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# Population Genomics for Breast Cancer: Return of Results, Cascade Testing, and Health System Readiness from Bench-to-Population Perspectives

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## ABSTRACT

Population genomics is reshaping breast cancer prevention by enabling the identification of individuals and families at elevated genetic risk before disease onset. Advances in genomic technologies have made population-scale screening for high-penetrance breast cancer susceptibility genes, particularly BRCA1 and BRCA2, increasingly feasible. However, translating discoveries from bench to population requires careful attention to the return of results, cascade testing of at-risk relatives, and the readiness of health systems to deliver these interventions equitably and effectively. This review examines population genomics for breast cancer through a bench-to-population framework, synthesizing evidence on strategies for returning genomic results, facilitating cascade testing, and addressing ethical, legal, social, and implementation challenges. We highlight the complexity of communicating genomic risk, managing uncertain and secondary findings, and ensuring informed consent in population-level contexts. Persistent barriers to cascade testing uptake, including reliance on proband-mediated communication, health system constraints, socioeconomic inequities, and cultural factors, are examined alongside emerging interventions and quality-improvement frameworks. Drawing on international case studies and national pilot programs, we assess health system readiness across infrastructure, workforce capacity, data governance, reimbursement, and policy environments. Finally, we identify key research priorities and future directions to support equitable, scalable, and sustainable population genomics initiatives. Integrating return-of-results strategies, cascade testing, and health system preparedness is essential to realizing the public health potential of population genomics for breast cancer prevention while minimizing harm and exacerbation of existing health inequities.

**Keywords:** Population genomics, Breast cancer, Return of genomic results, Cascade testing, and Health system readiness.

## INTRODUCTION

Population genomic screening highlights from breast cancer genomics illustrate the bench-to-population continuum, specifically, strategies for returning results to patients and cascade testing at-risk relatives alongside barriers, misconceptions, and foundational considerations for other areas of health system readiness[1]. Breast cancer is a leading cause of death worldwide. Germline pathogenic variants in BRCA1/2 represent the highest penetrance risk factors [2]. These genes, alongside PALB2 and ATM, significantly increase the risk of breast cancer. Certain variants can even lead to early-onset disease, indicating an increase in screening intensity (Harrison et al., 2022). Extensive population databases have recently identified rare, non-coding variants associated with breast cancer. An analysis predicted the average lifetime attributable risk for women with such a variant is 23.3% (95%-CI, 20.3%-26.2%), with a penetrance profile and screening age similar to those of BRCA1/2 [1]. Centralized, population-wide programs can collect longitudinal health data and assess the clinical impact of such programs at lower costs [3]. Guidelines for cascade testing, outreach, and engagement are detailed

elsewhere. However, equity considerations, social, systemic, and logistic barriers that disproportionately affect at-risk, underserved demographics require further examination [2]. The concept of "multiplier dirty risk," where an individual's position in the registry stimulates additional risk discovery, also holds broader relevance [1].

**Conceptual Framework: From bench to population**

Advancements in genomics create opportunities to screen for breast cancer predisposition at the population scale. Current efforts to document the return of results highlight the need for communicating uncertain findings without clear action [4]. Frameworks that describe progression along the bench-to-population continuum or that unified approaches for translating knowledge to decision-making illustrate pragmatic avenues to bridge population genomics and implementation sciences for breast cancer [4]. Genetic research constitutes one of the most effective and efficient means of countering the deleterious effects of environment, behaviour, lifestyle, or socio-economics on breast cancer health [2]. Nevertheless, multigene sequencing at the population level generates enormous volumes of data requiring comprehensive oversight in systems-grounded, stakeholder-centred ways. Such attention enables the development of return-of-results policies and cascade-testing strategies at the level of health systems [2]. Returning risk and carrier status has important ethical implications and consequences for intervention; articulating the ethical, legal, and social considerations surrounding these issues remains essential [3]. Furthermore, when focused on population-level interventions, constraints related to implementation science become salient [2].

**Return of Results in Breast Cancer Genomics**

Returning research results in breast cancer genomics is complex and debated. Despite this, data on the experience and impact of returning individual results remain limited [3]. Large-scale genomic studies have mapped cancer genomes, providing insights into prevention, early detection, and treatment. Returning results involves a labor-intensive, variable process, especially within large genomics research initiatives [3]. The increasing use of genome sequencing raises a challenge in returning secondary findings. Less attention has been paid to strategies that meet patients' needs and preferences [6]. A study investigated delivery preferences regarding who, how, and when to communicate individual genome sequencing results among women diagnosed with breast cancer at age 40 or younger [4].

**Ethical, Legal, and Social Considerations**

The concept of the return of research results has gained considerable uptake in human genome studies. Broadly construed, the return of results refers to any further information provided to data providers after termination of the specimen study [6]. Under this umbrella, the return of individual results pertains to feedback offered to individual contributors, with results important in cancer genomics repeatedly cited as eligible for return [5]. For such genomics, where somatic alterations arise de novo, a wider array of information, including population-level summaries and knowledge of actionable germline variants, can be supplied to all contributors [6]. By generating population-level specifications that improve participants' health, the aim should be to enhance research benefits. Given the nature of sequencing at cancer sites, nevertheless, the focus of population-level genomics remains the givers of specimens [11]. Where contributors to a study are subsequently identified as possessing predisposition variants, the health hazard extends to their undiagnosed kindred [9]. For these reasons, models of cascade testing supply a logical complement to the return of first-tier research results; and yet for a range of conceptual and operational factors, they occupy a distinct branch of the bench-to-population axis [4].

**Communication Strategies and Informed Consent**

Finalizing the ethical, legal, and social considerations, a balanced communication strategy includes risk and harm assessment, stakeholder involvement, and follow-up mechanisms to facilitate population-level engagement [12]. Beyond consent, sustaining relationships post-communication enhances understanding of uncertainties, risk factors, and preventive measures for those exposed through cascade testing channels [11]. Communication strategies and informed consent considerations are particularly relevant for population-level return of genomic results [2]. In accordance with established frameworks, findings signalling genetic predisposition to familial breast cancer or actionable measures underscore the importance of conveying risk information and options for preventive measures [7]. Several key parameters emerge as pivotal within the broader involvement of family members at the population interface. Risk characterises multiple aspects of such disclosure and significantly affects personal-level decision-making processes. Core components encompass the implications of BRCA1/2 genomic variants for close family members, the availability of cascade testing in the respective context, and the options for disclosing such information [3]. Timing is another determinant, influenced by the communication method adopted and the scope of communication, which may be restricted to other family members from an epidemiological viewpoint [5]. In-facility cascade-testing channels offer diverse frequency specifications (e.g., birth year or age) for gradual notification, signifying that fusion with communication about the initial test may not be apparent. Demographic and contextual factors interacting with separately communicated epidemiological data represent further aspects likely to condition personal-level decision actions [6]. Literacy and accessibility considerations add further complexity to the return-of-results challenge, with multifaceted implications for

communication structures and procedures [2]. Communication settings may not constitute formal consent procedures but bear considerable similarity in articulating preferences for follow-up [3]. Aiding understanding through increasingly complex occurrence documents varies significantly across targets, suggesting that communication structures attuned to these factors would benefit all pertinent return-of-results endeavors [8].

## Clinically Actionable Findings and Patient-Centered Outcomes

High-penetrance, clinically actionable variants are present in BRCA1, BRCA2, PALB2, CHEK2, and ATM, with speculative involvement of MSH6 and ERBB2. Such findings prompt pathway-specific follow-up, including genetic counselling, risk-reduction options, or therapeutic recommendations [9], and are relevant regardless of analytical framework, practice scale, or jurisdiction. Provisions for patient-reported outcomes and resource implications are consequently paramount for translation beyond isolated bench-to-population exercises [10]. In the United Kingdom, population-scale return-of-results initiatives have disclosed high-penetrance pathogenic variants in BRCA1, BRCA2, PALB2, and ATM. In Australia, the BRCA1 and BRCA2 genes remain priority targets; additional candidates warrant further consideration, including variants in the CHEK2, PALB2, and ATM genes. Impacting breast and other cancer types, germline pathogenic variants in the BRCA1, BRCA2, and CHEK2 genes present far-reaching public health significance [2]. Emerging data demonstrate that pathogenic variants, especially in BRCA1 and BRCA2, are not confined to surging breast cancer incidence but disseminate throughout the population [2]. The demand for population-level genomic testing is considerable, with widespread openness to cascade testing for at-risk kin following disclosure of clinically relevant pathogenic variants through individual clinical-sequence insights, genome-mining strategies, or mismatch-repair variant investigations[1].

## Cascade Testing in Familial Breast Cancer

Cascade testing extends genetic testing to biological relatives at risk for inheriting pathogenic variants previously identified in a patient with hereditary cancer syndromes [5]. It improves early detection and risk management, potentially reducing long-term morbidity and mortality. Despite its benefits and classification as a high-impact public health tool, uptake remains low, often below 30%, due to factors such as poor communication, limited understanding, access issues, and concerns about genetic discrimination [3]. Various interventions have attempted to improve referral rates, but many are not widely adopted in routine practice, highlighting a gap between research and implementation [2]. Efforts to enhance cascade testing include developing tools, checklists, and frameworks to facilitate implementation and replication. Current literature indicates a need for more comprehensive data on how interventions are effectively applied across different healthcare settings [11]. Cascade testing involves genetic counseling and testing among blood relatives of individuals with pathogenic or likely pathogenic germline variants, enabling them to pursue cancer screening and risk reduction. Effective cascade testing requires successful communication of genetic results within families, which is often limited by contact variability, timing, cultural barriers, and knowledge gaps [2]. Family communication about genetic risk varies widely, and connecting relatives without adequate skills can reduce the long-term benefits. At-risk adults need to process emotional impacts and communicate effectively with at-risk offspring [5]. Healthcare resources alone may be insufficient; trained peer supporters can provide role modeling, coping skills training, and family-centered support to improve cascade testing, especially across different developmental stages. This approach can extend standard care by facilitating family engagement and addressing communication challenges, ultimately enhancing cancer prevention efforts [12].

## Identification of At-Risk Relatives

Cascade testing facilitates the identification of at-risk relatives of individuals with pathogenic variants in BRCA1, BRCA2, or the five other gene pan-cancer panel genes with clinically actionable implications for breast health [12]. The scope of cascade testing can be limited by family dynamics, geographic separation, and migration histories that restrict communication of genetic results [13]. The short timeframe before individuals at risk reach 40 years of age for breast screening further constrains opportunities for sharing risk information and accessing screening; many relatives remain unaware of their at-risk status. Cascade testing notification strategies vary widely across health systems [13]. Approaches that combine pedigree-based notification and scenario-driven patient consent are the most common, still reliant on the patient to communicate directly with relatives. An alternative molecular-incident approach empowers healthcare professionals to notify at-risk relatives identified directly from the report and to initiate a consent cascade for further contact, with research support to establish broader readiness for implementation [4].

## Barriers to Uptake and Equity Considerations

Barriers to health-system uptake of genomic Cascade Testing for BRCA variants hinder extension of population-genomic benefits to at-risk individuals and families. A systematic review identified wide-ranging barriers at social, logistical, organisational, and systemic levels: inadequate awareness of the opportunity for extended testing is a salient impediment [14]. Societal barriers continue to drive inequities in genomic health care, with social conformism and stigma disproportionately affecting racial minorities, sexual minorities, and lower-income populations [15]. Equity-optimising strategies to advance Cascade Testing, therefore, fall into two categories.

First, broader system-level barriers, including a lack of engagement with population genomics, must be addressed through transitional initiatives such as proposed health-system interventions targeting training, infrastructure, policy, and access [12]. Second, strategies specifically querying awareness of the Cascade Testing opportunity may extend reach to at-risk families. Furthermore, the accompanying patient information should be tailored to the socio-cultural profile of the specific population addressed [13].

**Effectiveness and Resource Implications**

Cascade testing for hereditary breast cancer is underused in Canada's publicly funded health care systems. Informing at-risk relatives after an individual receives a pathogenic variant result is not a standard part of practice [12]. Family notification is challenging due to dependence on the affected individual's consent, and solutions are needed to facilitate outreach to first-degree and extended relatives [11]. Moreover, socioeconomic factors, geography, and health system dynamics create disparities in access to cascade testing, with populations lacking adequate support remaining vulnerable [10]. Uptake of cascade testing is low across jurisdictions, with rates reported between 5% and 28% in the first five years after initial testing [9]. Provinces organized in the Canadian Partnership for Tomorrow's Health and the Ontario Ministry of Health's Genetics and Genomics Program have begun to address the barriers affecting uptake, inform policy, and adapt programs. Cascade testing in familial breast cancer and the associated challenges serve as observations for health-system readiness for other areas of population genomics [16].

**Health System Readiness for Population Genomics**

The work of population or broad genomic screening is being conducted or contemplated in Canada, France, the Netherlands, Switzerland, Portugal, the U.S., and Australia, to name a few nations [17]. France is committed to introducing such a program [18]. Responsibilities associated with the return of results need to be established as early and comprehensively as possible. Among other items, the protocols and elements are envisaged that are needed for successful return-of-results and cascade-testing approaches [19]. Undertaking population-level genomic screening for breast cancer requires readiness of multiple health-system components. Certain features supporting population genomics have been identified within existing national healthcare functions. Comprehensive criteria define readiness for safe and effective deployment [15]. These criteria apply broadly across health determinants, enabling avoidance of screening strategies detrimental to health. Features relevant to breast cancer genomics are considered subsequently [13]. Population genomics depends upon advanced health-system capabilities for the timely and safe return of genomic findings, yet screening remains feasible even when capabilities are limited [11]. Documenting uptake, yield, cost-effectiveness, and extent of targeted deployment can inform prioritization of development efforts. Extant approaches to BRCA testing and cascade testing are of interest in this context because they exemplify characteristics likely to be found in many current health systems [10].

**Infrastructure and Data Management**

Population genomics has the potential to reshape the clinical management of breast cancer, yet successful interventions demand careful consideration of the health system in which they operate [20]. High-capacity laboratories evolve rapidly, but delivery structures and the accompanying data management remain daunting obstacles. The emergence of cloud-based modular platforms, however, promises a basis for overcoming these barriers [18]. Cost-effective short-read sequencing has advanced to a point where "whole-genome" analysis with adequate coverage lies within reach, yet large–scale initiatives have seldom addressed data management through an equivalent lens [17]. The central role of data management looms larger in the past than with classic biomedical disciplines, shadowed by the continuing challenge of data capture in clinical environments that remain predominantly paper-based [4]. Data preparation, the intricate process of curation, contextualization, organization, and linkage essential before subsequent formal statistical analysis and proves stubbornly enduring [2]. Data sets dislocated in disparate institutions, complex systems in use within those institutions, immature expertise in handling complex dispersed data, low prioritization of data modernization, and transformation misalignment constitute the recurrent bottlenecks historically so well documented on the open-access side[1].

**Workforce Training and Multidisciplinary Collaboration**

To ensure that evidence of medically actionable germline variants is communicated effectively to individuals with breast cancer, a comprehensive understanding of population genomics and its clinical implications must be shared with various health system professionals [11]. Healthcare providers involved in the delivery of population genomics, including medical oncologists, surgical oncologists, radiation oncologists, and oncology nurses, are the focus of initiatives aimed at promoting the return of results [9]. Training curricula need to cover a wide range of topics, such as the clinical utility of genomic variation, current conceptualization of hereditary cancer risk, cancer predisposition genes and their associated cancer syndromes, the population- and individual-level implications of breast cancer genomics, the specific clinical results that may arise from testing, and the management of patient inquiries after testing [13]. Incorporating the various perspectives of multiple specialties, including population genomics, genomics policy, public health and epidemiology, cancer prevention, health services and systems, and

analytical and evaluative aspects of health economics, substantially strengthens the return-of-results approach[13]. Occupying a central role across the continuum spanning the various components of genomics implementation, population genomics offers an overarching lens for defining the relevant issues; other perspectives contribute specialised expertise and insights for enriching the development of the population-gene approach [21].

**Reimbursement, Policy, and Governance**

Reimbursement, policies, and governance related to population health genetic testing face challenges in ensuring equitable access and implementation [4]. Socioeconomic disparities persist in the utilization of genetic testing. Population-based breast cancer family-genetics programs, predictive of future breast and ovarian cancer risk, are similarly affected by entrenched inequities, with underutilization of tests like BRCA1/2 contributing to disparities in preventive care and cancer risk management [16]. Organizations and efforts such as national surveys and population-based studies highlight persistent racial and income-related disparities in screening and testing for hereditary cancers [19]. Strategic approaches, such as defining priority levels for genomic applications and implementing targeted policies, are necessary to improve equitable access and governance of genetic testing programs [10].

**Equity, Access, and Patient Engagement**

Access to population genomics tools enabling breast cancer early detection, prevention, and treatment must expand to include underrepresented communities, especially racialized and marginalized populations [2]. Such groups are typically excluded from early health outreach, free testing, and treatment programs, yet experience high disease incidence and severity [22]. An inclusive public health strategy that pursues engaged collaboration with affected community leaders can broaden program reach; patient-centered co-design initiatives grounded in the lived experience of these communities can also empower their participation in research and program design [19]. Proactive outreach, including awareness campaigns, information sessions, and free testing at community-based venues, improves access [4]. Multilingual materials tailored to the needs of a diverse target population support participation, while patient advocacy networks help raise awareness and promote equity [5]. Continued public consultation ensures health equity remains a priority throughout population-scale implementation, with ongoing dialogue informed by community representatives able to point out ways to further promote involvement of underrepresented populations in sex-specific genomic health programs [18].

**Methodological Considerations for Population-Level Genomics**

Designing studies that provide population-level evidence for the health impacts of implementing genomics in a health system requires consideration of the overall approach, the synthesis of data from multiple studies, and the use of real-world data[7]. Three key considerations are defining the study type, evidence synthesis, and the use of real-world data [2]. Population genomics typically returns results at the individual level, but scaling up to the population level necessitates methodologies and reporting standards that focus on the population rather than the patient. Population-level prioritization is required to decide what actionable variants to communicate in a given implementation [5]. Principles from policy-relevant science highlight the importance of both the scientific basis for prioritization and the process through which decisions are made [17]. Cascade testing is a highly effective public health intervention for identifying high-risk relatives of individuals with familial breast cancer [5]. Cascade testing programs can also serve as a useful entry point for evaluating population-based genomics more broadly, as services may already be in place in a health system [2]. Several quality metrics for cascade testing have been identified. Continued monitoring of these metrics can ensure that the expected benefits of population-level genomics are realized and can facilitate continuous improvement in implementation quality and equity [2].

**Study Design, Evidence Synthesis, and Real-World Data**

For a population-level framework, study design becomes critical to assemble evidence at scale and to evaluate the full suite of population-genomics concepts [10]. Population-level studies span from single studies to large consortia addressing the same question; the former are often organized around the distribution of alleles, whereas bacterial adaptation examples examine selection on any allele [23]. Return of results alone encompasses several dimensions: indicators of scale and impact, prioritization of findings needing further action, and the standardization of what gets reported [11]. The design of cascade-testing studies reflects a trade-off between monitoring individual programmes or the collective experience across programmes, motivating complementary frameworks capturing separate metrics [10]. A similar issue arises in defining quality metrics for cascade testing, which may inform whether dedicated attention to such parameters is required [7].

**Return of Results at Population Scale**

Genome-scale, population-level studies across various human traits and diseases raise the prospect of generating and returning health-related results at such a scale [9]. In breast cancer genomics, initial large programs focused on identifying population-specific variants. As these efforts near completion, returning results derived from such investments has emerged as a consideration. Several factors influence the feasibility and specifics of returning results at the population level [10]. First, the data accumulated in these studies are predominantly germline variants that remain unchanged over a lifetime. Second, a considerable proportion of sequencing effort was

directed towards the analysis of genes, variants, and risk factors that had already been characterized in other populations, considerably facilitating, in principle, the organization of a return-of-results process [5]. Third, several frameworks for implementing and regulating the return of results at a programmatic or institutional level exist. Fourth, precise population-level requirements to ensure the safe return of findings to a suitably defined population continue to evolve; such requirements may warrant re-evaluation of what constitutes return of results at the population level [3]. Although the prospect of returning population-specific results at scale remains remotely conceivable, returning germline results for all breast cancer variants deemed reportable within the Canadian population and that arise from population-level studies appears feasible across an entire population genomics program [17]. Altering the timing of return and the routes through which results could be disseminated are also viable directions to explore. Standards have been developed for the classification and reporting of pathogenic germline variants that streamline the establishment of a population-genomic foundation for return [14].

**Cascade Testing Evaluation and Quality Metrics**

Cascade testing extends genetic testing to at-risk relatives of individuals with hereditary cancer syndromes, enabling early risk management and improved health outcomes [12]. Despite its benefits and being categorized as a high-impact public health intervention, current uptake rates remain low, often below 30%. Barriers include reliance on proband communication, limited genetics understanding, access issues, and concerns about discrimination [13]. Various strategies have been attempted to increase referrals, but many are not yet integrated into routine practice, resulting in a research-to-practice gap [15]. Advances in implementation research aim to improve how these interventions are applied across different healthcare settings. Cascade testing evaluation encompasses the analysis and measurement of cascade testing implementation at both practice and population levels. Interventions can target practice-based bottlenecks, while population-level evaluations focus on monitoring and improving implementation strategies through data collection. Quality improvement initiatives typically adopt one of two approaches [10]. The Monitoring Framework approach outlines a set of predefined indicators that delineate how the intervention is executed and identify quality improvement opportunities within each component. Continuous Quality Improvement (CQI) focuses on a single, prioritized metric, establishing a baseline and incentivizing regular re-measurement to gauge the impact of changes made to enhance that metric[16]. The following cascade testing evaluation and quality enhancement metrics have been proposed for methylation-associated breast cancer [12]. The designation of this analysis as a Cascade Testing Evaluation and Quality Framework reflects the anticipation of the scaled deployment of the breast methylation panel in settings projected to utilize cascade testing as a central business model. Evaluation of the anticipated pretest and post-test scenarios would probe the expected volume of individuals receiving ancillary papillomavirus testing, the uptake of the materials for initiating communication with relatives in diverse care systems, and other parameters indicative of desired delivery outputs [11].

**Case Studies and Comparative Perspectives**

National population-scale genomics programs and pilot studies are emerging worldwide to evaluate the feasibility, benefits, and harms of wide-scale germline genomic population screening [17]. These initiatives examine program design, data generation and sharing, effects on screening practices, uptake of preventive interventions, and access equity [9]. The architecture of these national initiatives varies significantly along the bench-to-population continuum. Canada's Genome and Health Action Plan promotes decentralization and direct-to-consumer engagement through a diverse network of population genomics pilot studies; the Belgian Population Genomics Programme focuses on risk-prediction polygenic scores for the general population, integrates additional value-laden consultations, and aims to reduce inequalities; France's Health Genome Plan defines a more centralized model; while the Netherlands Genomic Health Initiative encompasses federated, connected facilities[11]. Establishing a Genetic and Genomic Health Network (GENNET) that connects regional clinical genetics services is crucial for this initiative: federated access to genetic and genomic data ensures interaction with various health agencies [10]. Numerous lessons have already emerged from these new population genomics programs. Policy frameworks facilitating the integration of genomic and health data must be carefully defined to safeguard privacy and data security concerns, especially during the early stages [11]. Countries have different governance frameworks, which may uphold democracies or authoritarianism [11]. Implementation challenges vary widely across national jurisdictions. Common obstacles include post-analytical processes for reporting and returning results to participants, equity in the offer and access to genomic population screening, integration in the health system, data protection law, privacy regulation, stakeholder engagement, and public acceptability. The distinctive translational architecture of implementation across nations offers comparative learning opportunities [8].

**National Programs and Pilot Initiatives**

National policymakers in the United States, Canada, and France are exploring large-scale population-level screening for breast cancer risk genes such as BRCA1, BRCA2, and TP53 [17]. In the U.S., the target is the BRCA1/2 genes, and a national program is expected by 2024 in a region where the institutional architecture is

similar to that in breast cancer genomics programs. In Canada, a recent program mandated sequencing of the BRCA1 and BRCA2 genes [16]. France has proposed a national pilot for the BRCA1/2, TP53, and PTEN genes within the policies and regulations that frame population screening [15]. From a population perspective, these initiatives support the return of results and cascade testing. The first and second accompanying publications at the U.S. case study level present ongoing pilot studies to evaluate the return of results for pathogenic variants on an expanded panel and cascade testing for at-risk relatives of individuals with pathogenic variants in BRCA1/2 or TP53 [16]. From the breast cancer genomics perspective, evaluative efforts focused on the United States, Canada, and France can inform national policy development, system readiness, program implementation, and efficient issue identification through the review of national programs and pilot initiatives worldwide [14].

### Cross-Border Learnings and Global Applicability

Cross-border learnings from genetic testing globally reveal disparities and implementation challenges across diverse populations [17]. In the USA, for example, studies indicate significant racial disparities in BRCA1/2 testing and cancer risk management, particularly among Black and Hispanic women, who are much less likely than non-Hispanic White women to receive testing [19]. Racial disparities also persist in colonoscopy screening for individuals with a family history of colorectal cancer [15]. Participation of low-income women in genetic cancer risk assessment remains limited, and access to free genetic screening and counselling is available, but uptake remains weak. Efforts to apply genomic applications within population health programmes continue to underscore the importance of equitable access and the need for tailored strategies for diverse communities [16].

### Future Directions and Research Priorities

Population genomics holds great promise for large-scale breast cancer screening and prevention. Yet translating from bench to broader population remains challenging, prompting calls for a conceptual framework encompassing system plans, research priorities, and pathway selection [18]. Even with high uptake, low uptake among at-risk relatives limits intervention effectiveness, equity, and sustainability. Identification of informative relatives, cascade notification ethics, and international implementation have been prioritized [4]. Four key population-readiness dimensions, system infrastructure, workforce capacity, funding mechanisms, and equitable access, remain barriers to implementation [22]. Addressing these with appropriate strategies and pilot implementation across health systems can enhance the societal impact of early pre-emptive intervention before germline sequencing is completed [23-26].

## CONCLUSION

Population genomics offers a transformative opportunity to shift breast cancer prevention from reactive, case-based care to proactive, population-level risk identification and intervention. Evidence reviewed in this study demonstrates that large-scale genomic screening for high-penetrance breast cancer susceptibility variants is technically feasible and clinically meaningful, particularly when paired with effective return-of-results strategies and cascade testing for at-risk relatives. However, the translation of genomic discovery from bench to population is neither linear nor automatic; it depends fundamentally on the preparedness of health systems, the ethical management of information, and the equitable engagement of diverse populations. Returning genomic results at the population scale raises complex ethical, legal, and social questions, especially regarding uncertain findings, secondary results, informed consent, and long-term follow-up responsibilities. When pathogenic germline variants are identified, the associated health implications extend beyond the individual to biological relatives, making cascade testing a critical public health intervention. Despite its proven effectiveness, cascade testing remains substantially underutilized across jurisdictions, with uptake constrained by communication challenges, health system fragmentation, limited access to genetic services, and persistent social inequities. These barriers disproportionately affect underserved and marginalized populations, risking the amplification of existing disparities in breast cancer outcomes. Health system readiness emerges as a central determinant of successful population genomics implementation. Adequate laboratory capacity, robust data infrastructure, trained multidisciplinary workforces, supportive reimbursement mechanisms, and clear governance frameworks are all required to ensure safe, effective, and equitable delivery. International experiences from Canada, the United States, Europe, and Australia illustrate diverse implementation architectures, offering valuable cross-border lessons while underscoring the need for context-specific solutions. Importantly, population genomics initiatives must embed equity, patient engagement, and community partnership from the outset, rather than treating them as downstream considerations. Looking forward, future research and policy efforts should prioritize scalable models for return of results, innovative approaches to cascade testing that reduce reliance on proband-mediated communication, and standardized quality metrics to evaluate population-level impact. Investment in implementation science, real-world data generation, and inclusive program design will be essential to bridge the gap between genomic discovery and public health benefit. Ultimately, population genomics for breast cancer can achieve its preventive promise only if health systems are equipped not merely to generate genomic data, but to translate it responsibly, equitably, and sustainably into improved outcomes for individuals, families, and populations.

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