Making Sense of Genetic Testing Results

In the previous issue titled, “Genetic Testing for Hereditary Breast Cancers: A Story of Missed Opportunities,” we discussed the fact that only about 14% of women with hereditary breast cancer gene mutations have been identified and diagnosed through genetic testing, leaving the vast majority of gene mutation carriers undiagnosed and improperly managed by their healthcare providers.

The purpose of genetic testing is to determine if an individual is a carrier of a pathologic (harmful) mutation or likely pathogenic mutation that could increase the lifetime risk of cancer. In the genetic testing lab, the process calls for comparing the structure of specific genes present in the tested individual’s cells against a database of genes that may or may not be associated with an elevated lifetime risk of cancer.

Although most people have heard of genetic testing for BRCA1 and BRCA2 genes, commercial genetic tests widely used today employ multigene panels, which means that they test for not only two but as many as 70 different hereditary cancer-associated genes. Furthermore, although the rationale for ordering the test may be to determine if a breast or ovarian cancer mutation is present, most multigene panel kits test for other genetic mutations that are known to be associated with other types of cancer, such as colon cancer and melanoma. **Table 1** lists the most common hereditary genetic causes of breast and ovarian cancers that are analyzed in most commercial tests.

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

Interpreting Genetic Test Results

Genetic testing can be performed used either blood or saliva samples. Tests generally cost between $250-$400, which make them accessible to most people, even in instances when the test is not covered by insurance. Results usually come back in about 2-4 weeks depending on the commercial test and how it is ordered. For each gene that is tested, one of the following results will be reported.

1. Benign – Gene structure is normal and has no association with cancer.

2. Likely Benign – Gene structure is altered (mutated) but has no association with cancer.

3. Variant of Uncertain Significance – Gene structure is altered (mutated) but the cancer risk is unknown

4. Likely Pathogenic - The gene structure is altered (mutated) and appears to be associated with an increased risk cancer.

5. Pathogenic - The gene structure is altered (mutated) and is clearly associated with an elevated lifetime risk of cancer.

Managing Genetic Test Results

Benign and Likely Benign. These results are considered normal or “negative” and require no special care or follow-up. A benign or likely benign result does not mean that the individual is not at increased risk of cancer. It simply means that the risk is not related to a known mutation.

It is theoretically possible that the individual has a mutation that has yet to be discovered by science. However, based on what is known today, the patient's lifetime risk of cancer should be determined using other factors, such as the Tyrer-Cusick Breast Cancer Risk Model.

Variant of Uncertain significance. As genetic testing becomes more widespread, an increasing number of natural variations of genes are being detected. Most variants of uncertain significance are ultimately reclassified as benign or likely benign. Much less often, they may be reclassified as likely pathogenic or pathogenic. However, in the meantime, variants of uncertain significant should be managed as normal results and should not be used to justify specific follow-up, prophylactic surgery, or prevention measures. Similar to benign results, the patient's lifetime risk of cancer should be determined using other factors, such as Tyrer-Cusick Breast Cancer Risk Model.

Likely Pathogenic and Pathogenic Results. These results are considered abnormal and "positive" and require consideration of prevention or risk-reducing management to minimize the risk of the associated cancer. For example, for a woman with a BRCA1 or BRCA2 mutation, consideration should be given to bilateral prophylactic (preventive) mastectomy and removal of the fallopian tube and ovaries to reduce future risk of breast and ovarian cancer. A positive genetic test result should also prompt "cascade testing," which is the term used to describe the practice of testing all first degree female and male relatives to see if they, too, carry the same mutation, and if positive, followed by testing of their first degree relatives until all at-risk relatives have been tested. One genetic testing company offers free cascade testing to the first degree family members of mutations carriers.

Whereas the management of BRCA1 and BRCA 2 is relatively well known and widely applied, the management of less common breast and non-breast mutation is less established. To aid provider and patient communication about less common mutations, the Massachusetts General Hospital has maintained a website (www.ask2me.org) where users can select a mutation from a drop-down list to learn about the lifetime risk of associated cancers and to view evidence-based recommendations for how to manage each mutation.

A cautionary note about Direct-To-Consumer Testing

Direct-to-consumer (DTC) ancestry tests, like 23andMe, often tout their ability to detect hereditary breast and ovarian cancers. However, these DTC tests have not been validated for hereditary genetic testing and are not recommended for this purpose. A recent FDA advisory recommended that a negative genetic DTC test should not be accepted as normal and a positive test should be verified with a validated test for detection of hereditary cancer gene mutations. The most widely used validated tests are provided by Invitae, Myriad, and Ambry.