



## **Position Statement on BRCA Genetic Testing for Patients With and Without Breast Cancer**

### **Introduction**

Of the more than 200,000 breast cancers diagnosed annually in the United States, 5-10% are associated with obvious hereditary predisposition, which is mostly related to autosomal dominant mutations of the BRCA1 and BRCA2 genes. BRCA1/2 mutations confer an increased lifetime risk for the development of breast cancer (up to 80%), contralateral breast cancer (about 30% at 10 years), ovarian cancer (up to 40% for BRCA1 and 20% for BRCA2), and other cancers. BRCA mutations are rare in the general population, occurring in 1 per 400-800 individuals, but high-risk populations exist and include persons with the following:

- Early onset breast cancer (diagnosed before age 50)
- Two primary breast cancers, either bilateral or ipsilateral
- Family history of early onset breast cancer
- Male breast cancer
- Personal or family history of ovarian cancer (particularly nonmucinous types)
- Ashkenazi (Eastern European) Jewish heritage in the setting of a newly diagnosed breast cancer or family history of breast cancer
- A previously identified BRCA1 or BRCA2 mutation in the family
- “Triple negative” (ER-, PR-, Her2 normal) breast cancer diagnosed prior to age 60.
- Pancreatic cancer associated with a family history of hereditary breast and ovarian related

Any one of these features alone indicates a risk for harboring a BRCA1 or BRCA2 mutation, therefore, these patients should be counseled and have access to BRCA testing. A simple risk-calculation model based on the prevalence of mutations seen among women tested for BRCA mutations is available at <http://www.brcacalculator.com>.

Breast surgeons are in an ideal potential position to identify high-risk individuals, encourage and provide access for BRCA testing, and propose individualized management strategies for those patients who test positive. 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 the patients at high risk for other hereditary breast cancer syndromes, such as Li-Fraumeni syndrome (TP53 mutation) and Cowden syndrome (PTEN mutation).

### **Patient Education**

Patient education, which serves as the basis for informed consent by any patient, is currently provided in either of the following settings:

- Within the treating physician's practice
- By referral to an established genetic risk assessment program

Both approaches have been employed with success and have advantages and disadvantages. Physicians providing such patient education within their practice must have in-depth knowledge of the underlying

clinical biology, psychosocial considerations, insurance implications, as well as breast cancer-specific genetic counseling skills, all of which are beyond the scope of this document.

**Informed consent should be obtained prior to genetic testing. Relevant issues include the following:**

- A comprehensive family history, including evaluation of maternal and paternal lineage.
- Cancer risks associated with BRCA mutations.
- Medical and surgical management options for mutation carriers, including surveillance and chemoprevention, as well as prophylactic surgery.
- Information about testing, including types of possible test results. This should involve a discussion of the implications of a positive, negative, or inconclusive result. Of particular importance is properly interpreting a negative result in a patient without a previously identified mutation in the family, since this result significantly reduces but does not entirely eliminate the chance of a BRCA mutation. For example, patients with a very strong family history (3 or 4 relatives affected) may still have a clinical diagnosis of a hereditary cancer syndrome but current technology cannot detect the mutation.
- Medical and ethical implications of the decision to share information with at-risk relatives if a deleterious mutation is detected, or the decision not to be tested.
- Implications and potential for testing other family members if the result is positive.
- Insurance eligibility. With few exceptions, health insurance carriers in the U.S. are prohibited from discriminating against a patient based on a genetic test result. Life insurance carriers, on the other hand, suffer no such restrictions. Obviously, these considerations have less impact for a patient already diagnosed with breast cancer than for one with no such history.

Some patients may find that the decisions surrounding genetic testing are intellectually or emotionally overwhelming. In this setting, consultation with an experienced clinical geneticist can be particularly helpful.

### **Patients With Breast Cancer**

Patients with breast cancer who are at significant risk for harboring a BRCA mutation may undergo testing prior to definitive surgery. Many, but not all patients with a BRCA mutation will choose mastectomy plus contralateral prophylactic mastectomy over lumpectomy. For patients who choose breast conservation, careful surveillance, including breast MRI, and other risk-reducing strategies should be employed.

The patient may await BRCA test results before surgical treatment or elect to proceed with lumpectomy or unilateral mastectomy before results are available. Other patients may elect to defer testing until some time in the future.

If the informed patient chooses to proceed with breast conservation prior to the return of test results, one tested strategy is to defer radiation treatment until results can be discussed. These patients are thereby afforded a chance to finalize the decision for breast conservation or choose bilateral mastectomy with more complete information.

For mutation-positive women who choose breast conservation, tamoxifen has been found to reduce the risk of recurrence and contralateral breast cancer by at least 50%, regardless of estrogen receptor status of the index breast cancer. The risk reduction of tamoxifen is found predominantly in BRCA2 carriers, as compared to BRCA1 carriers. Moreover, 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. Tamoxifen does not appear to add protection in patients who have undergone premenopausal oophorectomy.

Mutation-positive women should consider prophylactic bilateral salpingo-oophorectomy to reduce ovarian and fallopian tube cancer risk. Timing depends on the age and reproduction desires of the patient. It is recommended that the patient consider a prophylactic bilateral salpingo-oophorectomy between the ages of 35 and 40. The timing of surgery, if appropriate for the patient, can occur concurrently with her breast cancer surgery.

Systemic adjuvant therapy for hereditary breast cancer is based on conventional criteria. BRCA1-related breast cancers have a higher incidence of triple-negative breast cancers (ER/PR-negative, and Her2-normal), while BRCA2-related tumors have characteristics similar to those of nonhereditary disease. It remains unclear whether BRCA mutations adversely affect survival independently of other criteria.

Increasingly, cancer patients are undergoing genomic testing through high-throughput SNP genotyping, or next-generation sequencing. These assays are often done to assess somatic tumor mutations, but they may also identify deleterious germline BRCA mutations. It is important that both patients and treating clinicians are aware of limitations of these assays, including the risk false negative and false positive testing. Genetic counseling and formal genetic testing is recommended for clinical-decision-making.

### **Patients Without a Diagnosis of Breast Cancer**

If a woman without a personal history of cancer seeks BRCA testing due to a high calculated personal risk, it is preferred to test one of her close relatives who has been diagnosed with breast cancer. This testing can establish whether the given familial pattern is actually associated with a BRCA mutation. If the affected family member has no BRCA mutation, the familial pattern in question can be assumed to be due to other genes and the family and the patient will continue to be managed as a high-risk group. On the other hand, for a woman whose affected family member carries a known BRCA mutation, a negative test means she has only ordinary risk for developing breast cancer and can thus avoid high-risk management. When an unaffected patient with no established familial BRCA mutation is tested, only a positive result can provide useful information. If no willing or living affected relative can be tested, a negative test does not provide information about an unaffected high-risk patient's true breast cancer risk; she will still be managed as high-risk based on her family history.

An informed patient without a diagnosis of breast cancer who is found to carry a deleterious BRCA mutation will want to be counseled on her options, which include close surveillance or medical and surgical risk-reduction strategies. In premenopausal patients, prophylactic bilateral salpingo-oophorectomy decreases ovarian and fallopian tube cancers and has the added benefit of reducing breast cancer risk by more than 50%, even if low-dose estrogen replacement is used to control postoperative menopausal symptoms. The breast cancer risk reduction is predominately seen in BRCA2 patients. Tamoxifen treatment results in a similar breast cancer risk reduction in premenopausal patients with intact ovaries, as well as in patients who have undergone natural menopause where the impact is higher in BRCA2 carriers compared to BRCA1 carriers. Carriers who retain breast tissue may be offered intensive breast cancer surveillance, including annual mammography, annual breast MRI, and clinical breast exam every 6 months. While most patients without a breast cancer diagnosis do not choose bilateral prophylactic mastectomy, those who do achieve a greater than 90% reduction in breast cancer risk.

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