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# Updates in Genetic Testing Guidelines for Breast Cancer Susceptibility Genes: a Change in the Paradigm

Lorena Gonzalez[1] · Laura Kruper[1]

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## Abstract

**Purpose of Review** Up to 10% of all breast cancers are associated with inherited germline mutations. Genetic testing guidelines for hereditary breast cancer susceptibility have changed significantly since their inception in the late 1990s. The purpose of this review is to discuss the changes in technology that have improved our ability to efficiently detect germline mutations, introduce the recent paradigm change towards population-based testing currently supported by the American Society of Breast Surgeons, and highlight the challenges that expansion of testing parameters presents.

**Recent Findings** Next-generation sequencing with multi-gene panels has replaced the traditional Sanger method of genetic testing and has quickly become the standard of care for germline mutation analysis. Benefits of this technology include increased efficiency and cost reduction. While National Comprehensive Cancer Network and US Preventive Task Force guidelines maintain family history as the basis for testing in both unaffected and affected women, new evidence supports testing of all newly diagnosed breast cancer patients and thereby cascade testing to increase rate of mutation detection prior to the diagnosis of breast cancer. Furthermore, recent studies of population-based testing in high-risk groups suggest that population-based screening in the general population is feasible and cost effective.

**Summary** Recent developments in technology and germline mutation testing studies support the expansion of genetic testing criteria for hereditary breast cancer. Consensus guidelines are starting to reflect these changes at a national level. The next great challenge will be determining the effectiveness of population-based testing for all women in an effort to increase breast cancer prevention for all.

**Keywords** *BRCA1* · *BRCA2* · Hereditary breast cancer · Germline mutation · Next-generation sequencing

## Introduction

The discovery of mutations in the high-penetrance breast cancer susceptibility genes *BRCA1* (1994) and *BRCA2* (1995) provided a golden opportunity for preventive care and early detection in women at high risk for developing breast and/or ovarian cancer [1, 2]. Several studies since then have shown that women with germline *BRCA* mutations have a > 5-fold relative cancer risk accounting for up to 10% of all breast cancers and up to 18% of ovarian cancers [3–5]. Original genetic testing criteria were limited to women with significant family histories of breast cancer, those diagnosed with cancer at very early ages, and cases of bilateral breast cancer or combinations of both breast and ovarian cancer [6]. The prohibitive cost of early-era sequential genetic testing (testing for one specific type of genetic mutation followed by testing for other mutations if the prior was negative) hampered the willingness of insurance companies to cover genetic testing services. Over time, as more evidence supporting the role of *BRCA1/2* mutations in breast cancer became available [7, 8], the benefits of risk-reducing surgery were made known [9] and new chemotherapy treatment strategies based on the presence of a *BRCA1/2* mutation were discovered [10], the national guidelines for genetic counseling and testing became more inclusive. Furthermore, genetic sequencing technology underwent rapid evolution and improvements, namely the development of next-generation sequencing (NGS) and multi-gene panels,

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✉ Laura Kruper
LKruper@coh.org

[1] Department of Surgery, Breast Surgery Division, City of Hope National Medical Center Duarte, 1500 Duarte Rd, Duarte, CA 91010, USA

allowing for more rapid and cost-efficient individual assessments for risk of hereditary breast and ovarian cancer (HBOC) [8, 11]. While mutations in *BRCA1* and *BRCA2* make up 50% of hereditable mutations in breast cancer, mutations in other high-penetrance breast cancer susceptibility genes (TP53, CDH1, PALB2) and moderate penetrance genes (CHEK2, ATM) make up the bulk of the remaining mutations detected. Advances in gene sequencing coupled with expansion of genetic testing criteria have significantly increased the number of mutation carriers identified.

Despite the evolution of testing criteria, the identification of mutation carriers prior to the development of breast cancer remains an elusive challenge. Current national guidelines maintain family history as the sole criterion for genetic testing in cancer-free women despite the fact that half of all women with *BRCA1/2* mutations detected at the time of cancer diagnosis do not meet the family history criteria for testing [12]. The significance is that the majority of mutations carriers are identified only after having developed cancer, representing a clear failure of breast cancer prevention. New data supporting the expansion of genetic testing criteria to all women diagnosed with breast cancer have led the American Society of Breast Surgeons (ASBrS) to issue a statement revising their consensus guidelines on genetic testing for hereditary breast cancer [13]. The purposes of this article are to discuss the changes in genetic testing guidelines supported by the ASBrS, review the recent literature in support of testing criteria expansion, and discuss the unintended risks and consequences of increased genetic testing in this cohort.

## Casting a Wider Net Increases Detection of Mutation Carriers

An estimated 10% of the breast cancers detected each year in the United States are likely related to heritable genetic mutations [14]. According to the American Cancer Society, this translates to about 30,000 of the breast cancer cases diagnosed per year. However, this number does not include unaffected relatives of these women who should also be tested. In the US population, the number of women with pathogenic (P) and likely pathogenic (LP) variants in *BRCA1/2* is about 1 in 300 to 1 in 500 women, or between 250,000 and 415,000 US women [15]. So, how do we target both affected and unaffected women for testing in a way that maximizes identification of genetic mutation carriers to either prevent development of disease or detect disease at an early stage while remaining efficient and cost-effective? The current National Comprehensive Cancer Network (NCCN) testing guidelines for germline mutations in cancer susceptibility genes for patients with breast carcinoma were established to detect carriers of *BRCA1/2* P/LP variants, primarily because close to 50% of HBOCs are secondary to BRCA1/2 mutations [16]. While the guidelines have become more inclusive in the era of panel-testing, studies estimate that less than 10% of all *BRCA1/2* mutations carriers have been identified and that up to 80% of unaffected women at risk have not been tested because they do not meet the family history criteria for testing [12, 17, 18•].

Most models available to assess an individual's probability of a *BRCA1/2* mutation were designed using data from multiplex families (families where multiple individuals are affected by a specific disease (i.e., breast and ovarian cancer), age of disease onset, family history of gene expression, and ancestry [19–21]. Because HBOC syndrome has an autosomal-dominant inheritance pattern, half of all *BRCA1/2* gene mutation carriers are expected to be men. However, recognition of this pattern is masked by the low penetrance of *BRCA*-associated breast cancers in men, particularly those with limited family structure (fewer than 2 first- or second-degree female relatives surviving beyond age 45 in either paternal or maternal lineage) making it difficult to identify mutation carriers in single cases of breast cancer [22]. This suggests that truncated family histories adversely affect the accuracy of probability models used in genetic cancer risk assessments and ultimately exclude a large number of genetic mutation carriers. A retrospective study comparing three commonly used *BRCA* gene mutation prediction models (Couch, Myriad, and BRCAPRO) in patients seen in a high-risk clinic without a family history of breast or ovarian cancer in first- or second-degree relatives found that while none of the models performed well, modification to the models correcting for limited family structure increased the predictive ability for single cases of breast cancer [23]. Furthermore, the study demonstrated that patients with truncated family histories had a higher incidence (13.7%) of BRCA mutations compared to those with adequate family structure (5.2%) [23]. The authors of this study recommend expanding genetic testing guidelines to account for single cases of breast cancer in limited family structures and revising probability models to include truncated family history as a variable.

It is now widely recognized that family history alone has been shown to be an unreliable method of capturing all mutations carriers. Two recent US studies [24••, 25•] presented at the last two annual meetings of the ASBrS support the need to expand genetic testing guidelines to include *all* women with breast cancer, not just those from high risk families. A prospective cohort study of 959 unselected breast cancer patients reported the findings of multi-gene panel testing in patients who met (49.95%) and did not meet (50.05%) the current NCCN germline genetic testing guidelines [24••]. Beitsch et al. found a 9.39% incidence of P/LP variants in the NCCN testing criteria cohort compared to 7.9% in patients who did not meet those testing guidelines ($P = .4241$). Additionally, only 1.56% or 15 out of 959 patients with recently diagnosed breast cancer or a personal history of breast cancer had a P/LP variant if only *BRCA1/2* testing was considered in this unselected cohort [24••]. A second study also

found a near identical rate of P/LP variants for patients meeting criteria (10.5%) compared to those who did not (9%; $P = .26$) in Medicare patients [25•]. Shortly after the publication of these studies, the ASBrS published updated guidelines favoring the expansion of genetic testing to all women with breast cancer. However, both of these studies have been heavily criticized citing funding sources from industry (Myriad Genetics Laboratories, Salt Lake City, UT and Invitae, San Francisco, CA) as conflicts of interest. In contrast, a quality of care study funded by the Norwegian Women's Public Health Association published just 1 year earlier also showed that using common guidelines for testing (American Society of Clinical Oncology (ASCO), NCCN, and the Norwegian Breast Cancer group) still missed 10–65% of mutation carriers [26]. These authors also recommended the expansion of BRCA testing to all breast cancer patients as well as cascade testing of family members to help prevent future cases of breast cancer.

The identification of genetic mutations in women after a diagnosis of breast cancer represents a failure in cancer prevention [27, 28]. But how do we increase the capture of healthy or unaffected BRCA1/2 mutation carriers? The US Preventive Services Task Force (USPSTF) recommends against testing for BRCA1/2 mutations in healthy women without significant family history of HBOC due to the lack of data on cancer risk in BRCA mutation carriers in the general population [15]. Outside of the US, population-based BRCA testing has been piloted in both Israel and the United Kingdom in the Ashkenazi Jewish population and has proven to be both feasible and cost-effective [28–30]. While family history-based testing was more efficient than population-based testing in this select population, the latter captured over 50% more mutation carriers and found very high cancer risks in BRCA1/2 mutation carriers irrespective of personal or family history of breast cancer [28]. These findings have led advocates of population-based testing to push for genetic screening of *BRCA1/2* mutations in all women over age 30, allowing for the identification of mutation carriers independent of family history or physician referral. This is significant because despite the fact that the USPSTF tasks primary care physicians with screening for high-risk patients, less than 20% of these primary care providers are accurately identifying candidates for genetic susceptibility testing [31].

## Evolution of Germline Mutation Testing Technology

The traditional model of clinical cancer genetics evaluated patients based on family history, age at disease diagnosis and/or tumor characteristics, as previously discussed. This would result in testing for specific genetic mutations followed by serial testing of other genes, should the most commonly identified mutations not be present. This method called "sequential testing" has fallen out of favor secondary to two major disadvantages: inefficiency and high cost. The original NCCN criteria were designed to limit testing to a population of patients with the most significant clinical presentation of highly penetrant BRCA1/2 variants [25•]. While this made testing efficient, it also excluded those patients with moderate penetrance mutations, thereby missing a large number of mutation carriers. Furthermore, the current NCCN genetic testing guidelines still reflect the historical sequential testing design when *BRCA1/2* mutation testing was prohibitively costly. For many years, one American company, Myriad Genetics Inc., held a patent and long-time monopoly on *BRCA* gene testing, with each test running between $2000 and $5000. The landmark US Supreme Court ruling of 2013 against Myriad Genetics, Inc. challenged the validity of gene patents, opening the market and allowing for competitive pricing [32]. But it was the advent of next generation sequencing (NGS) technology that would significantly impact the practice of genetic testing by addressing both efficiency of testing and cost effectiveness. By allowing for the assessment of multiple susceptibility genes at once or "multiplex testing", NGS not only improves efficiency of genetic testing, but also does so at a fraction of the original cost [33]. NGS uses similar technology to whole-exome and whole-genome sequencing while producing a more limited amount of information about predefined target genes through both deletion and duplication testing [33].

In addition to *BRCA1/2* mutations, current multiplex breast cancer genetic susceptibility testing panels currently include mutation testing for several other well-known and established hereditary breast cancer syndromes such as Li-Fraumeni syndrome (TP53; tumor protein 53), Cowden syndrome (PTEN; phosphatase and tensin homolog) as well as other related BRCA1/2 DNA repair genes (PALB2, partner and localizer of BRCA2; NBN, nibrin). These are examples of specific germline mutations with established actionable guidelines by the NCCN [34] regarding risk assessment, counseling, and surveillance of high-risk patients carrying these mutations. The issue with NGS is that multiplex panels now also include testing for other related genes like *BARD1* (*BRCA1* associated RING domain) and *BRIP1* (*BRCA1* interaction protein C-terminal helicase 1) which do not have specific guidelines for testing despite some having actionable recommendations for early screening [34]. In fact, a wide array of panels are now available, each testing a variety of different genes. A survey of the National Center for Biotechnology Information Genetic Testing Registry for BRCA1/2 panels [35] yielded 218 clinical tests and 1 research-only test available in over 10 different countries around the world. The ASBrS acknowledges in their most recent consensus guidelines statement [13] the limitations of the multiplex testing approach, namely the lack of agreement among experts

regarding which genes should be tested in different clinical scenarios as well as a lack of understanding of risk and appropriate clinical management of mutations for rare genes.

## Challenges in the Era of Multiplex Genetic Testing

Significant challenges must be met to guarantee the most sensible and successful application of multiplex genetic testing; specifically, promotion of adequate pretest counseling for patients [33], ensuring correct clinical interpretation of moderate-penetrance testing [36], appropriate interpretation of variants of uncertain significance [33], and development of a consensus on how to manage mutations carriers identified by direct-to-consumer testing. Studies supporting the safety of genetic testing in terms of self-reported levels of distress and anxiety have found only mild or temporary psychological distress. The women in these studies were also afforded high-quality pre-test genetic counseling and this may have affected their perception of distress [37–39]. These findings help bolster physician referrals however, these studies also focused on the effects of single gene testing, namely *BRCA1/2*. Arguments exist for modification of contemporary models of genetic counseling to include patient education for the simultaneous testing of multiple genes for diverse syndromes linked by a single cancer type [33], in this case breast cancer. The reasoning behind this recommendation is that detection of a pathogenic mutation in other non-*BRCA1/2* cancer syndrome susceptibility genes (such as *TP53* and *CDH1*) could have serious implications for clinical recommendations regarding surveillance and prophylaxis measures related to other potential cancers, not just breast or ovarian cancer. Patients should be appropriately counseled regarding the possibility of detecting mutations in these additional genes given the significant clinical ramifications.

Testing for moderate-penetrance genes also poses a significant challenge. While high-penetrance genes such as *BRCA1/2*, *PALB2*, *TP53*, and *CDH1* confer a 5-fold or greater risk for breast cancer [40] and have established management, surveillance and prophylaxis guidelines [34], moderate-penetrance genes associated with breast cancer (i.e., *ATM* and *CHEK2*) confer a smaller risk on the order of 2–4-fold [41, 42]. These mutations (and others [36]) have been identified in 2–5% of the population referred for genetic testing of breast cancer susceptibility genes [43–46]. Prior to NGS technology, these genes were not tested for routinely by cancer geneticists due to uncertainty about how identification of these genes should change medical management for these mutation carriers [47]. The clinical utility of finding these moderate-penetrance gene mutations is still unknown given that optimal management strategies for carriers remain incompletely defined [33, 36]. Once identified, these individuals may be harmed if they are incorrectly offered screening regimens, pharmacologic chemoprophylaxis, and/or prophylactic surgical interventions developed for high-penetrance gene mutation carriers.

Variants of uncertain significance (VUS) and their interpretation present another challenge associated with NGS technology because the chances of detecting a VUS is positively correlated with the number of genes tested. A VUS is a DNA sequence that is not clinically actionable and should be considered inconclusive if identified in genetic testing because the disease risk associated with a VUS is unknown. At least one study has shown that clinicians often misinterpret VUS results and make recommendations meant for patients with pathologic variants [48]. The NCCN and the ASBrS maintain that patients testing positive for a VUS, even if identified in a *BRCA1/2* gene, should be managed based on personal risk factors for breast cancer rather than the VUS result. While the overall rate of identification of VUS is approximately 42% [49], as labs accrue more data regarding those variant mutations, the rate of VUS identification will decrease. For example, 10 years ago, the VUS rate for *BRCA1/2* was still 13% compared to current day estimate of 2% [50]. However, while labs will re-issue a new report to carriers of a reclassified VUS, it usually takes several years for the reclassification of VUS to either pathogenic/likely pathogenic or likely benign/benign. A recent study has shown that while *BRCA* VUS carriers with cancer are selecting treatment options similar to those breast cancer patients with average risk, it also notes that unaffected patients (patients without breast cancer) with a detected VUS have elevated rates of prophylactic mastectomy influenced by strong family history and elevated risk assessment scores [51••]. These patients stand to benefit the most from contemporary comprehensive genetic counseling and efforts at expanding genetic counseling should focus on these patients in order to avoid inappropriate management of breast cancer risk.

Finally, direct-to-consumer genetic testing (DTCGT) presents a significant challenge for clinicians who manage and treat breast cancer since the dawn of NGS. In 2017, the US Food and Drug Administration (FDA) granted genetics company 23andMe the authority to sell at-home genetic testing for ten health conditions, including Parkinson's disease and late-onset Alzheimer's disease. Nearly a year later, the FDA also approved the same company to test for the three most common *BRCA1/2* mutations observed in persons of Ashkenazi decent to identify women at increased lifetime risk of breast cancer. Its competitor, Color Genomics, promotes its clinical grade genetic testing of 30 genes associated with breast, ovarian, uterine, stomach, and prostate cancer as well as melanoma. Color Genomics CEO, Elad Gil, told the New York Times that his

company's goal was to "democratize access to genetic testing" and to make testing affordable for women who do not meet guideline criteria for testing according to individual insurance policies [52]. As of 2017, the company began accepting insurance reimbursements for the cost of the test and the company has plans to develop a program to offer the test free of charge for women who cannot afford the cost ($246) of the test. In essence, DTCGT and companies like Color Genomics are making population-based genetic testing possible, not only for breast cancer susceptibility genes but for several other inheritable cancer syndromes. This will invariably increase the number of positive genetic carriers identified but will also dramatically increase the number of patients, both affected and unaffected by cancer, identified as VUS mutation carriers. The era of DTCGT underscores the need to refer patients to comprehensive genetic counseling, understand the meaning of testing positive for moderate vs high penetrance genetic mutations, and to appropriately interpret genetic testing results of the VUS variety.

## Conclusion

The current guidelines for genetic testing of breast cancer susceptibility genes miss56% of all mutation carriers supporting the need to modify inclusion criteria. Many questions remain regarding the feasibility and clinical validity of population-testing for breast cancer susceptibility genes. While new evidence points toward the benefits of expanding testing indications for genetic susceptibility to HBOC, we must keep in mind that some of the evidence supporting the expansion of genetic testing to all women with breast cancer came from studies sponsored by industry [24••, 25•]. However, the key question still remains: how do we effectively increase the successful identification of genetic mutations carriers prior to the development of breast cancer in a cost-effective, efficient manner? Though NGS and multi-gene panels represent important advancements in genetic testing of HBOC, it is clear that standardization of gene panels would help narrow the scope of testing to maximize identification of carriers and help eliminate confusion over how to handle VUS testing results.

### Compliance with Ethics Guidelines

**Conflict of Interest** Lorena Gonzalez and Laura Kruper declare no conflicts of interest relevant to this manuscript.

**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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