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Polygenic Risk Scores for Type 2 Diabetes in South Asian Populations: Transferability, Calibration, and Decision Thresholds

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ABSTRACT

Polygenic risk scores (PRS) are increasingly used to estimate genetic susceptibility to complex diseases such as type 2 diabetes (T2D). However, most PRS models are derived from genome-wide association studies conducted primarily in European populations, raising concerns about their accuracy and clinical applicability in other ancestry groups. This paper reviews the transferability and predictive performance of PRS for T2D in South Asian populations, who experience a disproportionately high burden of the disease. It examines how differences in genetic architecture, allele frequencies, linkage disequilibrium structure, environmental exposures, and phenotypic heterogeneity influence PRS validity across populations. The review highlights evidence showing reduced discrimination, calibration issues, and potential bias when European-derived PRS are applied to South Asians. It further discusses methodological strategies to improve performance, including ancestry-specific genome studies, multi-ancestry modelling, recalibration approaches, and integration of PRS with clinical and lifestyle risk factors. Ethical and implementation considerations, such as equitable representation in genomic research, data governance, and responsible clinical deployment, are also addressed. The paper concludes that while PRS holds promise for enhancing early risk stratification and precision prevention of T2D in South Asians, substantial improvements in population diversity, validation, and clinical integration are required before routine use can be justified.

Keywords: Polygenic Risk Score (PRS), Type 2 Diabetes, South Asian Populations, Genetic Risk Prediction, and Precision Medicine.

INTRODUCTION

Diabetes poses a major global health threat, and its burden is rapidly growing in South Asia. Polygenic risk scores (PRS) derived from genome-wide association studies (GWAS) can help identify individuals at high risk for type 2 diabetes (T2D) for targeted prevention and treatment [1]. Existing scores developed primarily from the European population exhibit substantial, still undescribed gaps in transferability and attenuation of predictive ability for South-Asian populations. PRS has the potential to identify individuals at increased risk for T2D in South Asian populations, and their successful transferability across diverse populations offers socioeconomic and strategic advantages [2]. However, such scores require a thorough investigation of the extent of transferability and conditioning of South-Asian-specific calibration for accurate risk categorisation by population stratification [3]. PRS for T2D has the potential to generate substantial health benefits in South Asian populations, and such scores are strategically well-positioned to enhance population-specific coverage.

Background on Polygenic Risk Scores and Type 2 Diabetes

Type 2 diabetes (T2D) is a multifactorial and polygenic chronic disease of high heritability, compelling environmental factors, and growing socioeconomic and health burdens [4]. Precise contributions of genetic intervention to T2D remain uncertain despite extensive investigations across diverse populations. Recent genome-wide association studies (GWAS) unveil a relatively simple and easy-to-interpret contribution of common DNA variants to T2D pathogenesis. The contribution of common DNA variants, along with demographic factors (e.g., age or sex), is adequately described using a polygenic risk score (PRS) [5]. As a stabler, bioinformatics field-exploitable, and higher-than-complete-priority variable, PRS consists of a linear weighted sum using GWAS summary statistics as input [6]. Within PRS, a recent theory of polygenic with changing weights, namely soft-

thresholding and redundancy effect, supplies an additional precise description of fine polygenic and enables SC-transform for simplified PRS construction [7]. Consequently, PRS becomes a very promising routine for revealing genetic contribution to T2D and broadening it to even disease variables with more favorable preconditions [1].

Genetic Architecture of Type 2 Diabetes

Type 2 diabetes (T2D) is a complex metabolic disorder characterised by elevated blood glucose levels due to various environmental and genetic factors. The global prevalence is rising rapidly, particularly among South Asians, who are more susceptible [2]. Continuous glucose monitoring (CGM) data from the UK Biobank have shown that individuals with a family history of T2D exhibit high-risk glucose profiles from early childhood, suggesting that pre-disease prediction of T2D is possible [1]. Such predictions can inform preventive measures tailored to micro-environment specificities, such as dietary advice, lifestyle change, and target screening regimes.

T2D exhibits moderate heritability (42%–71%) ascertained by family, twin, and adoption studies [3]. Several genome-wide association studies (GWAS) have identified 270 loci associated with T2D among six different populations. Polygenic risk scores have become a popular approach to assess genetic risk based on large-scale GWAS summary statistics since 2010[3]. T1D-GRS is built from 181 genomic loci significantly associated with T2D, and the performance on South Asian populations (FNB, NDCS, PhenoS) has shown significant reclassification in T2D risk [4]. In South Asian populations, phenotype definitions and ascertainment procedures are overly heterogeneous in T2D epidemiological studies [5]. A transcriptome-wide association study has identified the first extensive T2D transcriptome, providing previously inaccessible information to establish an unbiased, ancestry-independent risk score in the European population [5]. A South Asian-specific T2D risk score is constructed based on T1D-GRS, demonstrating substantial improvement in prediction and reclassification accuracy across diverse cohorts [6]. At the temperature extremes from 25 to 70 °C, a pronunciation identification model trained at room temperature maintains good performance [7]. It shows a 20% enhancement at the temperature of 40 °C and a 15% improvement at 50°C over the baseline in overall pronunciation error rate reduction. An additional 5% improvement at 50°C over the previously stored 40 °C model can be achieved with fine-tuning at 40 °C, demonstrating the potential for further gains from temperature adaptation through flexible data storage and model training [5]. The influence of temperature on the speech corpus is also concluded through further experiments [3].

Concept and Construction of Polygenic Risk Scores

Polygenic risk scores (PRS) based on common single-nucleotide polymorphisms (SNPs) predict susceptibility to complex diseases. The scores aggregate the cumulative effect of multiple genetic variants, the precise mechanisms of which remain unclear [1]. T2D PGS are particularly helpful in global studies of pathology, yet diverge considerably in South Asian populations [3]. Polygenic risk score associations with T2D in non-European populations remain uneven 4. Participating in hundreds of international consortia and employing large biobanks in multiple countries would improve South Asian risk scores [4]. The contemporary PRS construction process uses three broad stages. The first entails retrieving genome-wide association study (GWAS) summary statistics for the target disease, extracting SNPs in units of discovery and evaluation cohorts, and determining linkage disequilibrium (LD) structure to group variants with high ($r^2 \geq 0.1$) genetic correlations. Two large GWAS datasets, the first focused on T2D and the second on glycemic traits including fasting glucose, insulin resistance, and insulin secretion, provide major inputs to the construction of South Asian T2D PRS. Numerous methods, including commonly used clumping, score-size independent, and LDpred approaches tailored to existing PGS, enable the selection of variants most predictive of T2D risk in South Asian ancestries [6]. Comp insights into the cross-scale prediction of complex traits and diseases suggest that including non-European cohorts at GWAS stages to increase ancestral diversity would substantially enhance the global PGS framework and performance [3].

Performance assessments of T2D PRS constructed specifically from European ancestries in South Asian populations reveal significant gaps [6]. AUC values show that South Asian populations derive only between 38% and 61% of the risk of T2D predicted for European populations. Compounding these measures, effect sizes decline progressively across diverse South Asian cohorts to as little as 16%, which would not merit further development of a new T2D PRS family [8]

Transferability of Polygenic Risk Scores to South Asian Populations

Widely studied in populations of European ancestry, polygenic risk scores (PRSs) for type 2 diabetes (T2D) have the potential to guide early diagnosis and prevention in South Asian populations, where the disease is particularly prevalent. However, there is uncertainty regarding transferability from other populations, calibration, and decision thresholds [2]. Evidence of cross-population performance gaps has been documented: prediction of T2D in unrelated European individuals from a large biobank is attenuated by an average of 65% in non-European populations, and South Asians show greater attenuation than Latinos or East Asians [3]. Furthermore, PRS constructed from large, ancestry-specific genome-wide association study (GWAS) summary statistics yield substantial, population-specific differences in effect size when tested in South Asians. Transferability is notably

sensitive to the coverage of the reference panel, yet annotated metaGWAS for T2D in South Asia are scarce. Gaps in ancestry representation within the 1000 Genomes Project Phase 3, used for linkage disequilibrium (LD) reference, affect diverse South Asian populations, which exhibit longer LD than Europeans, marked regional structure, deleterious mutation load, and underrepresentation of low-frequency South Asian variants in current African or East Asian reference panels[4]. Factors influencing transferability in South Asian cohorts include high ancestry diversity among South Asian populations, differences in derived-allele and risk-allele frequencies relative to European GWAS, and distinct LD patterns across chromosomes [3]. Other contributors include relatively small sample sizes of South Asian genome-wide T2D case–control studies, differing phenotypes according to definitions of prediabetes and gestational diabetes, variations in imputation pipelines, and reliance on base-coverage and imputation-quality metrics instead of functional annotation in meta-analysis [2].

Evidence for Cross-Population Performance

Polygenic risk scores (PRS) developed using European populations have been shown to retain predictive value across several complex traits and diseases in non-European populations [1]. European-derived PRS for breast cancer effectively stratifies risk among Asian women, cardiovascular disease PRS developed in European cohorts demonstrates utility in South Asians, and the UK Biobank sample-wide polygenic score for educational attainment exhibits cross-population performance[7]. These findings affirm the value of PRS developed in European cohorts even when applied to genetically diverse populations. Nevertheless, systematic comparisons highlight substantial variability in PRS transferability across traits and diseases [5]. The performance of genetic prediction models is influenced by the genetic architecture of the trait, including the common-variant effect-size distribution and the peculiar genetic variation associated with the disease [2]. In type 2 diabetes (T2D), fundamental studies reveal signal attenuation and a lack of significant association between main variants and the disease status under European summary statistics, pointing to important discrepancies in the genetic architecture of T2D between European and South Asian populations [6]. Extensive population admixture and extensive population bottlenecks constitute the two crucial distinguishable aspects of South Asian genetic evolution, providing an opportunity to investigate factors that maintain polygenic-architecture [7]. Despite type 2 diabetes being a polygenic disease, large plaques are detected, and signal attenuation is observed when a European-derived PRS is used to measure genetic susceptibility [4]. Population-specific investigations underline the detrimental effect of long-distance LD structures combined with severe allele frequency shift on genetic prediction models and highlight the critical pathway for understanding the modeling of risk scores across different populations [3].

Factors Influencing Transferability in South Asian Cohorts

South Asian ancestry groups harbor the world's largest diabetic populations, yet the overwhelming weight of genome-wide association study (GWAS) datasets has predominantly favored Euro-American individuals. Consequently, polygenic risk scores (PRSs), which remain among the most tractable forms of genomic risk prediction, constructed from European GWAS, exhibit markedly reduced predictive utility in South Asian patients [5]. Several intrinsic and extrinsic factors pertinent to South Asian cohorts contribute to this substandard cross-ethnic transferability of T2D-PRSs. Ancestry diversity across South Asian countries remains disproportionately underreported in large-scale biobanks, saturated in Euro-American datasets, inhibiting optimal training set selection. Allele-frequency discrepancies from multiple ancestral sources substantially alter risk assignment despite robust PRS-tuning methodologies [6]. The stage of admixed populations (out of 10 exclusively-trained T2D-PRSs, South Asians represent 9) further complicates the derivation of more forecastable genomic models via European GWAS alone. Intricate linkage-disequilibrium (LD) structures occasionally challenge core imputation operations to accurately recover risk-variant haplotypes, while compound population-specific or GWAS-high-layer strategies aimed at larger training cohorts also frequently demand trans-European tuning, particularly for more complex, non-biomedical phenotypes such as T2D [2, 5].

Calibration of Polygenic Risk Scores in South Asian Populations

Polygenic risk scores (PRS) for type 2 diabetes (T2D) constructed from European genome-wide association studies (GWAS) are not optimally calibrated for South Asian populations, raising the possibility of miscalibrated absolute risk estimates and biased assessment against clinical action thresholds [1]. Significant genotype and phenotype variation exists between European and South Asian cohorts, and summary-statistics-based PRS transfer typically leads to incomplete transfer of effect sizes, posing risks of miscalibration [2].

Calibration gaps can be addressed through approaches such as recalibration, development of population-specific calibration curves, and external validation [3]. Several recalibration methods have been proposed, including isotonic regression and Platt scaling. Each South Asian study cohort that has evaluated the transferability of European-derived polygenic scores has applied one of these methods prior to risk assessment. The only available multi-cohort South Asian-specific PRS calibration analysis has identified pervasive miscalibration even after isotonic regression [5]. Furthermore, polygenic scores constructed from the two largest South Asian GWAS have exhibited considerable variation across South Asian cohorts. Understanding the extent to which calibration-based

risk estimates transfer across studies carrying distinct genotype–phenotype characteristics can provide insights into the potential utility of a population-specific score [7].

Methods for Calibration and Validation

Calculating and communicating absolute risk based on a polygenic risk score (PRS) remains an outstanding challenge [5]. An estimated one-quarter of risk loci for type 2 diabetes (T2D) have transferred across diverse ancestries, yet PRS constructed in one population often miscalibrate when applied to another because available data-sharing frameworks impose substantial constraints on the number and geographic range of suitable external cohorts. Assessment of transferability remains incomplete in South Asian populations, for which relatively few well-phenotyped [6]. Several approaches can address these two calibration challenges [4]. Recalibration methods such as isotonic regression and Platt scaling provide population-specific adjustments that align PRS with observed disease prevalence even when underlying genetic and environmental influences differ [4]. Population-specific calibration curves can be established to convey information on the corresponding absolute risk associated with given PRS values. External validation via independent geographic cohorts then constitutes a more conservative approach, checking for absolute miscalibration based on SHIP, JPHC, or other datasets [7]. As large-scale genetic studies of T2D and related traits advance in South Asia, a growing area of engaged research investigates calibration gaps for existing PRS. Population-specific absolute risk estimates become essential for effective clinical translation and prioritization of public health outreach [6]. Existing materials for individuals of South Asian heritage nonetheless remain limited. Concerns regarding confounding of absolute risk estimates by widely acknowledged non-genetic risk factors have prompted exploration of how population-specific data on these additional determinants might be integrated into joint modelling frameworks alongside PRS [2].

Current Calibration Gaps and Implications for Risk Estimation

Polygenic risk scores (PRS) can stratify the risk of type 2 diabetes (T2D) across individuals of diverse ancestry 2. However, existing scores calibrated to European populations are miscalibrated in South Asian samples, leading to biased absolute risk estimates and altering the effectiveness of population-specific actionable thresholds. Polygenic risk correlates with cumulative incidence of T2D in South Asian cohorts, demonstrating that the gap in calibration influences the clinical and public health utility of PRS within region 5.

Decision Thresholds for Clinical and Public Health Use

The implementation of a polygenic risk score (PRS) for type 2 diabetes (T2D) in South Asian populations benefits from the definition of clear and relevant decision thresholds for clinical use [5]. The concept of a decision threshold refers to a risk value (or established percentile cut-off) above which action is recommended, while threshold levels of actionability (i.e., higher-risk categories meriting greater intervention) specify further degrees of stratification. In general, risk strata or thresholds can be defined directly in terms of the PRS value, via percentiles (cut-offs of specific percentiles) or absolute risk (cut-offs of specific predicted probabilities) [4]. The dimensions of public health intervention, actionable versus non-actionable, constitute another important level of clinical decision-making [3]. An established decision threshold significantly aids the appropriate interpretation of the PRS, focusing attention on actionability rather than alternative attributes (e.g., predictive accuracy). For specifically South Asian populations, various, previously validated 5-year and 10-year absolute-risk thresholds exist, which are at least transferable to some degree [4]. The efficient "one-size-fits-all" approach to risk stratification inevitably introduces some gain-loss imbalance across populations (besides additional quantifiable biases, for instance, concerning case–control matching in the current case)[4]. The specific "best" cut-off point for South Asians recommended, therefore, still constitutes a matter for further deliberation [2].

Thresholds for Actionability and Stratification

A major goal of PRS studies is to identify risk thresholds that guide clinical decision-making and public health interventions. Percentile-based cut-offs, such as the top 1%, 5%, or 10% of the population, are often used to define extreme, high, or moderate risk strata [2]. Distance to clinical action thresholds then becomes a priority [3]. For the South Asian PRS, the population-specific 90th-percentile cut-off was selected as a reference for moderate risk, with clinical analyses suggesting interventions before the onset of diabetes [7]. Adiposity and family history were found to complement the PRS. Integration with diverse data types should thus be supported at the clinical and public health levels [2, 1].

Balancing Sensitivity, Specificity, and Equity

Drafting a risk-based action plan to curb type 2 diabetes incidence in South Asian populations requires careful balancing of three distinct but complementary trade-offs [5]. One considers the robustness of the prediction, seeking the threshold that maximises a composite criterion dependent on sensitivity and specificity. A second balance concerns the information needed to reach a prediction, weighing polygenic information alone against the incorporation of additional clinical data such as adiposity, family history, and socioeconomic factors [4]. The third trade-off pertains to the equitable distribution of risk predictions across population subgroups differing in ancestry and exposure to health-harming environments [3]. Population-level decisions must therefore embrace variations in prediction horizons, depending on the mix of risk factors incorporated and the desired degree of equity pursued.

Accelerated efforts to address polygenic risk prediction must focus on further embedding polygenic information within multi-variable frameworks that also consider clinical, behavioural, and socioeconomic context [2]. The urgency of the task is accentuated by global epidemiological trends hinting at marked increases in the adult prevalence of overweight and obesity in parts of South Asia historically insulated from such risk [1].

Integration with Non-Genetic Risk Factors and Lifestyle Data

Individuals' susceptibility to T2D depends not only on their genetic endowment and non-genetic influences but also on lifestyle behaviours. The incorporation of such additional information can improve risk assessment, inform decision-making, and motivate preventive measures [1]. Population-specific adjustments can account for differences in background predisposition attributable to complex ancestry and demographic history, in particular, concerning interpopulation admixture and introgression events [2]. T2D remains highly prevalent among many South Asian groups, and the risk of T2D is closely related to obesity. Therefore, integrating non-genetic risk factors provides a convenient way of exploiting the relevant information available [4].

Gaps in Evidence and Methodological Considerations

Advances in genomic knowledge over the last two decades have enabled the application of polygenic risk scores (PRSs) to estimate individual predisposition to diseases in diverse populations [2]. A recent analysis demonstrated the ability of such scores to predict type 2 diabetes (T2D) in South Asian cohorts [7]. Across six independent datasets, the area under the curve (AUC) was within 0.02 units of European scores PRS based solely on European genome-wide association study (GWAS) data. As the AUC for South Asian–specific risk factors remains low in South Asian cohorts, the transferability of European-based PRS adds clinical value [6]. Gaps persisted in the transferability of summary statistics from publicly available, European-derived T2D GWAS 5. Although South Asian individuals constitute a sizable and growing demographic in Europe, European-only reference panels remain prevalent in studies addressing South Asian diversity. Variants initially absent from South Asian-only T2D meta-analyses had now become relevant, further isolating existing South Asian datasets [3]. The limited availability of data on South Asian populations reinforces the requirement for public sharing of genomic datasets [4]. Researchers seldom publish phenotype details alongside genetic information, precluding meaningful cross-cohort comparisons. Prior analyses of differences in T2D risk between South Asian and European individuals suggest potentially lower effect sizes for South Asian participants, but discrepancies could result from factor variations in sample definition or study design [4]. The presence of T2D-associated single-nucleotide polymorphisms (SNPs) overlooked in South Asian cohorts may obscure even greater differences. The rise of multi-ancestry studies creates new opportunities for PRS construction. Diverse ancestral reference panels can now facilitate the development of T2D risk charts tailored to South Asian populations, finer mapping of variants associated with T2D risk, and the establishment of additional polygenic scoring methods more sensitive to ancestry. However, PRS design suitable for clinical implementation requires consideration of ethical, legal, and social consequences [4]. Globally, concern exists regarding data privacy, consent, the sharing of polygenic risk, potential stigmatization, and associated governance [4].

Ancestry Diversity and Representation In GWAS

Polygenic risk scores (PRS) derived from genome-wide association studies (GWAS) of type 2 diabetes (T2D) in European populations exhibit reduced transferability to South Asians, a demographic with high prevalence and mortality[3]. Mitigation of this gap is hindered by the limited representation of South Asian individuals in publicly available GWAS. In the 2021 UK Biobank T2D GWAS, for instance, only ~1% of the cohort self-identified as Black or South Asian 5. Even South-East Asian populations, such as Chinese, Vietnamese, and Thai, exhibit greater representation than South Asians in contemporary GWAS of shared ancestry [5]. Population-specific summary statistics, which account for the underlying diversity of South Asian ancestry, could improve transferability [6]. The absence of South Asian reference panels constrains effective imputation and limits the transfer of population-specific variants across South Asian subpopulations. Moreover, the spectrum of ancestries in South Asia is broader than that found in continental groupings used to define reference panels, implying that the potential to enhance population-specific imputation needs further exploration [7].

Sample Size, Phenotyping, and Harmonization Challenges

Underlying many common complex diseases are genetic risk factors and exposure to environmental influences that interact in a polygenic manner [3]. These polygenic risk factors are accessible through the construction of a polygenic risk score (PRS), a numerical metric reflecting the collective genetic risk for a disease. The PRS quantifies the correlation between genomic variant information and disease status for any individual, providing relative risk predictions [2]. The use of PRS alongside conventional risk factors has the potential to inform screening and prevention strategies. The overall aim of the project is to assess the transferability, calibration, and decision thresholds of PRS for type 2 diabetes (T2D) risk in South Asian populations, which have been highlighted as a high-priority research area [1]. For polygenic inferences to be valid, ancestry diversity should be considered in genome-wide association studies (GWAS) of common complex diseases. Despite the inclusion of over 1.2 million participants, South Asians remain underrepresented in T2D GWAS. Researchers have turned to meta-

analysis studies with modest sample sizes and diverse ancestry to evaluate representation in global GWAS. Such studies have identified key T2D risk variants that are uncorrelated or poorly correlated with locally common variants and are missed if PRS are built solely from local summary statistics [4]. Variants present in admixture are also likely to be missed. A diverse reference panel greatly enhances local imputation. Construction of a South-Asian-specific GWAS is needed for T2D and other complex diseases to increase the usefulness of imputation and improve transferability [2].

Ethical, Legal, and Social Implications

Polygenic risk scores (PRS) provide a promising new tool to identify individuals at a higher risk of developing type 2 diabetes (T2D). A number of studies have demonstrated that PRS, even when based on data from diverse populations, can accurately identify South Asian populations prone to T2D [2]. Nevertheless, despite the transferability of polygenic models developed in European populations, South Asian populations remain substantially underrepresented in genome-wide association studies (GWAS). Furthermore, reference panels derived from predominantly European individuals are inadequate to correctly annotate and predict genetic variation in South Asian individuals [4]. Harmonizing phenotyping, optimizing statistical imputation, improving access to existing datasets, and otherwise establishing separate South Asian T2D consortia is urgently needed to build a detailed picture of T2D genetic risk in diverse South Asian populations [6]. In addition to monitoring genetic variation, it is equally important to consider upstream health policy and implementation aspects to ensure equity and fairness in the rollout of PRS. The development of frameworks for the incorporation of genetic information into T2D risk stratification, linking the advice of health actors with actionable recommendations derived from PRS, controlling for relevant non-genetic influences, and safeguarding monitoring prolong the practical feasibility of PRS-derived stratification in diverse South Asian populations [1]. Ensuring the safe and fair utilization of PRS in the domain of T2D is an equally pressing issue as research efforts accelerate in this area. PRS opens previously unavailable horizons and holds substantial potential for advancing health policy, but the rapid emergence of transformative technologies often denotes an equally powerful prospect for misuse. An invitation to consider a set of ethical, legal, and social issues closely related to the first generation of PRS remains timely. Safeguards guaranteeing that PRS remains a powerful asset rather than a limiting factor to health equity must be firmly established from the outset [5].

Future Directions and Recommended Research Priorities

The prospective validation of polygenic risk scores (PRS) for type 2 diabetes (T2D) in diverse South Asian populations, covering multiple regions within the Indian subcontinent, represents an urgent research priority [5]. Longitudinal cohorts with genetic measurements at baseline would enable investigation of the association between T2D risk and subsequent disease onset [4]. Though cross-sectional evaluations retain utility for assessing operational transferability, a focus on prospective validation would facilitate characterization of absolute risk.

Additional South Asia-specific reference panels would advance the development of population-tailored PRS. Ancestry-aware models, applying summary statistics or fine-mapped causal sets from South Asian cohorts, could yield improved scores alongside enhanced imputation accuracy for variants with limited external reference coverage [4]. Continued reference genome diversity efforts aligned with global diversity patterns would further reduce representation gaps [2]. Implementing PRS within clinical settings remains an important objective, demanding operational frameworks that encompass training, integration with non-genetic risk factors, and multi-stakeholder input [6]. Guidelines could define governance principles, acceptable limitations, and best practices for outreach to at-risk populations. Hospital networks establishing PRS-based prediction in diverse clinical and public health contexts offer valuable opportunities for empirical monitoring [7].

Prospective Validation in Diverse South Asian Populations

Polygenic risk scores inform efforts to identify high-risk individuals for interventions to delay the onset of type 2 diabetes (T2D) and associated complications [5]. PRS for T2D derived from European genome-wide association studies (GWAS) have been shown to carry predictive power in South Asian populations, yet prospective validation of clinical utility in diverse South Asian cohorts remains a significant unmet need [4]. Validation studies have demonstrated that European-derived cardiovascular PRS have utility for stratifying risk of adverse outcomes in South Asian populations; therefore, PRS developed in European GWAS can serve as a first approximation for predicting T2D risk in South Asians [3]. Continued efforts are warranted to build on preliminary findings supporting South Asian transferability by prospectively validating PRS for diverse South Asian ancestries across a wide range of settings and populations. The distribution of the T2D PRS can be readily estimated from publicly available summary statistics, and the Southampton Genetics of Diabetes study offers multiple longitudinal cohorts of individuals of diverse South Asian descent who have been phenotyped for T2D and other cardiometabolic traits [2].

Development of Region-Specific Reference Panels

Polygenic risk scores can identify individuals at high risk for T2D, especially in high-risk populations like South Asians. Using South Asian-specific summary statistics, the developed SA-PRS showed better predictive power for

T2D than European-based PRS across validation and testing datasets [7]. The T2D prevalence increased with higher risk scores, and the top quartile of the SA-PRS population had over four times higher risk compared to the bottom quartile. Combining South Asian and European summary statistics did not significantly improve prediction. These findings demonstrate the potential of population-specific genomic reference panels to improve risk stratification in South Asian populations [5]. Integrating polygenic risk scores aids in predicting type 2 diabetes risk and subtypes in specific populations. Studies show that polygenic risk scores developed in European populations can perform differently across diverse populations, highlighting the need for population-specific reference panels [6]. Construction of polygenic scores must be accurate and scalable to large datasets, and using these scores can improve risk prediction for various diseases, including breast cancer, coronary artery disease, and schizophrenia. Validation in diverse populations, including South Asians and Hispanics, is essential. Resources like the polygenic score catalog facilitate reproducibility and systematic evaluation, driving the development of better tools for genetic risk prediction tailored to specific regions and populations [3].

Frameworks for Clinical Implementation and Monitoring

The implementation of Polygenic Risk Scores (PRS) in clinical practice represents a complex process that encompasses validation, acceptability, cost-effectiveness, regulatory requirements, and integration into care pathways. Various frameworks exist to guide the implementation of genomic technologies in low- and middle-income countries [5]. For instance, the National Academies of Sciences, Engineering, and Medicine propose two roads for genomic implementation: the route of promulgating mandatory pathways with comprehensive oversight to ensure the safe introduction of novel technologies and practices, assuring protection of the citizens, and the development-by-analogy route for countries where such strict oversight would become oppressive or prohibitive[6]. The former route provides a fixed course along which evolutionary change can occur, while the latter emphasizes the evolution of the regulatory framework built from requirements and practices already established elsewhere in the world. Integration of polygenic scores in the prediction of type 2 diabetes risk and subtypes in diverse populations is increasingly reported, indicating that polygenic scores can improve risk stratification even when developed exclusively on non-South-Asian individuals [5]. The performance of the polygenic risk score for type 2 diabetes derived from a European de novo genome-wide association study of over 180,000 individuals and its interplay with family history of diabetes is assessed in a cohort of 1 million South-Asian individuals. Score exhibits clear attenuation of effect sizes across populations, and yet provides sufficient information to contribute to risk estimation when combined with family history [5]. Determination of an optimal ethical framework for polygenic risk reporting remains unresolved, complicated by the absence of conclusive evidence on aversion to high polygenic risk coupled with commercially regulated health-related applications that differ from academia. Comprehensive Regulatory Framework for Genomic Implementation is a systematic initiative aimed at assuring that any genomic technology can be introduced swiftly and without undue barriers [7-12].

CONCLUSION

Polygenic risk scores (PRS) represent a promising tool for improving early identification, prevention, and management of type 2 diabetes (T2D), particularly in high-burden populations such as South Asians. However, the current evidence demonstrates that PRS developed predominantly from European genome-wide association studies exhibit reduced transferability, attenuated predictive performance, and substantial calibration challenges when applied to South Asian populations. These limitations arise from differences in genetic architecture, allele frequencies, linkage disequilibrium patterns, ancestry diversity, phenotyping approaches, and the persistent underrepresentation of South Asians in large genomic datasets. Addressing these challenges requires coordinated efforts to develop ancestry-informed PRS through expanded South Asian participation in genome-wide association studies, the creation of region-specific reference panels, and improved harmonization of phenotypic and genomic data. Robust recalibration strategies, external validation in diverse cohorts, and integration of PRS with clinical, behavioural, and socioeconomic risk factors will be essential to ensure accurate risk estimation and equitable clinical utility. Equally important are the ethical, legal, and governance frameworks needed to safeguard privacy, prevent misuse, and promote fair access to genomic technologies. Future research should prioritize prospective longitudinal validation, multi-ancestry modelling approaches, and the development of clinically actionable decision thresholds tailored to South Asian populations. With these advances, PRS could move from a primarily research-based instrument to a reliable component of precision public health strategies, supporting targeted screening, preventive interventions, and improved health outcomes for populations at elevated risk of type 2 diabetes.

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