



Helping Patients Understand and Cope with BRCA Mutations

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Abstract

Purpose of Review Individuals carrying germline mutations in *BRCA1/2* have unique psychosocial and educational needs that must be met to ensure informed clinical decision-making. In this review, we highlight the strategies used in clinical practice to support patients' needs as well as currently available pre- and post-disclosure support interventions.

Recent Findings Clinical risk communication is complicated by the uncertainty associated with gene penetrance, inconclusive results, variable effectiveness of surgical and screening interventions, and inadequate awareness of clinical genetics. Interventions to support patients' psychosocial needs, and strategies for effective and scalable clinical risk communication are in routine use and largely effective at meeting patients' needs. Research is underway to develop newer supportive resources; however, the inadequate representation of all mutation carriers persists.

Summary Effective clinical risk communication strategies, decision support aids, written educational materials, and supportive psychosocial tools can together have a large impact on meeting BRCA carriers' supportive needs.

Keywords BRCA1/2 · Coping · Genetic education · Psychosocial support · Clinical decision-making

Introduction

Germline genetic testing for variants in *BRCA1* and *BRCA2* genes comprise the majority of all clinical genetic tests as mutations in these two tumor suppressor genes have significant clinical utility for cancer previvors, survivors, and their family members. The discovery of *BRCA1* in 1994 and *BRCA2* in 1995 paved the pathway to routine clinical genetic testing for cancer susceptibility and their use has also steadily increased over time. Pathogenic variants in *BRCA1* increase susceptibility to breast (55–72%) and ovarian (39–44%) cancers with a lower increase in risk indicated for cancers of the prostate, pancreas, and melanoma [1–3]. Similarly, mutations in *BRCA2* increase susceptibility to

female breast cancer (45–69%), ovarian cancer (11–17%), male breast cancer (<6%), prostate cancer (15%), and to a lesser extent for pancreatic cancer, peritoneal cancer, Fanconi anemia, and myeloid leukemia [2, 3]. Around 3% of all breast cancers and 7% of all ovarian cancers have an underlying mutation in *BRCA1/2* [4]. Distribution of mutation carriers as well as mutational spectrums for *BRCA1/2* varies by race and ethnicity with the highest burden among those of Ashkenazi Jewish ancestry [5, 6].

Genetic test results can inform cancer prevention, therapeutics, and management. For example, *BRCA1/2* mutation carriers may consider prophylactic surgeries including bilateral mastectomy and salpingo-oophorectomy to reduce their risks for breast and ovarian cancer. Mutation carriers are recommended to undergo more frequent screenings and to undergo breast MRI in addition to annual mammograms. Although there is limited information about the efficacy of chemoprevention agents in *BRCA1/2* germline mutation carriers, retrospective subset analysis of the Breast Cancer Prevention Trial demonstrated a 2/3 reduction in breast cancer risk among *BRCA2* mutation carriers, but no risk reduction in *BRCA1* carriers [7]. Although this analysis is limited by very small cohort size, current guidelines do allow consideration of using these risk reducing agents as options for breast and ovarian cancer, after appropriate discussion of

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risks and benefits [8]. Cancer survivors carrying germline mutations in *BRCA1/2* may be increasingly offered targeted therapeutics with PARP inhibitor to improve their clinical outcomes.

Overall, about 1 in 400 people carry a *BRCA1/2* mutation and identifying them before they develop cancer would be groundbreaking for cancer prevention. Based on this estimated incidence, there are approximately 660,000 individuals with germline mutations in *BRCA1/2* in the USA — most of whom remain undiagnosed. The public health burden of cancers among mutation carriers, the significant potential for positive impact and clinical benefit afforded to mutation carriers combined with low genetic testing costs, has resulted in increased recommendations for uptake of testing in the general populations. Mutation carriers identified through testing need to understand these vast amounts of complex and uncertain information in order to make informed, preference-sensitive clinical decisions based on their genetic test results.

In this review, we highlight the strategies used in clinical practice as well as support interventions developed through research that are available to help patients understand and cope with *BRCA1* and *BRCA2* mutations. We focus on three broad inter-related areas: (1) clinical risk communication, (2) psychosocial impact of carrier status, and (3) decision aids, tools, and support strategies. We performed a comprehensive literature search in Ovid MEDLINE and Ovid EMBASE from inception to July 30, 2021, and retrieved 528 citations to review. Key concepts built into the search structures include “*BRCA*” and “Hereditary Breast and Ovarian Cancer,” in combination with multiple terms identifying “patient counseling,” “education,” “psychology,” “informational needs,” and “social support.” The full Embase search string can be found in [Appendix](#).

Not All *BRCA1/2* Mutations Are Alike

Although the term “mutation” commonly refers to pathogenic variants, technically, any genetic sequence that deviates from the standard sequence is a mutation which may or may not be deleterious. Per the technical definition of the term, variants of unknown significance (VUS) and benign variants are also mutations. Of note, American College of Medical Genomics prefers the term “variant” as lay audiences react negatively to the term “mutation” which has negative connotations and is associated with negatively valenced outcomes [9]. These pathogenic, likely pathogenic, VUS, likely benign, and benign variants have very different clinical implications; however, they all inform clinical management and are routinely communicated to patients. These results present different psychosocial challenges for patients which necessitates different strategies to help

patients understand, psychologically adjust, and cope with their results. For example, family/social relationship difficulties are more common among women receiving pathogenic variants than VUS or benign variants [10]. Uncertainty is a prevalent issue among those with VUS results, although contradictory reports of decreased psychosocial problems among those with VUS also exist [11]. On the other hand, patients with benign results who have family history of pathogenic variants tend to suffer from survivor’s guilt.

Mutations in *BRCA1* are different from mutations in *BRCA2* and present different lifetime risks of various cancers. Moreover, there is evidence to indicate that breast and ovarian cancer risks vary by type and location of mutations within *BRCA1/2* genes with risks coinciding with their putative functional domains. For example, mutations conferring nonsense-mediated decay are associated with differential breast or ovarian cancer risks and an earlier age of breast cancer diagnosis for both *BRCA1* and *BRCA2* mutation carriers [12]. Mutation-specific risks are often reported in genetic test reports, although infrequently used in counseling patients (except in some case-by-case basis) but may become more common in future once better mutation-specific absolute risk data are available.

Challenges of Risk Communication

Patients need to understand enough of genetically based risk information and the associated cancer risk estimates in order to make consonant behavioral choices and clinical decisions. Therefore, effective communication of quantitative risk information is a matter of necessity in clinical genetics as this knowledge is a necessary basis for effective decision-making. Once a pathogenic variant is identified in *BRCA1/2*, the objective of risk communication is to facilitate informed decision-making (e.g., whether and when to undergo prophylactic surgeries) and to change or modify health care behavior (e.g., intensive screening). These preference sensitive decisions are influenced by patients’ (and even providers’) *a priori* beliefs, knowledge, preferences, expectations, anxiety, and coping styles which in turn affect how patients and providers use the genetic risk information. Genetic and cancer risk information presented in a clinical encounter is frequently transformed in patients’ minds resulting in discrepant objective and perceived risks. It is probably no surprise that many patients misunderstand their breast cancer and genetic risks. For example, patients tend to largely overestimate their breast cancer and genetic risks at the pre-genetic counseling stage, and although their risk perception becomes more accurate upon undergoing genetic counseling, where the accurate risk information is communicated to them, it still remains up to 24% higher than their objective cancer risk conferred by a *BRCA1/2* mutation [13].

Previvors and survivors who are BRCA mutation carriers have specific and different information needs which requires tailored counseling conversations. Previvors request more information on risk-reducing surgeries and psychological aspects whereas survivors are keen to learn information on breast cancer treatment and risk of recurrence. Baseline knowledge of genetic testing and health information also needs to be accounted into counseling to meet the patient's specific support needs. Men and transgender patients have yet another set of unique needs and there is limited data on safety of treatment options and hormone therapies for them. Generally, patients and providers are more aware of *BRCA1/2* genes compared to less common breast cancer susceptibility genes (e.g., *PALB2*, *PTEN*, *ATM*); however, there is large variation in the awareness of the specific variant classifications within these genes, their associated clinical significance, and management that is necessary for proper counseling and follow-up. In fact, many patients, especially those seen outside the genetics research community or academic health care centers, report being ignored or "brushed off" or even having to counsel providers about their specific mutations [14]. These diverse set of contextual factors highlights the challenges of effective risk communication and need to help patients cope with their mutation status.

Uncertainty Adds to the Challenge of Risk Communication

Unlike many mendelian conditions, genetic testing for cancer susceptibility and downstream clinical decisions are riddled with uncertainty which complicates and highlights the importance of effective risk communication. Unaffected individuals without a personal history of cancer must grapple with the uncertainty of developing cancer. These gene penetrance estimates appear to vary from 40 to 66% for breast cancer and between 18 and 46% for ovarian cancer for *BRCA1/2* [3]. Mutation carriers without personal history of breast cancer need to decide between undergoing prophylactic mastectomy versus increased surveillance via breast MRI in addition to mammogram which involves balancing considerations of insurance coverage, cost, and quality-adjusted life years. Although surveillance methods substantially increase the probability of early cancer detection, false-positive tests are associated with increased distress rates. This "watchful waiting" surveillance approach is adopted by 20–50% of BRCA mutation carriers [15]; however, studies indicate that fewer than 70% of women are adherent to guideline-based screening recommendations. The effectiveness of preventive interventions is also associated with a great deal of uncertainty. Prophylactic bilateral mastectomy is associated with 90–100% relative reduction in breast cancer incidence, yet there remains a minuscule

residual level of risk of breast cancer from leftover breast tissue [16]. Prophylactic bilateral oophorectomy and salpingo-oophorectomy are associated with significant reduction in ovarian cancer risk of up to 80% in efficacy studies [17, 18], a 50% reduction in breast cancer risk when the surgery is performed before menopause [17, 19, 20], and a 68% reduction in all-cause mortality [21]. Those who opt for surgery over screening, the repercussions of unanticipated biopsy with its attendant anxiety are not negligible. In addition, potential unanticipated repercussion of change in body image/lack of satisfaction with body image/change in intimacy should be considered. Additional factors known to influence the decision of surveillance versus surgery include family history of cancer, perceived genetic risk, and fear of cancer [22, 23]. Given these complex issues and multifaceted effect of decisions, it is critical that specialists provide emotional support in addition to medical information.

Decisions that need to be made post-genetic testing include not only those of immediate importance to patients' cancer management, but also decisions that can have repercussions many years into the future, e.g., reproductive decisions [24]. Although mutation carriers can achieve greater risk reduction by undergoing both mastectomy and salpingo-oophorectomy than either alone, these life-altering decisions and their timing are often shaped by desire to have children. Although use of hormone replacement therapy does not negate the benefits of salpingo-oophorectomy in BRCA carriers, the decision to take hormone replacement therapy post-preventive oophorectomies needs to be weighed against its effects on bone health and quality of life. Other long-term decisions can impact individuals beyond the index patient such as whether or not to disclose genetic test results to family members that can inform cascade testing, how/when to relay results are also important decisions that individuals can be supported in. Although essential for cascade genetic testing, family communication of BRCA mutation status is a difficult process and proband's must balance knowledge of families' psychosocial function and cultural context in deciding whether, how, and when to share in order to best benefit their family.

Psychosocial Outcomes

Psychosocial outcomes of genetic testing in the context of single or multigene testing have been studied extensively and there is consensus that negative outcomes of genetic testing are few and far between [25, 26]. When observed, negative psychosocial effects are mild, transient, and return to baseline within a few months after testing [27, 28]. However, there are subgroups of tested individuals at greater than average risk of psychological distress following testing. Women, younger people [29], non-Whites, and individuals with less

satisfactory social support and lower educational levels had higher levels of general and cancer-specific distress, regardless of mutation status in the 12 months following testing. Other studies have reported that individuals with a prior history of major or minor depression or those with more affected first-degree relatives or those reporting more intense grief reactions had greater distress 1 to 6 months after disclosure. Psychosocial difficulties experienced by carriers of BRCA mutation can be varied and can arise from several sources — generic distress (i.e., anxiety and depression), concern about hereditary predisposition to cancer, familial and social issues, emotions, familial cancer risk, and personal cancer risk, self-worth, and cancer related stigma. Although post-test breast cancer worry and anxiety generally increase for women with positive results and decrease for women who test negative [30], these worry and anxiety tend to be short-lived [30] but a minority continue to have long-term elevated distress [26]. BRCA carriers report clinically significant state and health anxiety resulting from feelings of vulnerability, stigma, and health anxiety. Dysfunctional coping strategies, which refers to behavioral disengagement, denial, self-distraction, and self-blame, are often related to quality of life in BRCA carriers [31] and may be targeted through psychological therapy to improve quality of life. Unsurprisingly, type of *BRCA1/2* result differently affects distress [32] with higher distress reported by those carrying pathogenic variants.

Psychosocial well-being following risk-reducing surgery with regard to sexual function, distress, and body image are also areas that mutation carriers can be supported in. Such distress is lower among women without personal history of cancer who have undergone risk reducing breast and ovarian surgery compared to women who have not [33]. There is limited evidence about whether psychosocial interventions improve quality of life or emotional well-being in female BRCA carriers who undergo risk-reducing surgery [34]. Men with *BRCA1/2* mutations undergoing targeted prostate cancer screening do not report clinically concerning levels of general or cancer-specific distress or poor quality of life [35], but additional research using larger sample sizes of this underrepresented group is warranted.

Risk Communication Strategies

In clinical oncology, efforts to help patients understand and cope with genomic information begins well ahead of testing as all potential clients are required to undergo rigorous pre-test genetic counseling in preparation for genetic test results and their consequent clinical and psychosocial consequences. Although generally performed via in-person encounters with a genetic counselor, newer formats of pre-test genetic counseling are increasingly being used and data

suggests that they may be equally effective. Telegenetics, especially in the context of pre-test genetic counseling, is highly satisfactory to patients [36] due to its convenience [37] and cost and time savings. Participation in telegenetics during the COVID-19 pandemic has proliferated to both pre-test and post-test counseling to the extent that the majority of all counseling appointments are now completed virtually. Although telephone post-test genetic counseling was found to be non-inferior to in-person in randomized controlled trials [38, 39], patients in the telephone group had poorer long term engagement with surveillance and prophylactic surgery [38, 40]. Preliminary data on use of innovative chatbot-based genetic service delivery seems promising [41] and randomized trials to test their efficacy against standard of care genetic service delivery models as well as long-term outcomes are currently underway [42•]. Regardless of the mode of service delivery, it is important to tailor risk communication in genetic counseling appointments based on individuals' a priori knowledge and awareness of genetic testing, cancer worry, tolerance for uncertainty, and psychosocial needs [43].

Post-disclosure Support Interventions

Assistance to understand and cope with BRCA mutations can come from a variety of sources including physicians, genetic counselors, family members, and other mutation carriers. Healthcare providers including genetic counselors and oncologists remain the most trustworthy information sources for patients. However as noted previously, patients demonstrate some resistance to risk information given which highlights the importance of using effective risk communication strategies. A wealth of research from the field of risk communication suggests short-term age-related risk estimates may be of more value to patients than cumulative lifetime risks. Although patients prefer percentages, they often transform numerical estimates into discrete categories (high or low risk). As a result, the use of verbal description of the risk magnitude (e.g., “a higher risk than another woman in the general population”) leads to better understanding. Patients' inflated post-counseling risk perception and overestimation of risk is correlated with pre-counseling worry [13] so tailoring risk communication strategies based on pre-counseling self-reported worry is another strategy that could help patients comprehend their risks accurately, but it is not a part of routine clinical practice. European breast surgeons and general practitioners prefer to use absolute risks numerically and frame them negatively [44]. This negative framing is derived from a body of research which shows that loss-framed messaging is demonstrably more effective at behavior change than gain-framed messaging [45]. This applies to messages that aim to improve early detection including

mammography and breast self-exam — e.g., loss-framed, “If you don’t have regular mammograms, you reduce your chances of detecting breast cancer at an early, more treatable stage,” vs the gain-framed appeal of, “If you have regular mammograms, you increase your chances of detecting breast cancer at an early, more treatable stage.” However, the effectiveness of these loss- or gain-framed messaging strategies has not been studied in high-risk BRCA-positive populations.

Decision aids can help patients navigate many of the complex short- and long-term personal, familial decisions that need to be made upon genetic testing. Tailored decision aids are available for previvors and survivors who have different concerns regarding their *BRCA1/2* mutations. The main advantages of decision aids are linked to the actual decision process — studies show that female *BRCA1/2* mutation carriers using a decision aid had less decisional conflict, were more likely to reach a decision, and were more satisfied with their decision [46]. Decision aids have been shown to be effective at increasing the likelihood of reaching a management decision and decreasing decisional conflict among mutation carriers who were initially undecided about whether or not to undergo risk-reducing mastectomy [47].

A number of post-disclosure support interventions have been developed to help patients with *BRCA1* and *2* germline mutations cope with their mutation status as reviewed by a recent scoping review on this topic [48••]. These interventions primarily achieve their goal by increasing knowledge of hereditary breast and ovarian cancer and by providing emotional support with varying levels of success [49]. Some interventions work by providing peer support groups for mutation carriers by putting them in touch with other mutation carriers. These can be moderated telephone-based interventions where a mutation carrier serves as a support provider or online support groups (e.g., FORCE and Facebook) that are not moderated. Engagement in these communities has been shown to have variable but generally positive psychosocial outcomes (lower breast cancer distress and depression) and to help with post-test decision-making including risk-reducing surgery [50]. *BRCA* carriers engaged in these communities report high satisfaction [51], appreciation of psychological support, interest for future psychoeducational groups, and a higher likelihood of following through with risk-reducing surgery [50] but attendance in these groups did not change preference for management or surveillance [49]. Other coping tools also exist, e.g., *BRCA* Exchange: <https://brcaxchange.org/>, <http://brcatool.stanford.edu/>. Efforts to develop chatbots to address patients’ informational needs around *BRCA* germline mutations are currently underway [52]. However, chatbots that can mimic empathetic responses — a communicative behavior often used by humans to reduce emotional distress of another individual [53] — is yet to be developed for *BRCA* carriers and it is

unclear if the chatbots will be able to offer complex psycho-social support with today’s technology.

Other Supportive Resources and Educational Materials

Written educational materials work alongside telephone and in-person communication with patients to help them understand and cope with genetic test results. In genetic counseling, these include summary letters explaining genetic test results and their clinical implications, family letters intended for sharing with relatives to aid in family communication of genetic test results and cascade genetic testing, and the laboratory-generated genetic result report. Content and format of genetic result letters vary widely between genetic counseling practice settings and their impact on patient-centered outcomes is not understood. Upon formal content and format analyses, these letters were frequently found to be overly complex exceeding recommended readability measures [54] which highlight the complexity of genomic information that needs to be communicated in a clinical setting. Family letters and encouragement for disclosing results to at-risk relatives are a routine part of many genetic counseling practices [55] but the degree to which they help with family communication of *BRCA* mutations remains to be studied. Although rarely read by patients, laboratory generated reports of genetic test results present information in even more complex formats often containing variant specific information [56] that are likely incomprehensible to most lay readers. Most of these supportive materials are written well above CDC-suggested reading level for health communication and warrants reconsideration in design.

Conclusion

In order to effectively communicate complex genetic and cancer risk information associated with *BRCA1/2* mutations, we must better understand the unique needs of this population and find supportive resources to help them navigate the complex clinical space around risk reduction and management. In addition, we must tailor the clinical message to patients’ ability and willingness to cope with the information to facilitate informed decision-making around these preference sensitive topics. As clinical genetic services reach populations beyond those served by tertiary cancer centers of excellence, scalable post-test support interventions are essential to serve the psycho-social, emotional, and clinical decision support needs of individuals carrying *BRCA1/2* mutations. Lastly, many of the most substantial gaps in the *BRCA* literature have to do with the lack of representation of all individuals who

carry BRCA mutations. The vast majority of research on *BRCA1/2* mutation carriers only include females who are overwhelmingly non-Hispanic White, while men, racial/ethnic minorities, and transgender individuals are often excluded from this body of work. Understanding the needs, perspectives, and preferences of these underrepresented populations will be a critical step to ensuring that effective strategies are developed to help all *BRCA1/2* mutation carriers comprehend and cope with their diagnosis.

Appendix

Ovid Embase search string.

1. *Genes, BRCA1/
2. *Genes, BRCA2/
3. **“Hereditary Breast and Ovarian Cancer Syndrome”/
4. (BRCA* or “breast cancer type 1” or “breast cancer type 2” or “breast Cancer 1” or “breast cancer 2” or “hereditary breast and ovarian cancer”).ti.
5. OR/1–4
6. *Intervention Study/
7. *Patient Education/
8. ((patient* or women or female* or survivor* or carrier*) and (anxiety or communication or comprehension or cope or coping or counsel* or decision or distress or educat* or emotional or enhance* or “information need*” or instruct* or intervention* or knowledge or perspective* or program* or psychoeducat* or psychology* or “psycho-oncology” or psychosocial* or peer* or stress or support or teach* or understand)).ti.
9. OR/6–8
10. AND/ 5,9
11. Limit 10 to english

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Declarations

Conflict of Interest The authors declare no competing interests.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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- Of importance
- Of major importance

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