



Consensus Guideline on Hereditary Genetic Testing for Patients With and Without Breast Cancer

Purpose: To outline an approach to hereditary cancer genetic testing for patients with and without breast cancer

Associated ASBrS Guidelines or Quality Measures:

1. BRCA Genetic Testing for Patients With and Without Breast Cancer, September 13, 2016.
2. BRCA Genetic Testing for Patients With and Without Breast Cancer, September 30, 2012.
3. BRCA Genetic Testing for Patients With and Without Breast Cancer, June 12, 2006

Methods: Literature review included large datasets, basic science publications, and recent updated national guidelines. This is not a complete systematic review, but a comprehensive review of the modern literature on this subject. Pending Approval: The ASBrS Research Committee developed a consensus document that was reviewed and approved by the ASBrS Board of Directors.

Summary of Data Reviewed:

Indications

In 2016, more than 245,000 new cases of breast cancer will be diagnosed in the United States, and more than 40,000 patients will die from breast cancer.¹ Approximately 5-10% of breast cancer is associated with a hereditary predisposition from an inherited germline mutation², with 50% of mutations occurring in the *BRCA1* and *BRCA2* genes.³⁻⁸ Identifying patients who are mutation carriers may reduce the risk of future cancer and may prevent death from cancer through risk-reducing interventions.⁹⁻¹⁷ While mutations in *BRCA1*, *BRCA2*, and other hereditary cancer predisposition genes are rare in the general population, occurring in 1 per 400-800 individuals or less, an individual with a personal and family history with high-risk characteristics can help identify patients more likely to be mutation carriers.¹⁸⁻²⁰

Breast surgeons are ideally positioned to identify high-risk individuals, encourage and provide access for hereditary cancer genetic testing, and propose individualized management strategies for those patients who test positive.²¹⁻²² In many areas of the country, breast surgeons can fill the unmet need for appropriate counseling of these high-risk patients. Breast surgeons can also identify patients at high risk for other hereditary breast cancer syndromes, such as Li-Fraumeni syndrome (TP53 mutation), Cowden syndrome (PTEN mutation), and *ATM* carriers.²³⁻²⁵ This knowledge can influence radiation therapy as well as chemotherapy decisions.⁵¹⁻⁵³

The following personal and/or family characteristics suggest a high-risk individual who would be a candidate for genetic testing.²⁶⁻³²

- a. Age onset of breast cancer ≤ 50
- b. Triple-negative tumor (ER-PR-HER2-) and age ≤ 60
- c. Ashkenazi Jewish heritage and breast cancer at any age
- d. Two or more primary breast cancers (cancers can be asynchronous, synchronous, bilateral, or multicentric)
- e. First-degree relative with breast cancer age ≤ 50
- f. Two relatives on the same side of the family with breast cancer and/or pancreatic cancer
- g. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
- h. Male breast cancer
- i. Known mutation carrier in the family

Risk Assessment Tools

In addition to National Comprehensive Cancer Network (NCCN) guidelines for identifying patients appropriate for genetic testing,²⁶ there are numerous models and online calculators available to predict the likelihood of carrying a *BRCA1* or *BRCA2* mutation based on family and personal history.^{33,34} In general, patients with a 5-10% or greater likelihood of carrying one of these genes is recommended to consider testing and/or genetic counseling.³⁵

Online Risk Models: (not an exclusive list of all calculators)

BRCA Risk Calculator: https://www.breastsurgeons.org/new_layout/programs/mastery/risk.php

B-RST: <https://www.breastcancergenescreen.org/default.aspx>

Penn II Risk Model: <http://www.afcri.upenn.edu/itacc/penn2/>

Implications

Identifying a mutation in a hereditary cancer predisposition gene has implications for patients and their families. Before testing, patients need to be made aware of these implications (*pre-test counseling*) and when results become available, patients should be reminded of these implications and appropriate interventions and consultations should be recommended (*post-test counseling*).^{21, 26, 35}

The following is a list of pathogenic mutations in hereditary cancer genes with current NCCN guidelines for clinical management:²⁶

Guidelines accessed December 9, 2016. The current version of the guidelines is available online at https://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf.

Gene	Risk	Breast Management Options*
<i>BRCA1</i>	Breast cancer (up to 67%) Contralateral breast cancer (up to 30%) Ovarian cancer (up to 45%) ⁵⁰	Annual breast MRI (start age 25) Annual mammogram (start age 30) Risk-reducing bilateral mastectomy
<i>BRCA2</i>	Breast cancer (up to 66%) Contralateral breast cancer	Annual breast MRI (start age 25) Annual mammogram (start age 30)

	(up to 30%) Ovarian cancer (up to 12%) Male breast cancer Prostate cancer Pancreatic cancer ⁵⁰	Chemoprevention Risk-reducing bilateral mastectomy
<i>TP53</i>	Breast cancer Soft tissue sarcomas Osteosarcomas Brain tumors Adrenocortical carcinoma Multiple primary tumors	Annual breast MRI (start age 20) Annual mammogram (start age 30) Risk-reducing bilateral mastectomy
<i>PALB2</i>	Breast cancer (33%, but 58% with 2 first-degree relatives) Pancreatic cancer Male breast cancer	Annual breast MRI (start age 30) Annual mammogram (start age 30) Risk-reducing bilateral mastectomy
<i>CDH1</i>	Breast cancer (39% of lobular carcinoma) Gastric cancer Colorectal cancer	Annual breast MRI (start age 30) Annual mammogram (start age 30) Risk-reducing bilateral mastectomy
<i>PTEN</i>	Breast cancer Thyroid cancer Endometrial cancer Colorectal cancer Kidney cancer	Annual breast MRI (start age 30) or 5-10 years before youngest patient with breast cancer Annual mammogram (start age 30) Risk-reducing bilateral mastectomy
<i>CHEK2</i>	Breast cancer (20%, but increases with 44% with first- and second-degree relatives) 30% risk of contralateral breast cancer Male breast cancer Colon cancer Prostate cancer Thyroid cancer Kidney cancer	MRI (start age 40) Annual mammogram Risk-reducing bilateral mastectomy based on family history
<i>ATM</i>	Breast cancer (rare mutations with a 40-60%)	Annual breast MRI (starting at age 40) Annual mammogram Discuss risk-reducing mastectomy based on family history
<i>STK-11</i>	Breast cancer Ovarian cancer Colorectal cancer Duodenal cancer Pancreatic cancer	Annual breast MRI (start age 30) Annual mammogram (start age 30)
<i>NF1</i>	Breast Cancer before age 50 GIST	Annual breast MRI (start age 30-50) Annual mammogram (start age 30)

<i>NBN</i>	Breast Cancer	Annual breast MRI (start age 40) Annual mammograms
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*Guidelines are also available on screening and prophylaxis for non-breast-affected organs.

In addition to the breast-management recommendations above, prophylactic oophorectomy has been shown to reduce the risk of breast cancer by more than 50% in premenopausal women with *BRCA2* mutation, with less benefit to those patients with a *BRCA1* mutation.^{9,10,16,36} Patients with *BRCA1* or *BRCA2* mutations should consider prophylactic bilateral salpingo-oophorectomy after child-bearing or between the ages of 35-40 to reduce ovarian and fallopian tube cancer risk.

Limitations

There are limitations to genetic testing. Patients should be aware that negative test results do not eliminate the risk of developing breast cancer, even in a family with a known mutation. The probability of false negative results can be as high as 6-8% when the criterion is a 10% mutation probability estimated by genetic counselors or the computer model BRCAPRO.⁵⁴ In patients with no known family mutation, a negative test does not change the patient's risk of developing breast cancer from the risk before testing. In a patient with a known family mutation, the patient who tests negative has a risk similar to the general population or higher depending on both maternal and paternal lineages. Not all mutation carriers will develop breast cancer, regardless of intervention chosen or not chosen, due to the variable penetrance of some gene mutations and other possible environmental interactions.^{5,18,19} The BRCA Decision Tool, <http://brcatool.stanford.edu/brca.html>, can be useful to known BRCA mutation carriers to predict likelihood of developing breast or ovarian cancer and likelihood of dying from either disease based on patient age and a variety of interventions chosen for screening and prophylaxis.³⁷ Lastly, not all cancer predisposition genes are known or completely understood, and further information pertinent to a patient's test may become available years later.^{4,5,7}

Certified Genetic Counselors

The American College of Surgeons Commission on Cancer accreditation program mandates that cancer risk assessment, genetic counseling, and genetic testing services be provided to patients by a qualified genetic professional either on site or by referral.⁵⁵ A systematic review of the literature concluded that genetic counseling, whether by a geneticist, breast surgeon, oncology nurse, or other person with expertise and experience in cancer genetics, reduces distress, improves risk perception, and reduces intention for testing.⁵⁶ While breast surgeons can initiate and guide genetic testing for their patients, board-certified genetic counselors (CGCs), when available, may be beneficial for further counseling and recommendations. For families with more complex cancer histories, a CGC may help determine extent of testing, identify family members to be tested, and provide further guidance beyond that of a breast surgeon.

This is especially important when identifying cancer risk in non-breast tissues such as ovaries, thyroid, stomach, and colorectal.^{22,24,31,38,39} A CGC can provide a strategy for surveillance and intervention and often provides resources to patients undergoing the recommended regimen. Furthermore, when patients are found to carry a pathogenic mutation or a variant of uncertain significance (see below), a CGC may help guide additional family testing and screening.

Multi-Gene Panel Testing

Genetic testing has expanded recently due to improved technology with next-generation sequencing and more access to testing options.⁴⁰⁻⁴⁴ While *BRCA1* and *BRCA2* remain the most likely genes to be mutated in a family with high breast and ovarian cancer risk, there are now more than two dozen genes that can be tested either in sequence or simultaneously with BRCA testing that also confer hereditary cancer risk to a variable degree.^{3,6,21,45-48} Numerous recent studies have shown that panel testing can significantly increase the rate of detection of pathogenic mutations, with the most frequently identified mutations being in *PALB2*, *CHEK2*, and *ATM*.^{3,21,47} Of concern with this newer application of testing is that many genes with mutations do not yet have standard management guidelines available due to limited available data.²⁶ Furthermore, many genes found on panels, such as *CHEK2* and *ATM*, will have a low-to-moderate penetrance, meaning that many carriers will not express the malignant phenotype. This poses challenges for creating reliable management guidelines; however, much of this will likely be overcome in time as data accumulate.^{21,40,45}

Breast surgeons can consider panel testing for patients who qualify for hereditary breast cancer testing to more efficiently and cost-effectively evaluate genes that confer risk and affect management recommendations.²⁶ This approach is not only more efficient in evaluating patients at risk compared to sequential gene sequencing (i.e., evaluating BRCA mutations first, then selecting additional genes if BRCA tests are negative), but it is also more cost-effective.^{4,22,48} Insurance companies are urged to incorporate these advantages of panel testing into the algorithm of allowed hereditary cancer genetic testing for patients at high risk. The panel chosen may depend on family cancer history (if a pattern of cancers emerges that is suitable for Cowden's syndrome, then a panel that includes PTEN, for example, may be considered), test availability, and insurance coverage.

Variant of Uncertain Significance (VUS)

In the process of genetic testing, VUSs will be identified. These are DNA polymorphisms that are neither confirmed benign nor pathogenic, with the majority eventually re-classified as benign.^{45,49} The American College of Medical Genetics has published guidelines for reporting DNA sequence variations.⁵⁷ The rate of identifying VUSs will be high initially with newer genes and then will decrease as data accrue over time. Current reported rates of identifying a VUS with newer multi-gene panel testing range from 6.7-41.7%.^{21,45-47} There are still VUSs identified with BRCA testing. However, the rates are generally much lower, ranging from 2-5%, now that testing of these two genes has been available for nearly 20 years.

ASBrS Recommendations for Genetic Testing:

1. **Breast surgeons, CGCs** and other trained cancer-liaison staff with in-depth knowledge of genetic testing indications, implications, and limitations can provide genetic testing services and recommendations to their patients. Use of specialized risk-assessment services and certified genetic counselors when patient history and test results are more complex is encouraged. Testing qualified patients can include *BRCA1* and *BRCA2* only, or additional genes (i.e., panel testing) related to hereditary breast cancer, so long as it is within guidelines, and the provider feels comfortable with recommendations.

- 2. Patients with a personal history of breast cancer:** Always obtain information about family history of cancer. Ideally, a three-generation pedigree including maternal and paternal lineage should be obtained. This information can be used to guide the type of testing to be performed and the selection of patients who may benefit from further counseling with a CGC. Patients with a personal history of breast cancer meet criteria for genetic testing with any of the following characteristics:
- a. Age onset of breast cancer ≤ 50
 - b. Triple-negative tumor (ER-PR-HER2-) and age ≤ 60
 - c. Ashkenazi Jewish heritage and breast cancer at any age
 - d. Two or more primary breast cancers (cancers can be asynchronous, synchronous, bilateral, or multicentric)
 - e. First-degree relative with breast cancer age ≤ 50
 - f. Two relatives on the same side of the family with breast cancer and/or pancreatic cancer
 - g. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
 - h. Male breast cancer
 - i. Known mutation carrier in the family
- 3. Patients without a personal history of breast cancer:** Patients should be made aware that testing an affected relative first when available can be more informative than testing themselves since a negative result will not give them more insight into their family history. If an affected relative is not available, patients should be reminded of limitations of testing. Ideally, a three-generation pedigree including maternal and paternal lineage should be obtained. This information can be used to guide the type of testing to be performed and the selection of patients who may benefit from further counseling with a CGC. Patients without a personal history of breast cancer meet criteria for genetic testing for the following family history:
- a. First- or second-degree relative with early age onset of breast cancer ≤ 45
 - b. Ashkenazi Jewish heritage and family history of breast cancer at any age
 - c. Two or more primary breast cancers (cancers can be asynchronous, synchronous, bilateral, or multicentric) in a single family member
 - d. Two or more relatives on the same side of the family with breast cancer and/or pancreatic cancer
 - e. Family or personal history of ovarian cancer, fallopian cancer, or primary peritoneal cancer
 - f. Male breast cancer
 - g. Known mutation carrier in the family

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This statement was developed by the Society's Research committee, and on March 14, 2017, was approved by the Board of Directors.