

## Implications of multigene testing for hereditary breast cancer in primary care

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### Abstract

Approximately 1 in 8 women will develop breast cancer during their lifetime and the risk factors include age, family history, and reproductive factors. In women with a family history of breast cancer, there is a proportion in which a gene mutation can be the cause of the predisposition for breast cancer. A careful assessment of family and clinical history should be performed in these women in order to determine if a genetic counseling referral is indicated. In cases of hereditary breast cancer, genetic testing with a multigene panel can identify specific genetic mutations in over 100 genes. The most common genes mutated in hereditary breast cancer are the high-penetrance *BRCA1* and *BRCA2* genes. In addition, other mutations in high-penetrance genes in familial cancer syndromes and mutations in DNA repair genes can cause hereditary breast cancer. Mutations in low-penetrance genes and variants of uncertain significance may play a role in breast cancer development, but the magnitude and scope of risk in these cases remain unclear, thus the clinical utility of testing for these mutations is uncertain. In women with high-penetrance genetic mutations or lifetime risk of breast cancer > 20%, risk-reducing interventions, such as intensive screening, surgery, and chemoprevention, can decrease the incidence and mortality of breast cancer.

**Key words:** Genetic testing; *BRCA1*; *BRCA2*; Hereditary breast cancer; Multigene testing

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**Core tip:** Multigene testing for hereditary breast cancer is readily available and some panels can identify over 100 gene mutations. Risk-reducing strategies are available for women with mutations in high-penetrance genes, whereas strategies for managing women with mutations in low-moderate penetrance genes is less

clear. Appropriately identifying women who should undergo genetic counseling for hereditary breast cancer and implementing recommended guidelines in those who are found to be high risk can reduce the incidence and mortality of breast cancer.

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## INTRODUCTION

Approximately 1 in 8 women will develop breast cancer during their lifetime<sup>[1]</sup>. There are many risk factors for the development of breast cancer, including increasing age, reproductive factors, and family history of breast cancer. Thirteen percent of women diagnosed with breast cancer have at least one first-degree relative with breast cancer and the risk of developing breast cancer increases with increasing numbers of affected first-degree relatives when compared to women with no affected relatives<sup>[2]</sup>. A proportion of these women develop breast cancer due to inheriting a mutated gene. This is classified as a hereditary breast cancer. Hereditary breast and ovarian cancer (HBOC) syndrome is secondary to mutations in the *BRCA1* and *BRCA2* genes and accounts for 20%-25% of breast and ovarian cancers in families with multiple affected family members<sup>[3,4]</sup>. There are several other defined syndromes associated with hereditary breast cancer, including Cowden (*PTEN* mutation), Li-Fraumeni (*TP53* mutation), Peutz-Jeghers (*STK11* mutation), and hereditary diffuse gastric cancer (*CDH1* mutations) syndromes<sup>[5]</sup>. Additionally, there are other low and moderate penetrance genes, including *PALB2*, *CHEK2*, and *ATM*, that can cause clustering of breast cancer in affected families.

Genetic testing for these gene mutations can allow for identification of these patients prior to the development of cancer. In the case of some mutations, there are interventions that can reduce breast cancer incidence and mortality in mutation carriers. Recent advances in technology allow for rapid and low cost identification of inherited mutations. While individuals can be tested for only *BRCA1/2* mutations specifically, there is also multigene testing that utilizes next generation sequencing (NGS), which can identify mutations in over 100 genes in one test<sup>[6]</sup>. Though multigene testing is readily available in the clinics and through direct-to-consumer testing<sup>[7]</sup>, the clinical utility of evaluating the large number of genes remains uncertain.

This review article will summarize the indications for genetic assessment for hereditary breast cancer, the evidence on interpretation of multigene testing results, and breast cancer risk management options for women

who are found to be carriers of mutations.

## INDICATIONS FOR GENETIC ASSESSMENT IN HEREDITARY BREAST CANCER

Several professional organizations, including the National Comprehensive Cancer Network (NCCN)<sup>[8]</sup>, the United States Preventive Services Task Force (USPSTF)<sup>[9]</sup>, the American Society of Clinical Oncology (ASCO)<sup>[7,10]</sup>, the National Society of Genetic Counselors (NSGC)<sup>[5,11]</sup>, the American College of Medical Genetics (ACMG)<sup>[11]</sup>, and the American College of Obstetricians and Gynecologists (ACOG)<sup>[12]</sup> have published guidelines regarding genetic assessment for hereditary breast cancer in cancer-free women. As part of a genetic assessment, these guidelines all emphasize the importance of genetic counseling prior to and after genetic testing by a health care provider knowledgeable in genetic testing. While the specific criteria for referral to genetic assessment vary among different organizations, the criteria are based on the clinical features and history that increase the likelihood of a hereditary breast cancer. Table 1 shows the guidelines for hereditary breast cancer genetic assessment in a woman without a cancer diagnosis as published by the NCCN, USPSTF, ASCO, NSGC, ACMG, and ACOG.

There are also specific guidelines for genetic assessment in patients who have received a diagnosis of cancer and also for men; however, these guidelines will not be discussed in this review.

## MULTIGENE TESTING FOR HEREDITARY BREAST CANCER

There are several commercially available multigene panels for hereditary breast cancer, such as BreastNext by Ambry Genetics, OncoGeneDx by GeneDx, and myRisk by Myriad Genetics, that are capable of sequencing a range of 6 to more than 100 cancer-associated genes depending on the test<sup>[6,13]</sup>. The specific genes tested in each multigene panel vary depending on the laboratory offering the testing. Some of the genes included in these panels are genes that are known to be associated with cancer syndromes with breast cancer component (*i.e.*, *BRCA1/2* for HBOC syndrome, *PTEN* for Cowden syndrome, *TP53* for Li-Fraumeni syndrome), genes shown to have a moderate risk association with breast cancer, or genes that function in DNA repair pathways with or similarly to *BRCA1/2*. However, there are concerns that other genes included in multigene panels have breast cancer risk associations that are not well established<sup>[6,13,14]</sup>. This complicates the testing of these less-established genes on three levels of uncertainty: (1) the magnitude of cancer risk associated with the gene; (2) the clinical scope of cancer risk; and (3) the clinical relevance of variants of the genes<sup>[13]</sup>.

**Table 1 Guidelines for hereditary breast cancer genetic assessment in a woman without a cancer diagnosis**

Organization	Indications for genetic assessment referral
National Comprehensive Cancer Network <sup>[8]</sup>	<p>Family history of any of the following:</p> <ul style="list-style-type: none"> <li>A known mutation in a cancer susceptibility gene within the family</li> <li>≥ 2 breast cancer primaries in a single individual</li> <li>≥ 2 individuals with breast cancer primaries on the same side of family</li> <li>≥ 1 individual with invasive ovarian cancer primary</li> </ul> <p>First- or second-degree relative with breast cancer at age ≤ 45 yr</p> <p>Three or more of the following (especially if early onset): Pancreatic cancer, prostate cancer (Gleason score ≥ 7), sarcoma, adrenocortical carcinoma, brain tumors, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations and/or macrocephaly, hamartomatous polyps of gastrointestinal tract, diffuse gastric cancer (can include multiple primary cancers in same individual)</p> <p>Male breast cancer</p>
United States Preventive Services Task Force <sup>[9]</sup>	<p>Family history of any of the following:</p> <ul style="list-style-type: none"> <li>Breast cancer diagnosis before age 50 yr</li> <li>Bilateral breast cancer</li> <li>Breast and ovarian cancer</li> <li>Breast cancer in ≥ 1 male family member</li> <li>Multiple cases of breast cancer in the family</li> <li>≥ 1 family member with 2 primary types of BRCA-related cancer</li> <li>Ashkenazi Jewish ethnicity</li> </ul> <p>OR use of a familial risk stratification tool, such as the Ontario Family History Assessment Tool, Manchester scoring system, Referral Screening Tool, Pedigree Assessment Tool, and Family History Screen 7, to determine need for genetic counseling</p>
American Society of Clinical Oncology <sup>[7,10]</sup>	<p>When all 3 criteria are met:</p> <ul style="list-style-type: none"> <li>The individual being tested has a personal or family history suggestive of genetic cancer susceptibility</li> <li>The genetic test can be adequately interpreted</li> <li>The test results have accepted clinical utility</li> </ul>
National Society of Genetic Counselors <sup>[5,11]</sup> and American College of Medical Genetics and Genomics <sup>[11]</sup>	<p>If patient or any of their first-degree relatives meet one of the following criteria:</p> <ul style="list-style-type: none"> <li>Breast cancer diagnosis at age ≤ 50 yr</li> <li>Triple-negative breast cancer diagnosis at age ≤ 60 yr</li> <li>≥ 2 primary breast cancers in the same person</li> <li>Ashkenazi Jewish ancestry and breast cancer at any age</li> <li>≥ 3 cases of breast, ovarian, pancreatic, and/or aggressive prostate cancer in close relatives, including the patient</li> <li>Breast cancer and one additional Li-Fraumeni Syndrome tumor in the same person or in two relatives, one diagnosed at age ≤ 45 yr</li> <li>Breast cancer and ≥ 1 Peutz-Jeghers polyp in the same person</li> <li>Lobular breast cancer and diffuse gastric cancer in the same person</li> <li>Lobular breast cancer in one relative and diffuse gastric cancer in another, one diagnosed at age &lt; 50 yr</li> <li>Breast cancer and 2 additional Cowden syndrome criteria in the same person</li> </ul>
American College of Obstetricians and Gynecologists <sup>[12]</sup>	<p>Women with greater than an approximately 20%-25% chance of having an inherited predisposition to breast and ovarian cancer are recommended for genetic counseling referral, including:</p> <ul style="list-style-type: none"> <li>Women with a close relative with known <i>BRCA1</i> or <i>BRCA2</i> mutations</li> </ul> <p>In women with greater than an approximate 5%-10% chance of having an inherited predisposition to breast and ovarian cancer, genetic counseling referral may be helpful, including those with a close relative that has:</p> <ul style="list-style-type: none"> <li>Breast cancer at age ≤ 40 yr</li> <li>Ovarian cancer, primary peritoneal cancer, or fallopian tube cancer of high grade, serous histology at any age</li> <li>Bilateral breast cancer (particularly if the first case of breast cancer was diagnosed at age ≤ 50 yr)</li> <li>Breast cancer at age ≤ 50 yr and a close relative with breast cancer at age ≤ 50 yr</li> <li>Ashkenazi Jewish ancestry with breast cancer at age ≤ 50 yr</li> <li>Breast cancer at any age and 2 or more close relatives with breast cancer at any age (particularly if at least one case of breast cancer was diagnosed at age ≤ 50 yr)</li> </ul>

Additionally, NGS has the potential to discover variants of uncertain significance (VUS) at high rates<sup>[15]</sup>. In a study of 198 women who met NCCN guidelines for *BRCA1/2* mutation testing, multigene testing with a panel of 42 genes was performed and participants were found to have an average of 2.1 VUS among 42 genes<sup>[16]</sup>. The high rate of VUS poses a risk of causing unnecessary anxiety and potentially interventions that are without evidence base<sup>[13]</sup>.

In families that do not have *BRCA1* or *BRCA2* mutations, it is likely that other high-penetrance genes or a

number of moderate- or low-penetrant genes account for familial breast cancer<sup>[3]</sup>. In a study in the United States, among women who met NCCN guidelines for *BRCA1/2* testing and had negative genetic testing, 11.4% had pathogenic mutations in 1 of 40 other genes<sup>[16]</sup>. A study in Germany performed multigene testing with a panel of 10 genes on 620 patients who met criteria for HBOC genetic testing and found almost 33% more mutations could be discovered with the addition of 8 genes to *BRCA1* and *BRCA2* testing<sup>[17]</sup>. The use of multigene testing could help identify mutations

that may cause the predisposition to breast cancer of the approximately 75%-80% of familial breast cancers that are not associated with *BRCA1/2* mutations.

While mutations in genes that have a well-established risk association with breast cancer, such as *BRCA1/2*, have clear clinical implications, there is uncertainty with how to interpret and communicate the results of mutations in genes with less robust evidence, as well as gene *VUS*. Genes that have evidence of an association with breast cancer are described below.

### ***BRCA1/BRCA2 (HBOC)***

*BRCA1/2* genes play a role in DNA repair and mutations in these genes are of high-penetrance. Women with a *BRCA1/2* mutation have elevated lifetime risks of breast and ovarian cancer of 40%-60% and 20%-40%, respectively<sup>[18-21]</sup>. There is also an increased risk of other cancers, such as pancreas cancer. While the prevalence of the genetic mutation is less than 1% (1 in 400) in the general population, the prevalence of a founder mutation in the *BRCA1* (5382insC or 185delAG) or *BRCA2* (6174delT) genes is up to 2.5% (1 in 40) among individuals of Ashkenazi (Central and Eastern European) Jewish descent<sup>[21,22]</sup>. There are over 2000 different known mutations in the *BRCA1/2* genes<sup>[23]</sup>. There is also evidence to suggest that there are genetic modifiers of breast cancer risk for carriers of *BRCA* mutations and that the type and location of *BRCA* mutation affects breast cancer risk<sup>[24,25]</sup>. Genetic test results are reported as positive, *VUS*, uninformative-negative, or true negative<sup>[9]</sup>. The difference between uninformative-negative and true negative is that a true negative result is when no *BRCA* mutation is found in the setting of a known *BRCA* mutation in the family<sup>[26]</sup>. In a large cross-sectional study of non-Ashkenazi women who underwent *BRCA* mutation testing, 6.2% were found to have *VUS*. Populations that are genetically distinct and/or under-tested, such as racial/ethnic minorities, will have higher rates of *VUS* when compared to the white/European reference population; however, with increased volume of testing and reclassification of *VUS*, the rates of *VUS* reporting have declined over time<sup>[27]</sup>.

### ***Genes responsible for tumor syndromes***

There are several well characterized high-penetrance hereditary tumor syndromes in which breast cancer is one manifestation of the syndrome. While the association of these syndromes with an increase in breast cancer risk is known, the exact increase in risk is difficult to estimate due to ascertainment bias<sup>[6]</sup>. Li-Fraumeni syndrome is due to a germline mutation in the *TP53* gene, a tumor suppressor gene, and is characterized by an increased risk for childhood sarcomas, brain tumors, adrenocortical carcinoma, childhood leukemia, and other cancers, in addition to breast cancer<sup>[28]</sup>. In a study assessing the cancer incidence in 56 *TP53* germline mutation carriers and 3201 non-carriers, there was a significantly higher risk of breast cancer in female *TP53* mutation carriers, with a standardized incidence ratio of 105.1

(95%CI: 55.9-179.8)<sup>[29]</sup>. Cowden syndrome, or multiple hamartoma syndrome, is due to a germline mutation in the *PTEN* gene, a tumor suppressor gene<sup>[30]</sup>. The clinical phenotype has a wide array of abnormalities, including behavioral disorders, macrocephaly, gastrointestinal hamartomas, thyroid cancer, and endometrial cancer, in addition to breast cancer<sup>[31]</sup>. The estimated lifetime risk of breast cancer in a female *PTEN* mutation carrier is 85.2%, with a standardized incidence ratio of breast cancer of 25.4 (95%CI: 19.8-32.0)<sup>[32]</sup>. Germline mutations in the *STK11* gene, another tumor suppressor gene, cause Peutz-Jeghers syndrome. This syndrome is characterized by mucocutaneous pigmentation and gastrointestinal polyposis as well as an increase in gastrointestinal, breast, ovary, uterus, lung, and testis cancers<sup>[33]</sup>. The risk of developing breast cancer in a female *STK11* mutation carrier is 45% by age 70 years, a 6-fold increase when compared to the general population<sup>[33]</sup>. Hereditary diffuse gastric cancer is due to a germline mutation in the *CDH1* gene, which encodes for the E-cadherin protein. This mutation results in an increased risk of diffuse gastric cancer, colorectal cancer, and breast cancer, specifically lobular breast cancer. In female mutation carriers, the cumulative risk of breast cancer by age 80 is 39%, with a relative risk of developing breast cancer of 6.6 when compared to the general population<sup>[34]</sup>. Finally, neurofibromatosis type 1 (NF1) is caused by a germline mutation in the *NF1* gene, which encodes for neurofibromin, and is also a tumor suppressor gene. This syndrome has a phenotype of dermatologic manifestations, vascular disease, bone deformities, cognitive difficulties, and an increased risk of neoplasms, including breast cancer<sup>[35]</sup>. Cohort studies have shown a higher than expected number of breast cancer cases in women with NF1 with an estimated relative risk of 2.6 (95%CI: 2.1-3.2)<sup>[6,35,36]</sup>.

### ***Genes involved in DNA repair***

Mutations in other genes that are involved in DNA repair, such as *PALB2*, *CHEK2*, *ATM*, and *NBN*, have also been shown to be associated with an increased risk of breast cancer and are characterized as moderate-penetrance variants. The *PALB2* gene encodes a protein that interacts with both *BRCA1* and *BRCA2* in DNA repair<sup>[37]</sup>. Several studies have shown that mutations in *PALB2* are associated with increased risk of breast cancer<sup>[38-41]</sup>. A meta-analysis found the combined relative risk to be 5.2 (95%CI: 3.0-9.4)<sup>[6]</sup>. The *CHEK2* gene encodes a kinase that responds to DNA damage. In 2 large case-control studies, a specific variant of *CHEK2*, c.1100delC, was found to increase the risk of breast cancer by an estimated relative risk of 3.0 (95%CI: 2.6-3.5)<sup>[6,42,43]</sup>. The *ATM* gene encodes a protein kinase that functions in monitoring and repairing double-strand DNA breaks. The disease ataxia-telangiectasia is caused by biallelic mutations in the *ATM* gene. A case-control study of 964 patients found that the relative risk of breast cancer associated with *ATM* mutation is 2.37 (95%CI: 1.51-3.78)<sup>[44]</sup>. The *NBN* gene encodes a protein that,

like *BRCA1* and *BRCA2*, plays a role in the homologous recombination repair pathway. In a meta-analysis of 10 case-control studies on the association of *NBN* 657del5 variants and breast cancer risk, which included 25365 subjects, the pooled odds ratio was found to be 2.66 (95%CI: 1.82-3.90)<sup>[45]</sup>.

## INTERVENTIONS FOR HIGH RISK

### PATIENTS

#### **BRCA mutation carriers**

Risk management options for women found to have *BRCA1/2* mutations have been well studied and the NCCN has published expert-opinion based guidelines for the management of these patients. The risk management options for mutation carriers include intensive breast cancer screening with clinical breast exam, mammography, and breast magnetic resonance imaging (MRI), risk-reducing surgeries such as prophylactic mastectomy and bilateral salpingo-oophorectomy, and chemoprevention.

NCCN guidelines recommend clinical breast exam every 6-12 mo starting at age 25 years, annual breast MRI or mammogram (if MRI unavailable) from age 25-29 years, and annual breast MRI and mammogram from age 30-75 years<sup>[8]</sup>. Screening with MRI should begin earlier than 25 years if there is a family history of a breast cancer diagnosis prior to age 25 years<sup>[8]</sup>. In a meta-analysis of 11 prospective studies that screened women at high risk for breast cancer with mammography and MRI, the sensitivity of MRI was greater than mammography (77% vs 39%), but specificity of mammography greater than MRI (94.7% vs 86.3%). When mammography was combined with MRI, sensitivity was 94% and specificity was 77.2%<sup>[46]</sup>. In *BRCA1/2* mutation carriers, annual surveillance with MRI is associated with a significant reduction in advanced-stage breast cancer<sup>[47]</sup>.

With regards to risk reducing surgery, NCCN guidelines recommend counseling *BRCA* mutation carriers on risk-reducing mastectomy (RRM) and risk-reducing salpingo-oophorectomy (RRSO)<sup>[8]</sup>. In a prospective cohort study of 1619 *BRCA1/2* mutation carriers, of the 247 women who underwent RRM, none developed breast cancer, while there were 98 cases of breast cancer in the 1372 women who did not have surgery<sup>[48]</sup>. NCCN guidelines recommend RRSO between the ages of 35-40 and upon completion of childbearing<sup>[8]</sup>. RRSO resulted in 72%-86% reduction in risk of ovarian cancer, 37% reduction in risk of breast cancer in *BRCA1* carriers, and a 64% reduction in risk of breast cancer in *BRCA2* carriers<sup>[48]</sup>. Mutation carriers who underwent RRSO compared to those who did not had a 79% reduction in ovarian cancer-specific mortality, 56% reduction in breast cancer-specific mortality<sup>[48]</sup>, and a 60%-77% reduction in all-cause mortality<sup>[48,49]</sup>.

The use of tamoxifen, raloxifene, and aromatase inhibitors has been studied as chemoprevention in

women at high risk for breast cancer, though data in *BRCA1/2* mutation carriers is limited. The Breast Cancer Prevention Trial was a randomized placebo-controlled trial investigating whether tamoxifen reduces the incidence of breast cancer in high-risk women and found a 49% reduction in the incidence of breast cancer with the use of tamoxifen<sup>[50,51]</sup>. Of the 288 breast cancer cases in the trial, 19 were *BRCA* mutation carriers. Analysis showed that tamoxifen reduced breast cancer incidence among *BRCA2* carriers by 62%, but had no effect on breast cancer incidence in *BRCA1* carriers<sup>[52]</sup>.

#### **Negative BRCA1/2 testing**

Despite negative *BRCA1/2* testing, families with a significant family history of breast cancer still have an approximately 4-fold increased risk of breast cancer<sup>[26]</sup>. In these women, there are still interventions available that can decrease the risk of developing breast cancer. In women with a greater than 20% lifetime risk of breast cancer, either as calculated by a risk model or due to the presence of a high- or moderate-penetrance mutation (*i.e.*, *ATM*, *CDH1*, *CHEK2*, *PALB2*, *PTEN*, *STK11*, or *TP53*), NCCN guidelines recommend intensive screening with MRI<sup>[8]</sup>. Additionally, for women with *CDH1*, *PTEN*, or *TP53* mutations, option of RRM should also be discussed<sup>[8]</sup>.

In women who have a 5-year breast cancer risk  $\geq 1.67\%$  or lifetime breast cancer risk  $\geq 20\%$ , chemoprevention is also an option. There is evidence that in this high risk population, tamoxifen, raloxifene, and aromatase inhibitors can decrease the incidence of breast cancer by approximately 50%, 40%, and 65%, respectively<sup>[51,53-55]</sup>.

## CONCLUSION

Women with a family history of breast or ovarian cancer should be screened for referral to genetic assessment for hereditary breast cancer. Advances in NGS have made multigene testing for hereditary breast cancer readily available; however, there remain questions about the clinical utility of such testing. For high- and moderate-penetrance mutations, there is greater clinical utility as there are established guidelines on risk management interventions that can be performed to reduce incidence and mortality from breast cancer.

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