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REVIEW OF BRCA1 AND BRCA2 MUTATION SCREENING STRATEGIES FOR REDUCING CANCER BURDEN IN HIGH-RISK FAMILIES

(Review Article)

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Abstract

Background: Pathogenic variants in the BRCA1 and BRCA2 genes significantly elevate the lifetime risk of breast, ovarian, and other cancers, creating a substantial burden for high-risk families. Identifying carriers is paramount for implementing evidence-based risk-reduction strategies, yet the optimal approach to population screening remains a subject of refinement. This narrative review synthesizes the current landscape of BRCA screening methodologies and their impact on cancer outcomes.

Objective: This review aims to summarize and critically evaluate existing literature on various BRCA1 and BRCA2 mutation screening strategies, with a focus on their effectiveness in identifying carriers in high-risk families and their subsequent role in reducing familial cancer incidence.

Main Discussion Points: The discussion is structured around key thematic developments. It begins with the established model of family history-based screening and clinical prediction tools, acknowledging their utility and significant limitations. The review then explores the shift towards broader paradigms, including the mainstreaming of genetic testing into oncology care and the emerging evidence for population-based screening in specific founder populations. A critical analysis is presented on how a positive genetic test result translates into clinical action, encompassing risk-reducing surgeries and targeted therapies, and ultimately impacts cancer burden. The synthesis also addresses unresolved challenges, such as variants of uncertain significance and disparities in access to genetic services.

Conclusion: The evidence supports a move beyond reliance on family history alone towards more inclusive and proactive screening models to identify a greater proportion of BRCA carriers. While the clinical utility of genetic testing is well-established for guiding risk management and therapy, future efforts must focus on improving the implementation, accessibility, and equity of these strategies to maximize their public health benefit in diverse populations.

Keywords: BRCA1, BRCA2, Genetic Testing, Hereditary Breast and Ovarian Cancer Syndrome, Cancer Prevention, High-Risk Families.

Introduction

The identification of hereditary cancer syndromes has revolutionized the field of oncology, shifting the paradigm from reactive treatment to proactive risk management. Among these, hereditary breast and ovarian cancer (HBOC) syndrome, predominantly driven by pathogenic variants in the BRCA1 and BRCA2 genes, represents a significant clinical and public health challenge. These tumor suppressor genes are integral to the repair of double-strand DNA breaks through the homologous recombination pathway, and their impairment confers a profoundly elevated lifetime risk of malignancies. Carriers of a pathogenic BRCA1 variant face a 55-72% cumulative risk of developing breast cancer by age 70-80, and a 39-44% risk for ovarian cancer. Similarly, BRCA2 pathogenic variants are associated with a 45-69% risk of breast cancer and an 11-17% risk of ovarian cancer (1). The penetrance of these genes extends beyond these primary cancers, with increased risks for male breast, pancreatic, and prostate cancers, creating a multi-generational burden of disease that impacts entire families (2). The global burden of BRCA-related cancers is substantial, with an estimated prevalence of pathogenic variants in the general population being 1 in 300 to 1 in 500, though this frequency is markedly higher in certain founder populations, such as the Ashkenazi Jewish community, where 1 in 40 individuals may carry one of three founder mutations (3). The landscape of managing individuals from high-risk families has been fundamentally transformed by the advent of genetic testing and the development of evidence-based risk-reduction strategies. The current knowledge base firmly establishes that identifying a pathogenic BRCA variant in an index case unlocks a cascade of clinical actions. For the unaffected carrier, intensive surveillance protocols, such as annual breast MRI supplemented with mammography, and risk-reducing surgeries (RRS), namely bilateral salpingo-oophorectomy (RRSO) and bilateral risk-reducing mastectomy (BRRM), have demonstrated a powerful impact on cancer incidence and mortality. RRSO, in particular, is associated with an approximately 80% reduction in the risk of ovarian cancer, including fallopian tube and primary peritoneal cancers, and a 50% reduction in all-cause mortality (4). Similarly, BRRM can reduce the risk of breast cancer by over 90% in BRCA carriers (5).

Furthermore, for those diagnosed with BRCA-related cancers, the identification of the mutation has profound therapeutic implications, guiding the use of poly (ADP-ribose) polymerase (PARP) inhibitors, which exhibit targeted efficacy in tumors with homologous recombination deficiency (6). This transition to a precision medicine approach underscores the critical importance of effective mutation screening. Despite these significant advances, the optimal strategy for screening high-risk families for BRCA1 and BRCA2 mutations remains a subject of ongoing refinement and debate, revealing several critical research gaps. The initial model of referral based solely on a strong personal or family history of cancer, while foundational, is now recognized as imperfect, potentially missing a substantial proportion of carriers due to incomplete family histories, small family size, or the de novo emergence of mutations (7). This has spurred the investigation of alternative and complementary screening approaches. Population-based screening, particularly in populations with a high founder mutation frequency, has been proposed as a means to overcome the limitations of clinical criteria-based testing. However, the feasibility, cost-effectiveness, and psychosocial impact of such broad screening strategies in diverse, general populations are not fully elucidated and require further evidence (8). Concurrently, the rapid evolution of testing technology, from single-gene tests to multi-gene panels, introduces new complexities in counseling and result interpretation, where variants of uncertain significance (VUS) and secondary findings can create clinical dilemmas (9). The integration of tumor-based screening, such as testing for homologous recombination deficiency in ovarian cancers, to trigger germline genetic testing is another developing area that promises to increase identification rates but necessitates standardized implementation pathways (10).

The objective of this narrative review is to synthesize and critically appraise the existing literature on various BRCA1 and BRCA2 mutation screening strategies, with a specific focus on their comparative effectiveness in identifying carriers within high-risk families and their subsequent impact on reducing the familial incidence of cancer.

This review will explore the spectrum of screening methodologies, from traditional family history-based models and clinical prediction tools to more contemporary approaches like mainstreaming genetic testing in oncology clinics and the potential for population-based initiatives. The scope is deliberately focused on strategies aimed at identifying at-risk individuals within familial contexts, evaluating the evidence for each approach's diagnostic yield, associated clinical outcomes, cost-effectiveness, and the critical ethical and accessibility considerations that influence their real-world application. The review will concentrate on evidence published within the last decade to ensure relevance to current clinical practice and technological capabilities, drawing from key cohort studies, randomized trials, and systematic reviews. The significance of this review lies in its timely synthesis of a rapidly evolving field. As genetic testing becomes more accessible and affordable, and as therapeutic options for BRCA carriers expand, the imperative to identify these individuals accurately and efficiently has never been greater. A fragmented or inefficient screening system results in missed opportunities for life-saving interventions in some families, while potentially causing unnecessary anxiety and resource utilization in others. By providing a comprehensive overview of the strengths and limitations of different screening paradigms, this review aims to inform clinical guidelines, health policy decisions, and future research directions. It seeks to clarify for clinicians, genetic counselors, and public health planners how to best navigate the complex interplay between maximizing identification rates and managing healthcare resources, ultimately contributing to the overarching goal of reducing the devastating burden of cancer in families harboring BRCA1 and BRCA2 pathogenic variants.

Thematic Discussion

Family History-Based Screening and Clinical Prediction Models

The foundational strategy for identifying individuals at risk for BRCA mutations has historically relied on meticulous collection and analysis of personal and family cancer history. This approach forms the basis for most current professional guidelines, which specify criteria for genetic testing referral, such as early-onset breast cancer, bilateral breast cancer, the presence of both breast and ovarian cancer in an individual, or a known family mutation (11). The strength of this model lies in its targeted nature, aiming to maximize the pre-test probability of identifying a pathogenic variant, thereby making it a cost-effective initial strategy. To refine this process beyond simple checklists, several clinical prediction models have been developed and validated. Tools such as the Manchester Scoring System, BOADICEA (Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm), and the Tyrer-Cuzick model integrate detailed family history data to provide a quantitative estimate of an individual's probability of carrying a BRCA1/2 mutation (12). These models help standardize referral practices and assist clinicians in triaging patients, ensuring that those with a calculated probability above a certain threshold are offered genetic testing.

However, the reliance on family history is fraught with significant limitations that can lead to a substantial number of carriers being missed. Incomplete penetrance, the small size of modern families, and limited knowledge of paternal family history can obscure an inherited cancer pattern. A critical study by Sun et al. demonstrated that even rigorous application of family history-based criteria fails to identify a notable

proportion of mutation carriers; their model suggested that universal genetic testing for all breast cancer patients would identify more pathogenic variants than testing based on current guidelines alone (7). This is particularly true for BRCA2, where cancer risks can be more moderate and family histories less striking than those associated with BRCA1. Furthermore, the emergence of de novo mutations, though rare, means that a negative family history does not completely rule out a hereditary syndrome. These gaps in the family history-based model have prompted the exploration of more inclusive screening strategies to cast a wider net and reduce the number of "unidentified" carriers within the population.

The Shift Towards Broader Screening: Mainstreaming and Population-Based Approaches

In response to the limitations of traditional models, two major paradigms have gained traction: mainstreaming genetic testing in oncology care and population-based screening. Mainstreaming involves the integration of genetic testing into the standard oncology workflow, where the treating oncologist, rather than a specialist genetic counselor, initiates the testing process for patients with a relevant cancer diagnosis (13). This approach, particularly for women with ovarian cancer, has been shown to dramatically increase testing rates. A study by George et al. implemented a mainstreaming pathway for all women diagnosed with non-mucinous ovarian cancer, resulting in a testing completion rate of over 90%, compared to historical rates that were often below 40% when reliant on traditional genetic clinic referrals (14). This strategy ensures that a cancer diagnosis itself becomes a primary criterion for testing, efficiently identifying probands and enabling cascade testing of their unaffected relatives.

Parallel to mainstreaming in affected individuals is the controversial yet promising concept of population-based screening for BRCA1/2 mutations. This approach seeks to identify carriers in the general population before they develop cancer, maximizing the potential for primary prevention. The most compelling evidence for this comes from studies in the Ashkenazi Jewish population, where a high frequency of three founder mutations makes screening logistically feasible. A landmark study by Metcalfe et al. demonstrated that population-based screening in this group was not only feasible but also highly effective in identifying previously unaware carriers, the majority of whom did not meet family history-based testing criteria (8). The subsequent adoption of risk-reducing strategies in these identified individuals holds the potential to significantly reduce cancer incidence at a population level. However, the translation of this model to more genetically heterogeneous populations raises complex questions regarding cost-effectiveness, infrastructure, and the preparedness of healthcare systems to manage the influx of identified unaffected carriers, including the psychological impact and the challenge of variant interpretation on a mass scale.

The Impact of Screening on Clinical Decision-Making and Cancer Risk Reduction

The ultimate value of any screening strategy is measured by its ability to translate a positive genetic test result into effective clinical actions that reduce cancer burden. For unaffected women identified as BRCA carriers through cascade testing or population screening, the evidence supporting risk-reducing interventions is robust. Bilateral risk-reducing salpingo-oophorectomy (RRSO) remains the cornerstone of management, associated with an approximate 80% reduction in the risk of ovarian cancer and a significant reduction in all-cause mortality (4). Furthermore, for BRCA1 carriers, RRSO has been shown to reduce the risk of pre-menopausal breast cancer by approximately 50% (15). The decision to undergo bilateral risk-reducing mastectomy (BRRM) is more personal, but it offers the highest level of protection against breast cancer, with risk reductions exceeding 90% (5). The effectiveness of these surgeries underscores the life-saving potential of identifying mutation carriers before cancer develops.

For individuals already diagnosed with cancer, a positive BRCA test result directly influences therapeutic management, creating a powerful feedback loop that reinforces the value of screening. The most significant advancement in this area has been the development of PARP inhibitors, which exploit the homologous recombination deficiency in BRCA-mutated cells. In patients with metastatic HER2-negative breast cancer and a germline BRCA mutation, adjuvant therapy with olaparib has been shown to significantly prolong progression-free survival compared to standard therapy alone (6). Similarly, in ovarian cancer, PARP inhibitors have become a standard of care in both the frontline and recurrent settings for BRCA-mutated tumors. This therapeutic implication means that genetic screening is no longer solely a tool for family risk assessment but a critical component of precision oncology, directly dictating treatment choices and improving survival outcomes for affected patients.

Unresolved Challenges and Future Directions

Despite the clear benefits, the expansion of BRCA screening strategies is not without its controversies and unresolved challenges. The move towards multi-gene panel testing, which often includes BRCA1/2 alongside other moderate- and high-risk genes, has compounded the issue of variants of uncertain significance (VUS). A VUS is a genetic alteration whose association with disease risk is unknown, and its identification can lead to clinical uncertainty and patient anxiety. Kurian et al. reported that VUS rates are substantially higher in multi-gene panels compared to single-gene tests, particularly in individuals of non-European ancestry, due to less well-characterized reference populations (9). The management of a VUS is complex, and it typically does not lead to changes in clinical management, potentially undermining the benefits of testing if not accompanied by expert genetic counseling.

Furthermore, significant disparities in access to genetic testing and counseling persist, creating an equity gap in the implementation of these advanced screening strategies. Studies consistently show that racial and ethnic minorities, individuals from lower socioeconomic backgrounds, and those in rural areas are less likely to receive genetic counseling and testing, even when they meet established criteria (16). Barriers include lack of provider awareness, cost, insurance coverage issues, and cultural or linguistic obstacles. Addressing these disparities is a critical frontier for the field. Future directions will likely involve the continued refinement of risk models, the integration of artificial intelligence to analyze complex family histories and tumor genomic data, and the development of streamlined, culturally competent counseling delivery methods, such as tele-genetics, to ensure that the life-saving benefits of BRCA screening are accessible to all high-risk individuals and families, irrespective of their background.

Critical Analysis and Limitations

A critical appraisal of the literature on BRCA screening strategies reveals several methodological constraints that warrant careful consideration. A predominant limitation across the field is the overwhelming reliance on observational study designs, primarily retrospective cohorts and single-arm prospective studies. While these designs are pragmatic for evaluating genetic screening programs, they are inherently susceptible to confounding and selection biases. For instance, studies demonstrating the efficacy of risk-reducing surgeries often draw their participants from dedicated high-risk clinics, a population that may be more health-literate, motivated, and have better access to care than the general at-risk population (15, 17). This selection bias can lead to overestimations of the uptake and effectiveness of interventions in real-world, diverse clinical settings. The near-total absence of randomized controlled trials (RCTs) is understandable given the ethical and logistical challenges of randomizing individuals to receive or not receive genetic information; however, this lack of the highest level of evidence means that the observed benefits of screening are consistently inferred from non-randomized comparisons, leaving

room for unmeasured confounding variables to influence the outcomes. Further compounding the issue of study design is the pervasive problem of limited long-term follow-up data, particularly for emerging strategies like population-based screening. Many studies report on the initial uptake of testing and short-term psychological outcomes, but data on the longitudinal adherence to recommended risk management protocols, the ultimate impact on cancer incidence and mortality over decades, and the long-term psychosocial sequelae are less robust (8, 18). For example, the true clinical utility of identifying a BRCA variant in a young, unaffected woman through population screening will only be fully realized decades later, depending on her sustained engagement with risk-reducing strategies. The scarcity of this lifelong follow-up data makes definitive conclusions about the cost-effectiveness and overall benefit of broad screening strategies somewhat provisional.

Similarly, studies on mainstreaming genetic testing often report testing completion rates as a primary outcome, but may not adequately track whether positive results lead to successful cascade testing of family members, which is the critical step for amplifying the cancer prevention impact across the family unit (14). The literature is also marked by significant heterogeneity in how outcomes are defined and measured, creating challenges for cross-study synthesis and meta-analysis. "Uptake of risk-reducing surgery," for instance, can be measured as intention-to-treat, per-protocol, or as a simple proportion of carriers, with studies often failing to account for the timing of surgery relative to the test result or for contraindications to surgery. This variability complicates direct comparisons between different screening models. Moreover, the assessment of psychological outcomes—such as anxiety, distress, and quality of life—employs a wide array of validated and non-validated instruments, making it difficult to draw uniform conclusions about the psychological safety of different screening approaches (19). This methodological variability extends to economic analyses, where assumptions about the cost of testing, counseling, and long-term medical management, as well as the chosen willingness-to-pay thresholds, can dramatically influence conclusions about cost-effectiveness, leading to seemingly contradictory findings between studies (7, 20). A critical and often underacknowledged limitation is the limited generalizability of findings from many of the seminal studies in the field. Research on population-based screening, for example, is heavily dominated by work in the Ashkenazi Jewish population, a group with a unique genetic architecture characterized by high-frequency founder mutations (8). The lessons learned from these studies regarding logistics, acceptability, and yield may not be directly transferable to more genetically heterogeneous populations where the spectrum of mutations is broader, VUS rates are higher, and the cost per identified carrier is consequently greater.

Furthermore, the participants in most major research studies are disproportionately of European ancestry, well-educated, and possess higher socioeconomic status. This lack of diversity means that the evidence base provides insufficient guidance on how to optimally implement and evaluate screening strategies in racial and ethnic minority groups, who often face compounded barriers including distrust of the medical system, higher rates of loss-to-follow-up, and poorer access to genetic counselors (16, 21). Consequently, the current literature may offer an overly optimistic view of the feasibility and effectiveness of BRCA screening that does not fully hold in under-resourced or diverse healthcare contexts. Finally, the field is undoubtedly subject to publication bias, where studies with positive or statistically significant findings—such as those showing high mutation detection rates or successful reductions in cancer incidence—are more likely to be published than those with null or negative results. This creates a distorted evidence base that may overstate the benefits and underreport the pitfalls, such as low uptake in certain demographic groups, poor understanding of genetic results, or failures in the cascade testing process. The relative scarcity of published studies detailing unsuccessful implementation of screening programs hinders the

ability of the field to learn from past mistakes and iteratively improve screening protocols. Together, these limitations do not invalidate the profound importance of BRCA screening but rather highlight the need for more rigorous, long-term, inclusive, and transparent research to solidify the foundation upon which widespread clinical and public health recommendations are built.

Implications and Future Directions

The synthesis of current evidence carries profound implications for reshaping clinical practice, moving it towards a more proactive and inclusive model of care. A principal clinical takeaway is the necessity of moving beyond a rigid, checklist-based approach to genetic testing referral. Given the documented limitations of family history, clinicians, particularly oncologists and gynecologists, should maintain a low threshold for considering genetic testing, especially in individuals with specific cancer types like high-grade serous ovarian carcinoma or early-onset breast cancer, where the pre-test probability is inherently high regardless of family structure. The successful implementation of mainstreaming models provides a clear blueprint for integrating genetic testing into standard oncology workflows, suggesting that the responsibility for initiating testing must become a shared duty across specialties (13, 14). For primary care providers and other front-line clinicians, the implication is a need for heightened awareness and improved literacy regarding the evolving indications for BRCA testing, enabling them to act as effective gatekeepers to genetic services and initiate early conversations about familial cancer risk. At the policy level, the accumulating data on the effectiveness of broader screening strategies demands a critical re-evaluation of existing clinical guidelines and reimbursement structures. The findings from this review suggest that professional societies and health technology assessment bodies should consider expanding their testing criteria to be more inclusive, potentially endorsing a "test all" approach for specific cancer types, such as ovarian and pancreatic cancer, as is already becoming standard in many centers. Furthermore, the compelling results from population-based screening in founder populations like the Ashkenazi Jewish community provide a strong justification for policymakers to fund and evaluate pilot programs in other well-defined, high-prevalence groups (8, 22). A significant policy challenge will be to address the equity gaps in genetic service delivery. This will require dedicated funding for patient navigation services, support for tele-genetics to reach underserved rural and urban populations, and mandates for insurer coverage of genetic testing and counseling without prohibitive co-pays, ensuring that scientific advancements do not become privileges for the affluent (16, 21).

Looking ahead, this review illuminates several critical unanswered questions that must guide future research agendas. A primary gap lies in understanding the long-term outcomes of population-based screening in diverse, non-founder populations. Rigorous studies are needed to quantify not only cancer incidence reduction but also the overall impact on quality-adjusted life years, cost-effectiveness, and the psychological well-being of individuals identified outside the context of a strong family history. Another pressing question revolves around optimizing the delivery of post-test care. Research must investigate effective strategies for ensuring adherence to risk management plans, improving the efficiency and success of cascade testing, and developing novel interventions to support informed decision-making about risk-reducing options, particularly in communities where cultural beliefs may influence medical choices (18, 23). The rapid integration of multi-gene panels also presents a research frontier: how to best manage the deluge of VUS results and secondary findings, and how to communicate the risks associated with moderate-penetrance genes effectively without causing undue anxiety or prompting unnecessary medicalization. To robustly answer these questions, future research must employ more methodologically sophisticated designs. While RCTs comparing different screening strategies may remain challenging, well-designed prospective cohort studies with long-term follow-up, embedded in diverse healthcare systems,

are urgently needed. These studies should proactively oversample participants from underrepresented racial, ethnic, and socioeconomic backgrounds to ensure generalizable findings. Implementation science frameworks should be leveraged to study the real-world rollout of new testing models, identifying the barriers and facilitators to their success across different clinical contexts (24). For evaluating psychological and behavioral outcomes, mixed-methods approaches that combine standardized quantitative scales with in-depth qualitative interviews will provide a richer, more nuanced understanding of the patient experience than either method alone. Finally, comparative effectiveness research that directly contrasts the outcomes, costs, and patient satisfaction between traditional genetic clinic-based care and mainstreamed or tele-genetics models will provide essential data for health systems planning to scale their genetic services efficiently and equitably. By addressing these gaps with rigorous and inclusive science, the field can ensure that the promise of BRCA screening is fully realized for all individuals and families at risk.

Conclusion

In conclusion, this review affirms that the identification of BRCA1 and BRCA2 pathogenic variants through systematic screening strategies is a powerful tool for reducing the cancer burden in high-risk families. The evidence compellingly demonstrates that while traditional family history-based models remain a foundation for testing, they are insufficient alone, and the integration of more inclusive approaches—such as mainstreaming testing in oncology care and exploring population-based screening in select groups—is critical for capturing the full spectrum of mutation carriers. The strength of the evidence is robust in establishing the clinical utility of a positive test result, which unlocks access to highly effective risk-reducing surgeries for unaffected carriers and guides targeted therapies, such as PARP inhibitors, for affected individuals. However, the reliability of the literature is tempered by a predominance of observational data, heterogeneity in outcome measurement, and limited generalizability to diverse populations, highlighting an urgent need for more standardized and inclusive research. Therefore, it is recommended that clinicians adopt a lower threshold for genetic testing, moving beyond strict familial criteria, and that healthcare systems invest in infrastructure to support mainstreaming and address disparities in access. A concerted call for further research employing long-term, prospective studies in diverse populations is essential to solidify the evidence base and ensure that the life-saving potential of genetic knowledge is equitably realized for all.

Author' Contributions

Author	Contribution
Murtaza Khodadadi	Designed the study, performed data collection and analysis, and prepared the manuscript. Approved the final draft for submission.
Alina Mansoor	Contributed to study design, data acquisition, interpretation of findings, and performed critical review and editing of the manuscript. Approved the final draft for submission.

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