Genetic Testing for Hereditary Breast Cancers: A Story of Missed Opportunities

The story of genetic testing is largely a story of missed opportunity. It is estimated that there are nearly 350,000 BRCA 1 and BRCA 2 mutations carriers in the U.S., but only 50,000 (about 14%) have been identified as carriers of this potentially life-threatening diagnosis. Included among the 350,0000 BRCA 1/2 carriers are 200,000 women who have already been treated for breast and/or ovarian cancer but are completely unaware that they are also carriers of a BRCA 1/2 mutation, which leaves them at a markedly increased risk of another BRCA-related cancer.

The missed opportunity for detection of BRCA1/2 mutations is only part of the story. Indeed, there are at least seven (7) other major mutations that account for the majority of hereditary breast cancers (Table 1). Altogether, these hereditary breast cancer mutations account for 1 of every 10 breast cancers diagnosed today. Ironically, each of these breast cancers could be prevented if the individual were given the opportunity to be diagnosed as a mutation carrier before they develop breast cancer.

Table 1. Overview of Major Hereditary Breast and Ovarian Cancer Predisposition Syndromes

Gene	Clinical Syndrome	Breast and Ovarian Cancer Risk	Other Cancer Risks
BRCA1	Hereditary breast and ovarian cancer	Lifetime breast cancer risk: 57% Lifetime ovarian cancer risk: 40%	Prostate (five- to ninefold increase), pancreatic (two- to fourfold increase), colorectal, skin (melanoma), endometrial, gastric, and biliary cancers
BRCA2	Hereditary breast and ovarian cancer	Lifetime breast cancer risk: 57% Lifetime ovarian cancer risk: 18% Increased risk of second primary breast and male breast cancer	
STK11	Peutz-Jeghers	Lifetime breast cancer risk: 55% Lifetime ovarian cancer risk: 55%	Colon and rectal, stomach, small intestine, and pancreatic cancers
TP53	Li-Fraumeni	Lifetime breast cancer risk: 50%	Sarcomas, brain cancer, leukemias, and adrenocortical cancers
PTEN	Cowden	Lifetime breast cancer risk: 85.2%	Endometrial and thyroid cancer
MLH1, MSH2, MSH6, PMS2, EPCAM	Hereditary nonpolyposis colorectal cancer	Lifetime ovarian cancer risk: 4%–12%	Colon (52%–82% lifetime risk), endometrial (25%–60% lifetime risk), and gastric cancer
CHEK2	Hereditary breast cancer	Lifetime breast cancer risk: 37% Increased risk of second primary breast cancer	Colorectal, prostate, male breast, thyroid, and kidney cancer
PALB2	Hereditary breast cancer	Lifetime breast cancer risk: 33%–58% Increased risk of ovarian cancer	Pancreatic and prostate cancer
ATM	Ataxia-telangiectasia (in biallelic carriers)	Twofold increase in the risk of breast cancer (in monoallelic carriers) compared with the general population	Leukemias and lymphomas

The opportunity for prevention also extends to a carrier's blood relatives, each of whom has a 50:50 chance of carrying an identical hereditary mutation as their relative. Thus, every missed opportunity to detect a mutation carrier leads to a sequence of missed opportunities to screen blood relatives for the same mutation. A crucial aspect of genetic testing is offering "cascade testing" to blood relatives so that they, too, can be offered risk-reduction and/or early-detection.

Although the focus of this article is on hereditary breast cancer mutations, it is well recognized that breast cancer gene mutation carriers may also be at an increased risk of other types of cancers (Table 1). Consequently, failure to detect a hereditary breast cancer mutation might deprive the carrier of the benefit of knowing that she/he has an increased risk of other potentially preventable cancers.

Why have so many mutation carriers remained undiagnosed?

There are several reasons that 86% of breast cancer gene mutations remain undiagnosed. The main reason is that people are unaware of the personal and family history risk factors that suggest that they might be a gene mutation carrier and that indicate that genetic testing would be appropriate. The indications for breast cancer genetic testing are updated regularly by the National Comprehensive Cancer Network (NCCN), which provides genetic testing guidelines for those who would benefit from genetic testing due to personal and/or family history of cancer (Table 2 and Table 3).

Table 2. Indications for genetic testing for those with a personal history of cancer
An individual with current or prior diagnosis of any of the following at any age:
➢ Ovarian cancer
➢ Male breast cancer
➢ Pancreatic cancer
➢ Metastatic prostate cancer
➢ Breast cancer or high-grade prostate cancer and Ashkenazi Jewish ancestry
➢ Pancreatic cancer
An individual with a current or past history of breast cancer meeting any of the following criteria:
➢ Breast cancer diagnosis age 50 years or younger
➢ Triple-negative (ER-, PR-, HER2-) breast cancer diagnosed age 60 years and younger
➢ Two breast cancers (e.g., bilateral breast cancer and recurrence in a different quadrant of the same breast)
➢ Breast cancer at any age plus any of the following:
o One or more 1st, 2nd, or 3rd degree relatives with breast cancer age 50 years and younger
o Invasive ovarian cancer
o Male breast cancer
o Pancreatic cancer
o High-grade or metastatic prostate cancer
o Two or more 1st, 2nd, or 3rd relatives with breast cancer at any age

A key reason that people often underestimate their cancer risk is that they only consider their maternal family history when evaluating their risk of hereditary breast cancer. In fact, paternal family history is of equal importance. Another mistake is that they include only *first* degree (parents, siblings, offspring) family history of cancer when considering their risk. However, for individuals who have already been diagnosed with breast cancer or ovarian cancer, family history assessment should factor in not only first degree (parents, siblings, offspring) relatives, but also second degree (uncles, aunts, nephews, nieces, grandparents, grandchildren, half-siblings, and double cousins) and third degree (great-grandparents, great grandchildren, great uncles/aunts, and first cousins) family members. For those who have not been personally diagnosed with breast or ovarian cancer, family history assessment should factor in first and second degree family history but not third degree. The challenges of assessing family history is magnified by the tendency of individuals to remain private about their personal health history, thus withholding vital family history that might influence whether or not a relative is advised to undergo genetic testing. Therefore, it is imperative that family members share their cancer history with other family members so that no opportunities for genetic testing are missed. Now is a great time to start or continue that conversation.

Table 3. Indications for genetic testing for those with a family history of cancer, but NO personal history of cancer
An individual with a 1st or 2nd degree family history of the following:
➢ Breast cancer age 45 years and younger
➢ Ovarian cancer
➢ Male breast cancer
➢ Pancreatic cancer
➢ Metastatic prostate cancer
➢ Two or more breast cancers with bilateral breast cancer
➢ Two or more individuals with breast cancers on the same side of the family age 50 years and younger
An individual with a family history of 3 or more of following cancers on the same side of the family (personal history can also be counted)
➢ Breast cancer, sarcoma, brain tumor, leukemia, adrenal gland cancer
➢ Colon cancer, uterine (endometrial) cancer, thyroid cancer, kidney cancer
➢ Lobular breast cancer, gastric (stomach) cancer

Even when properly assessed, we now know that personal and family history do not identify everyone who would benefit from genetic testing. The limits of the NCCN guidelines for identifying cancer mutations carriers were recently demonstrated by a study that examined the frequency of hereditary cancer mutations among breast cancer patients who did not meet NCCN criteria for genetic testing. As it turns out, the study found no significant difference in the frequency of harmful hereditary cancer mutations comparing those that met NCCN criteria to those that did not meet NCCN criteria. Consequently, a newly released consensus guideline from the American Society of Breast Surgeons calls for universal genetic testing for all women and men currently or previously affected by breast cancer.

Are there any insurance barriers to genetic testing?

Expanded indications for genetic testing have overcome many of the insurance coverage barriers to genetic testing. However, not all health plans have embraced the idea of universal genetic testing. Fortunately, recent developments in genetic testing technology and competition among multiple genetic testing companies have reduced the cost of genetic testing from $2,000-5,0000 to under $300, such that most patients are able to afford the out-of-pocket cost of genetic testing, even if coverage is denied by their health plan. Genetic testing companies have also made efforts to facilitate testing. For example, in response to the American Society of Breast Surgeon's consensus statement, one company now offers free genetic testing to anyone currently or previously diagnosed with breast cancer, whereas another company offers free cascade testing to family members of anyone testing positive for a harmful hereditary genetic mutation.

What's next?

Now that you understand the importance of genetic testing, look out for the next issue of *L.A. Breast Chronicles* to learn what to do about a positive genetic test results.