Genetic Testing After Previous BRCA Testing: A Case Study

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Mutations linked to hereditary cancer syndromes may increase an individual’s risk of developing cancer, as well as its recurrence. New genes that may also carry pathogenic mutations associated with cancer risk have been identified; as a result, individuals previously tested should consider additional testing. This article provides a case study illustrating the importance of such testing.

At a Glance

- Although just a small percentage of cancers have a genetic link, individuals identified as having pathogenic mutations may develop cancers earlier—and cancers that are more aggressive—than the general population.
- Oncology nurses are often among the first to discuss with patients their fears regarding the risks of cancer development in future generations.
- Identifying a pathogenic mutation early can assist in cancer prevention or earlier detection.

About 5%–10% of all cancers are related to a genetic mutation inherited from an individual’s parents (National Cancer Institute, 2013). These identified mutations are related to hereditary cancer syndromes that may significantly increase an individual’s risk of primary and secondary cancers, as well as cancer recurrences (Yurgelun et al., 2015). In 2013, the U.S. Supreme Court ruled against the ability to patent specific genes (Association for Molecular Pathology v. Myriad Genetics, Inc., 2013); as a result, genetic testing for cancer risk exploded because more than just one third-party lab could perform BRCA1/2 testing. The growing availability of genetic testing through reduced costs and improved insurance coverage, as well as the continued identification of new genes related to cancer risk, raises the possibility of multiple pathogenic variants in a single individual. Individuals previously tested for BRCA1/2 mutations may now need to consider additional testing because of the identification of new genes that may also carry pathogenic mutations associated with an increased risk of cancer.

The National Comprehensive Cancer Network (NCCN, 2016) provides guidelines and recommendations for testing individuals for hereditary breast and ovarian cancer (HBOC). The guidelines in Figure 1 depict very specific criteria for practitioners to identify when considering genetic testing. Although recommendations are available for commonly known genes or those that pose a significant increase in cancer risk, recommendations are still lacking for testing individuals with extensive cancer histories on both sides of the family or even within the same side.

Genetic counselors are in demand and hard to find throughout the United States, except in larger cities or commercial laboratories. Therefore, training primary care providers (physicians, nurse practitioners, clinical nurse specialists, physician assistants, and nurse midwives) who plan to order genetic testing to understand that no case or family history is the same and can often be more involved than what is expected is imperative. For instance, with the introduction of multigene panel testing, an individual with a strong family history of breast cancer may exhibit a genetic mutation in an unexpected gene, such as CDH1, which puts the individual at an extremely high lifetime risk of gastric cancer, in addition to the breast cancer risk. The following case study will illustrate how S.L., a patient known to be positive for HBOC, was previously managed based solely on her known BRCA2 mutation. However, after discussion with and evaluation by a genetic practitioner, she was determined to be qualified for additional testing; ruling out any other potential pathogenic mutations was also thought to be prudent.

Case Study

S.L. is a 41-year-old female patient presenting to the clinic to discuss her known pathogenic mutation in BRCA2. She was diagnosed with invasive lobular carcinoma of the left breast at age 33 years; afterward, she underwent bilateral total mastectomy with reconstruction
and chemotherapy, and she has continued antihormonal therapy for a total of 10 years. At age 39 years, S.L. was diagnosed with squamous cell carcinoma of the nail bed, which led to a partial amputation of the fourth right digit. S.L.’s family history is illustrated in Figure 2.

At the time of her breast cancer diagnosis, S.L. was tested for mutations in BRCA1/2 at the recommendation of her oncologist. When any pathogenic mutation is found, standard practice is to recommend testing both parents of the individual to identify from which side of the family the gene originates. S.L. was shocked to discover that her father carried the gene, not her mother, despite her personal and family histories of cancer. Because S.L.’s father tested positive for BRCA1, his siblings were encouraged to undergo testing; each sibling has a 50% chance of carrying the same mutation. In contrast, S.L.’s mother, with her significant history of cancer, was the most concerning for carrying a different pathologic mutation, which could only be identified through panel testing. If S.L.’s mother was still living, she would be the most ideal candidate for testing; however, she died from cancer before the introduction of panel testing. For this reason, S.L. was recommended to undergo testing again for additional mutations.

Case Progression

Genetic counseling was performed with S.L., and the implications of additional testing and the potential results (positive, negative, variant of uncertain significance) were discussed. Counseling also included education on screening and prevention services regarding her known BRCA2 mutation, which involved the recommendation for a risk-reducing salpingo-oophorectomy. S.L. indicated that her oncologist had discouraged her from having this surgery because she was young and had no children. Further discussion led to the possibility of an additional pathogenic mutation and how screening or prevention recommendations may be changed. For instance, certain positive findings may indicate the need for more frequent colonoscopies or skin screenings. Unfortunately, testing may also identify mutations that increase the risk of a cancer for which no efficient screening method or adequate treatment exists on diagnosis (e.g., pancreatic cancer). Therefore, S.L. had to be prepared for the possible inability to make changes to her plan of care based on a newly identified mutation. In addition, a plan of care may not yet exist because of the lack of understanding of many of the newer genes.

After counseling, S.L. verbalized her understanding of all presented information, noting that she wished to proceed with a comprehensive cancer panel following the completion of informed consent. The panel used consisted of 29 genes known to increase an individual’s risk of a variety of cancers, including breast, ovarian, gastric, colon, prostate, and pancreatic cancers. The results of this panel confirmed a pathogenic variant in BRCA2, in addition to a likely pathogenic variant in CDKN2A. A “likely pathogenic” variant is an identified mutation with evidence linking it to an increased risk for developing cancer; however, the evidence does not exist to definitively say this variant increases an individual’s risk for developing cancer.

S.L.’s case was presented at a genetics case conference for multidisciplinary discussion. Links between BRCA1 and breast and ovarian cancers are frequently published; however, an increased risk of pancreatic cancer and melanoma also exists with this mutation (Mersch et al., 2015). Because the true risk is still unknown, additional screening is not recommended unless a significant family history of either pancreatic cancer or melanoma exists. Pathogenic mutations in the CDKN2A gene, also known as melanoma-pancreatic cancer syndrome, indicate an increased risk of developing melanoma and pancreatic cancers (Goldstein, Struwing, Fraser, Smith, & Tucker, 2004).

Screening for pancreatic cancer may be considered in individuals who have a first-degree relative diagnosed with pancreatic cancer. However, with two separate mutations increasing S.L.’s risk for pancreatic cancer, the team recommended an annual endoscopic ultrasound (EUS). S.L. was referred to a gastroenterologist; during her first EUS, a 2 mm cyst was found on her pancreas. The cyst was too small to be biopsied, so S.L. was instructed to undergo EUS every six months. S.L. also was referred to a dermatologist for skin screenings at least every six months and instructed in how to perform self-screenings and what to report to physicians; this varied from her previous recommendations.

An individual with a breast cancer meeting any of the following:
- A known mutation in a cancer susceptibility gene within the family
- Early-age–onset breast cancer
- Triple-negative breast cancer diagnosed at age 60 years or younger
- Two breast cancer primaries in a single individual
- Breast cancer at any age, and
  - One or more close blood relatives (within three degrees) with breast cancer aged 50 years or younger, or
  - One or more close blood relatives with invasive ovarian cancer at any age, or
  - Two or more close blood relatives with breast cancer and/or pancreatic cancer at any age, or

- From a population at increased risk (e.g., Ashkenazi Jewish)
- Male breast cancer
- An individual of Ashkenazi Jewish descent with breast, ovarian, or pancreatic cancer at any age
- An individual with a personal and/or family history of three or more of the following: breast, pancreatic, prostate (Gleason score of seven or greater), melanoma, sarcoma, adenocortical carcinoma, brain tumors, leukemia, diffuse gastric cancer, colon cancer, endometrial cancer, thyroid cancer, kidney cancer, dermatologic manifestations, and/or macrocephaly, hamartomatous polypos of gastrointestinal tract
- An individual with ovarian cancer

FIGURE 1. Criteria for Genetic Risk Evaluation

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because no specific instructions were given following diagnosis of the squamous cell.

Because of S.L.’s mother’s history of recurrent pheochromocytoma, S.L. was also recommended to undergo a pheochromocytoma/paraganglioma panel. She was found to have a pathogenic mutation in SDHA, which is indicative of hereditary paraganglioma/pheochromocytoma syndrome (Korershoek et al., 2011). The presence of a pheochromocytoma can greatly increase a patient’s risk when undergoing surgical procedures; therefore, the identification of a pheochromocytoma prior to surgery is imperative. Although no official guidelines exist, individuals with this mutation are encouraged to have their metanephrine levels evaluated annually, as well as undergo magnetic resonance imaging of the chest, abdomen, and pelvis every one or two years; doing so may alert healthcare providers to the presence of a pheochromocytoma (Lefebvre & Foulkes, 2014). In individuals with a pheochromocytoma, surgical procedures without appropriate monitoring can be catastrophic, and a pheochromocytoma, by itself, can cause hypertension, stroke, and other life-threatening conditions.

Implications for Practice and Conclusion

Since the introduction of BRCA testing in 1995, women identified as having high-risk breast cancer and strong family histories of breast cancer started being evaluated and tested for BRCA mutations (Sankar, Wolpe, Jones, & Cho, 2006). Until the introduction of multigene panel testing, the option of additional cancer risk genetic testing was not available. Even today, with genetic testing expanding and becoming more accessible, many practitioners are still only testing for mutations in BRCA1/2, instead of looking at the full expanse of a patient’s pedigree and considering the possibility of additional mutations. Testing for only BRCA genes creates an environment of uncertainty, possibly giving someone a sense of false hope if found to be negative; many other genes that are significantly related to breast cancer can be missed by not testing.

Although S.L. had tested positive for a BRCA2 mutation, most individuals tested for BRCA mutations will be found to be negative. Just 10% of instances of breast and ovarian cancer in women are associated with germ-line mutations (Wright et al., 2016). In addition, individuals tested prior to the introduction of multigene panels received only BRCA testing. Nurses and practitioners are responsible for continually reviewing a patient’s personal and family history of cancer. Although a patient may have been tested in the past for mutations, the practitioner must consider the possibility of retesting an individual for other mutations. In the case study presented, the BRCA2 mutation arose from the paternal side of the family; however, the patient’s maternal side of the family, in combination with her personal history, qualified her for testing for not only HBOC but also for a hereditary melanoma syndrome.

Identification of a pathogenic variant, or in some cases, as is presented,
a secondary pathogenic variant, may significantly change the management of an individual case by adding and/or increasing screening recommendations, discussing additional interventions for prevention, and educating on new cancer risks. The job of oncology professionals is never finished. They must continually observe, reevaluate, and educate individuals on their cancer risk and refer them to genetic professionals to assist in identifying those who may benefit from additional screening and/or testing.

References

Association for Molecular Pathology v. Myriad Genetics, Inc., 689 F. 3d 1303 (2013)