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Polygenic Risk Scores for Breast Cancer in African Ancestry Populations: Transferability, Calibration, and Decision Thresholds

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ABSTRACT

Polygenic risk scores (PRS) have emerged as promising tools for stratifying breast cancer risk and informing screening and prevention strategies. However, their clinical utility in African ancestry populations remains limited due to poor transferability, miscalibration, and uncertainty surrounding appropriate decision thresholds. Most existing PRS are derived from genome-wide association studies (GWAS) conducted predominantly in European ancestry populations, resulting in reduced predictive accuracy and systematic over- or underestimation of risk when applied to individuals of African ancestry. This review examines the current evidence on the transferability of breast cancer PRS to African ancestry populations, with particular emphasis on population-specific genetic architecture, methodological challenges, calibration performance, and threshold derivation strategies. Empirical findings consistently demonstrate diminished predictive performance and substantial miscalibration of European-derived PRS in African ancestry cohorts, raising concerns for equitable clinical implementation. We further explore calibration methods, decision-curve analysis, and ancestry-sensitive thresholding approaches, highlighting their implications for risk stratification, screening eligibility, and preventive interventions. Finally, we identify key evidence gaps, including underrepresentation in GWAS, limited biobank infrastructure, and heterogeneity in phenotype definitions, and propose future directions emphasizing multi-ancestry GWAS, integrative multi-omics models, standardized reporting, and equity-centered implementation frameworks. Addressing these challenges is essential to ensure that PRS-based breast cancer risk prediction contributes meaningfully and ethically to precision medicine for African ancestry populations.

Keywords: Polygenic risk scores, Breast cancer, African ancestry populations, Risk calibration, and Decision thresholds.

INTRODUCTION

Polygenic risk scores (PRS) estimate the genetic predisposition to polygenic diseases using aggregate information from genome-wide association studies (GWAS). PRS are widely used for breast cancer risk prediction, yet their clinical implementation in African ancestry populations remains underexplored. Importantly, PRS derived from European-ancestry SNPs tend to show poor predictive performance in African ancestry cohorts, indicating that generalized PRS approaches are unlikely to provide accurate risk estimates [1]. Moreover, factors such as the population structure of breast cancer, low study participation, and nonstandardized phenotype definitions have limited the development of broad yet sufficiently detailed African-ancestry GWAS [2]. Consequently, inclusive PRS construction and broad application for scoring African ancestry individuals remain unmet research needs. Many approaches for risk-stratified breast screening and preventive intervention decisions rely on absolute risk estimates over specific PRS thresholds [3]. By modeling the breast cancer phenotype as either a PRS or risk prediction target, different strategies may yield similar predictions across diverse populations and subgroups,

thereby enhancing transferability, yet neither strategy obviates the necessity for population-specific models, data gathering, and supported clinical implementations [3].

Background on Polygenic Risk Scores and Breast Cancer

Breast cancer ranks among the most prevalent cancers and is a leading cause of cancer mortality among women. In the United States, one in eight women is expected to be diagnosed with breast cancer in her lifetime; this statistic is even higher for women of Ashkenazi Jewish ancestry. In 2020, breast cancer accounted for an estimated 30% of newly diagnosed cancer cases in women and approximately 15% of cancer-related deaths in women [4]. Estimates indicate that approximately 15% of breast cancer cases have a hereditary component and are associated with germline pathogenic variants carried by BRCA1 or BRCA2, with several additional genes currently being investigated [5]. Polygenic risk scores (PRSs) that aggregate the effects of common genetic variation are increasingly seen as complementary tools for assessing breast cancer risk. PRSs have been constructed for multiple breast cancer subtypes defined by the cancer's expression of estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) statuses [5]. Cross-ancestry genetic studies suggest that individuals of African ancestry tend to carry high-risk breast cancer variants at lower frequencies compared to individuals of European ancestry [2]. Breast cancer PRSs derived primarily from Europeans exhibit good, but not optimal, predictive performance when applied to Latino and African ancestry populations. There is growing interest in evaluating the applicability of PRSs across diverse ancestry groups [3].

Transferability of Polygenic Risk Scores to African Ancestry Populations

Breast cancer is the most frequently diagnosed cancer for women globally, and the second most common cause of cancer death [3]. It is the most common cancer for Black women and the most significant cause of cancer mortality for both women and men of African ancestry [2]. Large-scale genome-wide association studies (GWAS) alongside polygenic risk score (PRS) analyses have successfully established genetic and non-genetic factors that contribute to the risk of breast cancer. Meanwhile, estimates indicate that two out of every three Black women diagnosed with breast cancer are younger than 50 when compared with one out of every four European ancestry women diagnosed with breast cancer [5]. PRS established through GWAS of breast cancer and other forms of cancer provides remarkable promise for risk-discriminatory applications in preclinical cohorts of thousands of women of African ancestry in diverse settings [3]. These cohorts include substantial proportions of Black adult women who are married, cohabiting, or with a long-term partner; have only completed primary schooling; and have less than a secondary, Senior Secondary, or Ordinary Level of education[6]. Efforts to develop broader registries with more extensive and detailed follow-up covering the entire African continent, other nations with comparable ancestry, and more diverse settings, such as adolescents and women with different longitudinal distributions of paragenics, remain critically important for combating persistent inequality in breast-cancer survival and mortality across different racial and ethnic groups [6].

Methodological Considerations

Polygenic risk scores (PRS) constructed from genome-wide association studies (GWAS) provide an efficient means of summarising the combined effects of common genetic variants on the risk of disease [7]. The development of polygenic risk scores for breast cancer has been rapid since the publication of the first associated variants, yet their clinical implementation is underdeveloped in people from Africa and of African ancestry [2]. Several challenges have prevented the widespread adoption of PRS for breast cancer, specifically in people of African ancestry. These include differences in linkage disequilibrium (LD) structure between continental populations that limit the portability of effect sizes, lower imputation quality, larger allele frequency differences, and the consideration of models for PRS that are adjusted for ancestry [9]. Cross-ancestry meta-analysis provides a simple extension to enhance transferability, while alternative methods have been proposed to compute multi-ancestry PRS that better accommodate population-specific effect sizes from European-derived GWAS [6]. Most published polygenic risk score models for breast cancer, be it those that have undergone cross-ancestry validation or those computed from European-descent GWAS, have comparatively poor predictive performance in people of African ancestry [7]. Group-level calibration of polygenic risk scores enables the quantification of systematic over- and under-estimation of risk, and may indicate whether models should be employed in decision-making [8]. Breast cancer incidence is often lower in people of African ancestry than in those from non-African populations. Consequently, the observed functioning of polygenic risk scores in Northern Europe does not straightforwardly translate to populations of African ancestry [3].

Empirical Findings and Gaps

The transferability of polygenic risk scores (PRS) for breast cancer to individuals of African ancestry continues to be investigated. Empirical assessments of predictive performance in African ancestry cohorts indicate a significant decrease in risk prediction accuracy compared to European-ancestry cohorts [3]. This drop in accuracy follows extensive fine-mapping efforts aimed at capturing the complete association signal within European-ancestry datasets. Additionally, although the ability to replicate PRS associations is established for individuals of African

ancestry, a concerning number of PRS remain unreplicable [4]. Underrepresentation of African ancestry populations across the PRS publication landscape is likely responsible for both the observed drop in predictive performance and the existence of non-replicated PRS [6]. Such observational data on predictive performance, replication status, and population coverage collectively highlight the need for continued exploration of the transferability of PRS for breast cancer risk prediction within African ancestry populations [3].

Calibration of Risk Scores in Diverse Populations

In models predicting the risk of breast cancer, calibration quantifies the agreement between predicted and observed risk, enabling optimal risk stratification decisions [2]. Jointly calibrated cohort-specific and region-specific transferability analyses demonstrate that risk scores originally trained on European ancestry cohorts are consistently miscalibrated in several cohorts of African ancestry [6]. Population-specific calibration is vital for ensuring safe clinical implementation of risk scores validated in populations of mixed ancestry [1]. Polygenic risk scores for breast cancer exhibit considerable interpopulation variation in predictive performance between African and European ancestry populations 2. Such differences underscore the necessity of evaluating the distribution of non-communicable disease-associated polygenic risk scores across populations with diverse genetic ancestry [2].

Calibration Methods and Metrics

Calibration quantifies how well predicted risks align with observed outcomes. The ideal prediction model produces, on average, the same disease risk for individuals within a given risk group [3]. A well-calibrated score can estimate risk directly, while a poorly calibrated score must derive estimates from more informative scores to guide screening and prevention decisions [7]. Calibration plots depict predicted versus observed risk for subgroups of individuals ranked by predicted risk; perfect calibration is represented by a 45-degree line. Informal slope and intercept calibration adjusts predicted risks based on the linear relationship between predicted and observed risk [5]. The Brier score (BS) computes the squared difference between predicted and actual outcomes; lower values indicate better calibration [6]. Decision-curve analysis evaluates the net benefit of action on the predicted risk versus a population-level threshold. Age- and region-specific approaches reflect unique risk profiles for women of different ages and geographic locations [2].

Current Calibration Performance in African Ancestry Groups

Polygenic breast cancer risk scores are miscalibrated in groups with African ancestry, leading to overestimation and underestimation of the absolute probability of disease [3]. In a population of female individuals aged 40-69 years, European-ancestry genetic variants caused the observed risk to be largely overestimated [4]. The median observed-to-expected ratio was 3.09 (90% CI 2.17-4.74), and the slope of the observed-risk-to-expected-risk regression was 3.81 (2.43-5.61), indicating threefold overestimation [5]. In a population aged 30-69 years, risk was still overpredicted, with a median ratio of 2.35 (1.58-4.56) related to the same cohort, and almost 30% of the individuals exhibited overestimation greater than fivefold. This degree of miscalibration is of great concern for clinical applicability in breast cancer prevention and intervention decisions [6]. Calibration is paramount for utility in risk stratification, screening recommendations, and patient counseling 7. On the cross-section of environmental exposure (Age, BMI, Comorbidity, Menarcho, Parity, Smoking, and Time_of_Use), skin cancer risk changed by less than a factor of two for the cohort distribution considered, and the inclusion of 44 genetic loci yielded no measurable effect on overall calibration [7]. In contrast, the use of existing UK estimates led to grossly exaggerated risk in individuals of African-derived physiology [8]. The relative overestimation by the UK distribution available was almost a factor of six, and in the later cohort considered, the complete inclusion of the cohorts originating in East Africa resulted in an observed risk of roughly the correct magnitude [6].

Implications for Clinical Utility

PRS-based risk scores for breast cancer exhibit population-specific calibration characteristics [2], which can significantly influence their clinical utility. Accurate calibration is essential for determining screening eligibility and obligations and for advising individuals on preventive or therapeutic measures. In cohorts of African ancestry, risk scores derived from large European-population GWAS studies show widespread over- and underestimation, alongside substantial uncertainty surrounding predicted risk [8]. Such miscalibration, which is exacerbated for scores based on summary-statistic-based PRS-informed modeling of African ancestry, diminishes both the relevance of polygenic information and the value of supplementary risk-factor data [9]. Polygenic risk scores intended to guide risk stratification can be optimally calibrated during threshold selection to mitigate the adverse influence of poor transferability observed in diverse populations [10]. Consideration of calibration and thresholding is thus vital in assessing the potential of PRS to enhance breast cancer risk estimation in individuals of African ancestry [11].

Decision Thresholds for Risk Stratification

Computation of decision thresholds for risk stratification requires a two-step approach, typically starting with the estimation of monitored parameters from training cohorts and their subsequent transfer to target populations for joint evaluation [9]. To this end, three common threshold-derivation strategies can be distinguished [3].

Percentile-based approaches select a threshold by applying the same percentile cut-off in the target cohort (e.g., 99th percentile) as assumed during the definition of the risk estimate in the training population [6]. Alternatively, absolute-risk thresholds can be set to align with the target cohort, such as a specified lifetime or 5-year absolute risk. The most comprehensive, however, optimizes the maximum net-benefit across all considered cut-offs simultaneously on the basis of the auxiliary information [5]. Implementation of this last alternative can be further enhanced by integrating information on the baseline risk of breast cancer, provided that the corresponding data are available [4]. Estimates of the optimal thresholds thus obtained indicate that the guidance for the highest net-benefit still supports screening at 40 years of age and treatment at 50 in both African ancestry cohorts and other populations [7]. Risk thresholds for appropriate stratification during this timeframe are accordingly found to be in the range of 2.0% to 3.5% over 5 years and 8% to 14% across a lifetime [6]. When comparing different strategies across ancestries, considerable differences in the shape of the decision curves reveal important variations in the effect of the threshold on the relative priority of competing objectives. All cut-offs with respect to African ancestry yield lower net-benefit values than those derived from other groups, thereby requiring stronger influence or more urgent action than is usually implied elsewhere[5]. Clinical applicability of any method depends not only on the nature of the task but also on equity and accessibility factors, awareness of which is fundamental to ethical deployment. Choice of the appropriate GRS score thus becomes an especially sensitive issue if policies must ensure not only compliance with regulatory frameworks but also informed consent for the human study participant [5]. The potential magnitude of harm also varies across the decision scores under consideration. Additionally, several practical obstacles hinder the adoption of BRCA1 and BRCA2 testing outside North America despite the public health gains involved [3].

Threshold Derivation Approaches

Polygenic risk scores were first proposed in the context of breast cancer in the late 2000s and have since been identified as a powerful tool for individual risk prediction [10]. Breast cancer is a heterogeneous disease with various environmental, lifestyle, and genetic risk factors associated. To study these factors, large genome-wide association studies (GWAS) have been conducted [11]. For breast cancer alone, over 150 susceptibility loci have been identified, which are estimated to explain approximately 25% of the observed familial relative risk [9]. With the increasing availability of genotypic data, the use of polygenic risk scores to derive absolute risk estimates has gained popularity, especially for breast cancer [9]. Ancestry-specific data are lacking for African populations, and until appropriate alternatives are derived, clinical utility limitations remain for non-European populations [8].

Comparative Performance Across Ancestries

Polygenic risk scoring (PRS) for breast cancer affords the possibility of estimating individual-level risk based on many associated single-nucleotide polymorphisms (SNPs). Polygenic risk is captured by PRS constructed in terms of either effect-size weights derived from large genome-wide association studies (GWAS) or the estimated number of risk alleles (RAP)[1]. Risk, once summed, can be further calibrated to yield personalized, absolute risk estimates that take into account additional factors such as age. Such scores can inform targeted approaches to preventive intervention and risk-reducing strategies [2]. In the case of breast cancer, the consequences of a PRS-based risk stratification scheme on the receiver-operating characteristic curve (sensitivity vs specificity) depend on at what risk threshold a subject is declared positive and eligible for a preventive or risk-reduction intervention [3]. The selection of a suitable threshold affects the population benefit and equity impact of applying PRS toward screening and prevention [11]. The recent construction of breast cancer PRS for individuals of African ancestry presents an opportunity to assess comparative clinical implications between individuals of African ancestry and individuals of European ancestry [10]. Among individuals of African ancestry, the choice of threshold that maximizes population net benefit locations the 90th percentile. In contrast, among individuals of European ancestry, a PRS-based method that does not incorporate information on prior commonly inherited riskful variants, and therefore enables independent risk stratification, a recent improvement accommodates explicit population level of polygenic risk when determining threshold; among such individuals, thresholds that maximize population net benefit correspond to the 70th percentile for breast cancer 2 and the 80th percentile for colorectal cancer [10]. The 70th percentile best reflects equity considerations, since it is the highest threshold at which post-test probability of a positive result relative to baseline does not diminish across ancestry groups; between individuals of European and African ancestry, this post-test probability increases by a factor of five[9]. For a threshold set at the 80th percentile, the post-test probabilities of a positive PRS given breast cancer between these groups are approximately equal to that of the prior baseline between these same groups [10].

Clinical and Ethical Considerations

Polygenic risk scores (PRS) identify individuals at high risk of breast cancer based on the presence of common genetic variants. PRS offers the opportunity for early engagement and effective risk-reduction options if tailored for non-European ancestry populations [7]. Adequate transferability to these populations is therefore especially important; such transferability depends on both the underlying genotype data and the risk model applied to those data. Among individuals of African ancestry, two major barriers to adequate transferability remain: [1] high

GWA study informativity gaps and [2] population-specific differences in polygenic genetic architectures [2]. Genetic discrimination models can be designed to respect equity objectives, including attention to development and adoption in underserved populations; avoidance of predatory valuations of individuals without access to risk-reduction strategies; and acknowledgment of statistical limits to hazard identification among high-prevalence variants, as well as of cytogenomic regulatory types still under thorough analysis [7]. Attention to the high-stakes nature and current state of any technology considered for deployment assumes heightened relevance within a domestic U.S. context [8]. Clinical and ethical considerations surrounding brief risk estimates of potential interest include accessible clinic and lawyer accords, yet extend also to harm and coercion eventualities particular to PRS for breast cancer [3].

Evidence Gaps and Methodological Challenges

Polygenic risk scores (PRS) for breast cancer developed using individuals of European ancestry remain underrepresented in populations of African ancestry [6]. The knowledge of the genetic architecture of breast cancer in African ancestry populations remains incomplete, and therefore, constructing PRSs to target African descent cohorts remains challenging [8]. Existing PRS construction is lacking in the knowledge of relevant and transferable founding genetic variants and pathways. The next step towards the goal requires characterising the joint genetic architecture of breast cancer among African and European populations, as this compared detail studies for Africa cohort remain lacking [10]. Breast cancer, the most commonly diagnosed cancer and the leading cause of cancer death among women, is a heterogeneous clinical and molecular entity representing at least five distinct subtypes: luminal A, luminal B, basal-like, human epidermal growth factor receptor 2 positive (HER2+), and normal-like. Vaccination status and screening practices for Human Papillomavirus (HPV) vary widely across regions and populations [11]. Harmonising these features, as well as tumour grade and stage, across large datasets for early-onset cancer analysis will enable rendering a reproducible modelling framework estimating immediate reproductive years and childhood ends. However, the collection of these data remains incomplete, even in relatively homogeneous settings such as the African continent [9]. Cohorts of African ancestry, especially South African populations, are underrepresented in publicly available genetic data. Per a recent African Genome-phenome program investigation, African Genome Resources datasets do not cover these populations, and they remain largely absent from major biobanks. Few biobanks in Africa currently share genotype data with minimal harmonisation or dendrograms depicting population structure [11]. Supporting the construction of a dedicated biobank readily featuring these cohorts remains paramount to elaborating a comprehensive understanding of breast cancer and other pressing health challenges suffered by the South African population [10].

Ancestry-specific Genetic Architecture

Polygenic risk scores (PRS) for breast cancer are increasingly being integrated into risk estimation systems to facilitate clinical decision-making [4]. PRS aims to estimate the genetic portion of breast cancer risk, and the field has reported genetic variants that are robustly associated with disease risk [3]. While PRS based on European ancestry genome-wide association studies (GWAS) show data on representation in African ancestry cohorts are scarce [6]. Furthermore, transferability of existing PRS to women of African ancestry, calibration of scores among individuals with African, Asian, Hispanic, and Latino ancestry, and performance of thresholding strategies across ancestry groups remains undocumented[8]. Validation of both breast cancer risk models and annualized breast cancer incidence rates varied by geographical region, consistent with other studies characterizing the epidemiology of breast cancer in an African ancestry population [7]. Genetic architecture differs across ancestries; African populations exhibit a higher proportion of rare variants, more gene–based variation, and a greater number of segregating haplotypes [6]. Notably, 88% of common breast cancer susceptibility variants identified in African ancestry women fall within regions with strong evidence of natural selection, suggesting a complex population history and the potential for missed associations within the European data [2].

Phenotype Definition and Cancer Heterogeneity

Breast cancer, which is characterised by the growth of malignant cells in breast tissue, can be classified into a spectrum of tumour subtypes and behaviours that are not equally affected by socio-environmental factors [10]. Current interventions that target risk adaptation for some of these factors exhibit limited clinical utility across all patients; thus, a narrower-binned risk continuum can help improve their relevance [11]. Screening activities often adhere strictly to national recommendations without accounting for regionally-varying incidence or etiological factors, instead applying clinical trials of insubstantial relevance to multi-ethnic settings; even counselling is affected by a lack of harmony across sub-phenotype categories [3]. In these contexts, cancer classification has been further complicated by the growing adoption of multi-omics approaches for improved stratification through the assessment of gene mutations, mRNA and microRNA expression, epigenomic patterns, and other factors [2]. Unfortunately, these facets remain poorly represented in multi-continental cohorts [5].

Data Availability and Recruitment

Polygenic risk scores (PRS) for breast cancer are derived from genome-wide association studies (GWAS) and aim to provide individual risk estimates of developing breast cancer [4]. The purpose of this study is to evaluate the

transferability, calibration, and decision thresholds of PRS for breast cancer in African ancestry populations. Existing studies suggest that PRS are transferable to populations with African ancestry, but empirical evidence across African ancestry cohorts is limited [5]. The distribution of European-pruned PRS, as calculated using variants associated with breast cancer in a multi-ancestry meta-analysis, is compared in the Africa 2 cohort to multiple European-ancestry populations in the Men of African Ancestry and the Multi-Ethnic Study of Atherosclerosis and on the Women's Health Initiative African dataset [7]. A breast cancer PRS derived from Project Mini, focused on cancer-relevant variants in non-European populations, further evaluates performance. These analyses offer an overview of PRS distribution, the transferability of polygenic risk estimation methods to African ancestry populations, and the extent of reported gaps in breast cancer polygenic risk score assessment [9]. The construction of PRS utilizes genome-wide association studies (GWAS) to identify thousands of common genetic variants associated with disease [5]. Because GWAS are conducted predominantly in European populations, scores derived from these studies may not generalize well to non-European ancestry groups. Modelling based on the linkage disequilibrium structure estimated from the 1000 Genomes Project (1000 G) African Ancestors dataset suggests that most large-scale European GWAS results transfer to at least some African ancestry populations, albeit with lower predictive performance than to European populations [6]. Effect size estimation from multi-ancestry meta-analyses does not appear to be directly portable across ancestry groups, and different methodologies have been proposed for calculating cross-ancestry PRS. African ancestry groups remain underrepresented in the assessment of polygenic scoring, limiting understanding of distribution patterns and the potential existence of population-specific variants [7]. The available genetic architecture of breast cancer and established study designs make it a prime candidate for assessing cross-ancestry PRS transferability [6].

Future Directions and Recommendations

An integrative modeling approach that simultaneously considers various biological and clinical factors, including polygenic, transcriptomic, and epigenomic information, along with exogenous elements such as human papillomavirus vaccination status and screening history, is recommended to improve transferability in breast cancer risk prediction [1]. Transparent reporting of study design and methodology, including standardized definitions of breast cancer phenotypes and explicit characterization of the ancestry structure of the supporting datasets, is crucial for guiding the adaptation of polygene-based risk prediction strategies to new populations 2. Decision-support frameworks and implementation strategies to facilitate focused guidance, further advance integration into health promotion programs, and promote equity in deploying risk stratification interventions targeting breast cancer are warranted [5]. Transferability improvements could involve the incorporation of transcriptomic, epigenomic, and clinical covariates. Providing standardized definitions for phenotypes, ancestry structure, and modelling frameworks would facilitate adaptations. Decision-support frameworks are needed to promote policies enhancing equity in programme implementation [6].

Integrative Models and Multi-omics

The concept of preventive strategy integrates genetic, transcriptomic, epigenomic, and clinical risk factors to build an integrative model for breast cancer risk prediction in African populations [1]. Integrative models based on multi-omics data could address these gaps, while transferability remains compulsory[2].

Study Design and Reporting Standards

Polygenic risk scores (PRS) estimate an individual's genetic predisposition to diseases, including breast cancer, based on the cumulative effects of common variants across the genome [10]. These scores are derived from genome-wide association studies (GWAS), which identify single-nucleotide polymorphisms (SNPs) associated with the disease of interest. Given that the linkage disequilibrium (LD) patterns and allele frequencies of variants differ across populations, many of whom are under-represented in genetic studies, the transferability of PRS from one population to another may be limited [2]. Moreover, the clinical utility of PRS hinges on their calibration—how well predicted risks correspond to observed outcomes, particularly "calibration to appropriate reference points" across diverse strata 1 such as geographic regions and age groups [3]. The choice of decision thresholds further affects the implementation of PRS in diverse populations. The identification of high-risk individuals based on their score can help determine whether to recommend preventive measures such as screening, and it is crucial to strike a balance between sensitivity and specificity when determining these thresholds [8]. Transferability, calibration, and decision thresholds are interlinked aspects of clinical applicability: how well a score transfers from one population to another can affect calibration, and the threshold at which a screening strategy is deemed optimal may differ across populations [7].

Policy and Implementation Considerations

The implementation of clinical polygenic risk scores (PRS) for breast cancer in populations of African and African-derived ancestries raises critical social and policy issues [11-15]. Operational frameworks, such as those proposed by the National Academy of Sciences, provide guidance for the use of genetic information in clinical practice, addressing equity concerns across the Research Ethics Landscape 2 and establishing principles to facilitate the equitable and ethical implementation of genomic information[10]. Guidelines specific to PRS emphasise the need

for careful consideration of access, availability, and equitable implementation, along with strategies for addressing potential harms. Given the lack of availability of current risk models for African ancestry populations, continued consideration of both clinical and ethical issues will be necessary as PRS-based applications for diverse populations are considered for deployment [9].

CONCLUSION

Polygenic risk scores hold considerable promise for improving breast cancer risk prediction and enabling more targeted screening and prevention strategies. However, current PRS models, largely derived from European ancestry genome-wide association studies, demonstrate limited transferability, poor calibration, and reduced clinical utility when applied to African ancestry populations. Differences in genetic architecture, linkage disequilibrium patterns, allele frequencies, and population-specific disease epidemiology contribute to systematic misestimation of risk and undermine equitable clinical implementation. Evidence reviewed in this study highlights persistent over- and underestimation of absolute breast cancer risk in African ancestry cohorts, with miscalibration severe enough to compromise screening eligibility decisions and preventive interventions. While methodological advances such as cross-ancestry meta-analyses, multi-ancestry PRS construction, and cohort-specific calibration strategies improve performance, they do not fully overcome the fundamental limitations imposed by the underrepresentation of African ancestry populations in genetic research. Decision threshold selection further complicates clinical deployment, as thresholds optimized in European ancestry populations yield lower net benefit and may exacerbate disparities when transferred without adjustment. To realize the potential of PRS for breast cancer in African ancestry populations, sustained investment in large, well-phenotyped African and African diaspora cohorts is essential. Future efforts should prioritize ancestry-specific and multi-ancestry GWAS, improved biobank infrastructure, standardized phenotype definitions, and integrative modeling approaches that incorporate clinical, environmental, and multi-omics data. Equally important are transparent reporting standards, population-specific calibration, and ethically grounded decision-support frameworks that center equity, accessibility, and informed consent. In conclusion, PRS-based breast cancer risk prediction can contribute meaningfully to precision medicine only if its development and implementation are inclusive by design. Without deliberate efforts to address transferability, calibration, and thresholding in African ancestry populations, PRS risk models risk reinforcing existing health inequities rather than alleviating them.

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