



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

### **INTRODUCTION**

Of the more than 200,000 breast cancers occurring in the US each year, 5-10% are associated with obvious hereditary predisposition, and most of these are related to autosomal dominant mutations of the BRCA1 and BRCA2 genes<sup>1,2</sup>. BRCA1/2 mutations confer an increased lifetime risk for the development of breast cancer (about 80%), contralateral breast cancer (about 40%), ovarian cancer (about 40% for BRCA1 and 20% for BRCA2), and other cancers (much less often). BRCA mutations are rare in the general population, occurring in 1 in 400-800 individuals, but high risk populations exist and include persons with:

1. early onset breast cancer (diagnosed before age 50)
2. two primary breast cancers, either bilateral or ipsilateral
3. a family history of early onset breast cancer
4. male breast cancer
5. a personal or family history of ovarian cancer (particularly non-mucinous types)
6. Ashkenazi (Eastern European) Jewish heritage
7. a previously identified BRCA1 or BRCA2 mutation in the family

Any one of these features alone indicates a risk for harboring a BRCA1 or BRCA2 mutation, commonly termed Hereditary Breast and Ovarian Cancer Syndrome (HBOC). The presence of more than one of these features raises that risk to greater than 10%, the traditional cutoff for recommending a BRCA test. Such patients should 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 position to identify such high-risk individuals, to encourage and provide access for BRCA testing, and, most importantly, to help devise individualized management strategies for those who test positive.

### **PATIENT EDUCATION**

Patient education, which serves as the basis for informed consent by any patient, is currently provided in either of two settings: within the treating physician's practice or by referral to an established genetic risk assessment program. Both approaches have been employed with success and both have advantages and disadvantages. Physicians who provide 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:**

1. A comprehensive family history
2. Cancer risks associated with BRCA mutations
3. Medical and surgical management options for mutation carriers, including surveillance and chemoprevention as well as prophylactic surgery
4. 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 HBOC. For example, patients with a very strong family history (3 or 4 relatives affected) may still have a clinical diagnosis of HBOC since there is a small chance the genetic testing did not identify a mutation that is undetectable with current technology.
5. Testing for other family members if the result is positive.
6. 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.
7. 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, under ideal circumstances. 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 may be employed.

The patient may desire BRCA test results before surgical treatment or she may choose 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. (This apparent paradoxical prevention of estrogen receptor negative breast cancer is not seen in non-carriers). Moreover, prophylactic oophorectomy has been shown to reduce the risk of breast cancer by more than 50% in premenopausal women with BRCA mutations. Tamoxifen does not appear to add protection in patients who have undergone premenopausal oophorectomy.

Mutation positive women should consider prophylactic oophorectomy to reduce ovarian cancer risk, usually after management of the index breast cancer is complete. This is important due to the combination of high risk and the lack of effective surveillance measures to identify ovarian cancers at an early, treatable stage.

Systemic adjuvant therapy for hereditary breast cancer is based on conventional criteria. BRCA1-related breast cancers tend to be high grade, ER/PR-negative, and her2-negative, while BRCA2-related tumors have characteristics similar to those of non-hereditary disease. It remains unclear whether BRCA mutations adversely affect survival independently of other criteria.

## **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 makes sense to first test one of her close relatives who has been diagnosed with breast cancer. This 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; 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 there is no willing or living affected relative to 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 consider oophorectomy after child-bearing is complete, since even intensive screening for ovarian cancer is not effective in this setting. In premenopausal patients prophylactic oophorectomy has the added benefit of reducing breast cancer risk by more than 50%, even if low-dose estrogen replacement is used to control postoperative symptoms. 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. Carriers who retain breast tissue may be offered intensive breast



cancer surveillance, including breast MRI. 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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Approved, June 12, 2006,  
Board of Directors,  
The American Society of Breast Surgeons