and disparities in predictive performance across different ancestral populations.

Despite these advances, performance remains constrained by data quality and representation (Cronjé et al., 2023). Multi-ancestry models such as PRS-CSx leverage statistical power from larger European datasets, assuming that some genetic effects are shared across populations to stabilize estimates (Ruan et al., 2022). However, this assumption may introduce bias when population-specific architectures differ. MUSSEL extends this framework by allowing both

shared and population-specific effects, likely contributing to its higher explained variance (R^2), which is 67.5% higher than PRS-CSx in African samples (Jin et al., 2024). However, these gains may also reflect more efficient use of existing, often European-biased data rather than improved modeling of biological mechanisms (Jin et al., 2024). Borrowing from large datasets improves prediction but can reinforce bias if population-specific effects are missed (Momin et al., 2026). In addition, MUSSEL requires separate validation datasets, which limits scalability for underrepresented populations (Gunn et al., 2024).

To improve predictive accuracy, integrated strategies are often necessary, as PRS alone frequently underperforms clinical markers such as HbA1c and BMI (Prasad et al., 2025). Combining PRS with clinical factors such as age, BMI, and family history enhances predictive performance, with integrated models generally outperforming either approach used in isolation (Ashenhurst et al., 2022; Lennon et al., 2024; Wedekind et al., 2023). Across studies, approaches combining PRS with clinical variables and, in some cases, machine learning models, are associated with modest improvements in predictive performance, with AUC increases averaging approximately 0.04 (range: 0.007 to 0.149), although the magnitude of improvement varies and is not always statistically significant (Ashenhurst et al., 2022; Chikowore et al., 2022; Furukawa et al., 2025; Hahn et al., 2022; Liao et al., 2025; W. Liu et al., 2021; Wedekind et al., 2023; Wu et al., 2021). Incorporating biological context, such as pathway-based approaches, further improves interpretability by linking variants to disease mechanisms. For example, Liao et al. (2025) identified associations between Type 2 diabetes genes and the IL-15 pathway, demonstrating how biological insight can guide feature selection.

Variations in PRS performance reflect interactions between modeling approaches and genetic architecture rather than ancestry alone (Muneeb et al., 2022; Weissbrod et al., 2022). For example, as heritability increases, traditional PRS performance improves, whereas machine learning models may show reduced gains; conversely, in low-heritability settings, machine learning approaches can outperform linear models (Muneeb et al., 2022). This suggests that performance depends on matching the model to the trait's genetic architecture.

Fine-mapping approaches such as PolyPred improve biological specificity by estimating the effects of likely causal variants rather than proxy SNPs, assuming that causal effects are shared

across populations (Weissbrod et al., 2022). In contrast, deep learning models such as DisPred improve generalizability by disentangling ancestry-specific and phenotype-specific signals, reducing reliance on population structure (Gyawali et al., 2023). While PolyPred prioritizes biological interpretability, DisPred prioritizes separation of confounding signals, reflecting distinct strategies for addressing bias. However, both remain constrained by data availability: PolyPred requires large GWAS datasets and functional annotations, while DisPred depends on individual-level data, which are less accessible for underrepresented populations (Gyawali et al., 2023; Weissbrod et al., 2022).

Overall, no single method consistently outperforms others across all scenarios. Performance is driven by interactions between sample size, genetic architecture, and population-specific variation (Momin et al., 2026). These findings demonstrate that methodological advances alone cannot overcome structural limitations in genomic data. Without more diverse datasets and population-aware modeling strategies, PRS applications risk reinforcing existing health disparities. However, emerging equitable machine learning frameworks offer a promising direction for improving prediction across diverse populations (L. A. Smith et al., 2025).

Conclusion

This review examined ancestry-related disparities in the performance of polygenic risk scores (PRSs) for type 2 diabetes (T2D), focusing on both population-level genetic factors and methodological approaches. The evidence consistently shows that performance gaps are driven primarily by the historical lack of diverse GWAS datasets and by models trained on this unbalanced data (Ge et al., 2022; Ruan et al., 2022). As a result, improving predictive accuracy can't be achieved without both expanding dataset diversity and integrating population-specific genetic architectures into more refined modeling techniques (Chande et al., 2020). Consequently, PRS predictions remain insufficient as independent clinical decision-making tools, particularly for groups underrepresented in current datasets.

Differences in genetic architecture across populations help explain why PRS performance varies so widely, through variations in allele frequencies and linkage disequilibrium (LD) patterns that influence how genetic risk is captured and estimated (Momin et al., 2026; Zhu et al., 2025). Even within broadly defined ancestry groups, environmental and demographic factors further shape

these patterns, adding complexity (Kamiza et al., 2022). These challenges are further amplified in admixed populations, where individuals inherit genetic variation from multiple ancestral backgrounds, making predictions based on single-ancestry models particularly unreliable (Chande et al., 2020). Although multi-ancestry models have been developed, their performance remains limited by the imbalances in training data. As a result, both statistical PRS approaches and machine learning models trained on data from one population often fail to generalize to others, leading to reduced transferability and diminished predictive performance. These limitations necessitate methods that explicitly model population-specific genetic architecture.

While methods such as PRS-CSx, PolyPred, and LDpred represent advanced statistical approaches for calculating PRSs, they share limitations that can hinder performance across diverse populations. These approaches, which rely primarily on additive SNP effects, often fail to capture non-linear genotype-phenotype relationships and can be sensitive to small or unrepresentative target samples. In addition, many require an accurate specification of ancestry, limiting their reliability in underrepresented and highly admixed populations (Elgart et al., 2022; Gunn et al., 2024; Gyawali et al., 2023; Ruan et al., 2022). To address these challenges, nonlinear machine learning approaches, including MUSSEL, XGBoost, PhyloFrame, FairPRS, and DisPred, have been developed to model more complex relationships or reduce dependence on ancestry labels. However, even these advanced methods can't fully compensate for missing or underrepresented training data, reinforcing the central role of data diversity in improving predictive performance (Elgart et al., 2022; Gyawali et al., 2023; Jin et al., 2024; Machado Reyes et al., 2022; L. A. Smith et al., 2025). These advances also reveal key trade-offs, where gains in predictive performance often come at the cost of increased data requirements, reduced interpretability, potential overfitting, or limited applicability across populations.

Collectively, these findings emphasize that PRS performance gaps are not merely technical shortcomings but reflect deeper structural issues in genomic research. The overrepresentation of European ancestry populations in GWAS has shaped both the data and the models built from it, limiting the generalizability of predictions across diverse populations (Majara et al., 2023). As a result, PRS often provide uneven clinical value, with reduced reliability in populations that are already underrepresented in biomedical research (Majara et al., 2023). In many cases, PRS

predictions offer only modest improvements over traditional clinical risk factors such as BMI or family history. PRS use should be critically evaluated in clinical settings, particularly to avoid reinforcing existing health disparities and inequities in clinical care (Martin et al., 2019).

Ongoing efforts are addressing multiple dimensions of the PRS diversity challenge. Large-scale initiatives such as the All of Us Research Program are expanding representation in genomic datasets in the United States, while consortia such as H3Africa are strengthening research infrastructure and data-generation capacity in historically underrepresented regions (Ginsburg et al., 2023; Sengupta et al., 2025). On the methodological side, models such as DisPred and FairPRS aim to reduce or eliminate reliance on explicit ancestry labels (Gyawali et al., 2023; Machado Reyes et al., 2022). For admixed populations, approaches developed by the eMERGE network use principal components analysis (PCA) to account for genetic variation without requiring discrete ancestry assignments (Lennon et al., 2024). Ultimately, achieving equitable and clinically meaningful PRS applications will require sustained investment in diverse datasets and the intentional design of inclusive genomic research frameworks.

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