



Next-Generation Gene Sequencing: Looking Beyond Hereditary Breast and Ovarian Cancer

Sylvia S. Estrada, DNP, MSN, MSHCM, WHNP-BC, CBCN®, Bridget LeGrazie, RN, MSN, APN-C, AGN-BC, AOCN®, Tammy McKamie, RN, MSN, OCN®, GCN, and Susan Montgomery, RN, BSN, OCN®, GCN

Oncology nurses have long been aware of the significance of recognizing patients' hereditary risk of cancer. Obtaining an accurate family history is an integral part of patient assessment and has helped to guide referrals for genetic counseling and testing for hereditary breast and ovarian cancer syndrome (HBOC) and Lynch syndrome. The genes associated with HBOC (*BRCA1*, *BRCA2*) and with Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*) have well-defined cancer risks, and patients who test positive for pathogenic mutations in these genes have traditionally followed surveillance and prevention recommendations outlined in the National Comprehensive Cancer Network (NCCN), 2015b) guidelines.

However, multigene panel testing, which is a form of DNA analysis also known as next-generation gene sequencing, has become available to patients. Panels test for mutations in multiple genes associated with an increased cancer risk. Some of these genes confer a significantly elevated lifetime cancer risk (greater than 50%), whereas others have a more moderate risk (20%–50%) or a lesser risk (less than 20%). Medical management recommendations can vary depending on the genetic mutation identified. Because some genes have not been extensively studied, recommendations may be extrapolated from other genetic mutation research. About 20% of genetic mutations identified in multigene panel testing are considered to be variants of uncertain significance (VUSs), meaning that their association with increased cancer risk is unknown. Reclassification of VUSs may take months or years.

The advent of multigene panel testing has created controversy among members of the oncology genetics com-

munity. Some practitioners embrace the ability to test for a variety of gene candidates, feeling that the information gained from this expanded testing will help to better define the cancer risks of some of these rarer genes (Hall, Forman, Montgomery, Rainey, & Daly, 2015). Others are more cautious, wanting multigene panel testing to be offered in the context of research to better assess novel counseling approaches and risk and management information (Domcheck, Bradbury, Garber, Offit, & Robson, 2013). The following case studies illustrate the unique challenges that accompany genetic assessment with multigene panel testing.

Case Study 1

S.M. is a 46-year-old Caucasian woman who was diagnosed with breast cancer at age 37 years. She first presented to the genetics clinic for risk assessment at the time of her initial diagnosis with a family history that included a sister and a maternal uncle with melanoma at age 34 years and at age 79 years, respectively. Paternal history included S.M.'s father with bladder cancer at age 54 years, an aunt with breast cancer at age 36 years, and two paternal cousins with prostate cancer in their 50s (see Figure 1). S.M.'s family history of early breast cancer, melanoma, and prostate cancer was suggestive of a *BRCA1* or *BRCA2* mutation (NCCN, 2015b). After undergoing *BRCA* genetic testing, S.M. was found to be negative; however, S.M. returned to the genetics clinic because her sister had been diagnosed with breast cancer at age 41 years. S.M. and her sister underwent multigene panel testing that tested for 17 genes known to be associated with breast cancer:

ATM, *BARD1*, *BRCA1*, *BRCA2*, *BRIP1*, *CDH1*, *CHEK2*, *MRE11A*, *MUTYH*, *NBN*, *NF1*, *PALB2*, *PTEN*, *RAD50*, *RAD51C*, *RAD51D*, and *TP53*. Both sisters were found to have a deleterious or pathogenic mutation (associated with an increased risk of disease) in the *PALB2* gene.

PALB2 is a moderate risk cancer predisposition gene that increases an individual's risk of a primary breast cancer. However, the extent of cancer risk with *PALB2* is not entirely known. Initial research has shown that the breast cancer risk for female mutation carriers is 14% by age 50 years and 35% by age 70 years (Antoniou et al., 2014). Management for *PALB2* mutation carriers has not yet been determined; the effect of magnetic resonance imaging (MRI) screening and mammograms on outcomes for these carriers is unknown, and surgical interventions for prevention have not been studied (Antoniou et al., 2014). *PALB2* mutation carriers may have a higher risk of male breast, pancreatic, and ovarian cancers, but the lifetime risk, as well as screening and prevention interventions, are not yet understood (Antoniou et al., 2014). Because the lifetime risk of breast cancer exceeds 20%, *PALB2* mutation carriers are recommended to undergo annual breast MRI screening in conjunction with annual mammograms (NCCN, 2015b).

Both sisters were recommended to receive annual screening with MRI and mammography in the affected and unaffected breasts. The sisters have daughters who are aged younger than

ONF, 42(6), 691–694.

doi: 10.1188/15.ONF.691-694

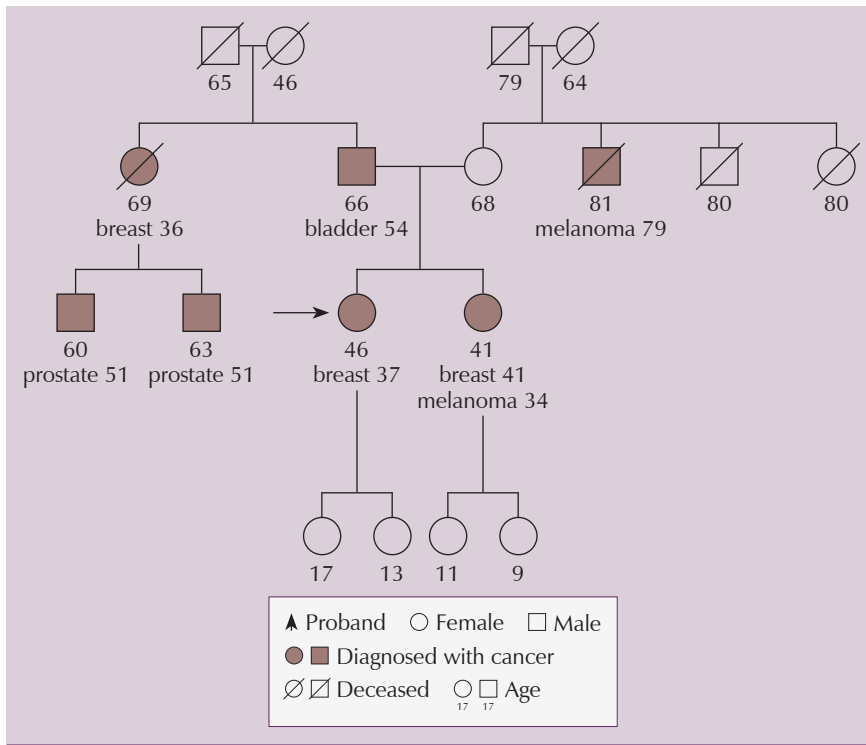


Figure 1. Case Study 1 Pedigree

18 years; they will not be tested until they are aged 18 years or older because of the unknown incidence of childhood cancers. S.M.'s two cousins with prostate cancer have not been tested for *BRCA1*, *BRCA2*, or *PALB2*. Although multigene panel testing has given the women in S.M.'s family the option of breast MRI screening, it has also left the family with many unanswered questions. As such, they should keep in touch with the genetics clinic regarding ongoing *PALB2* research findings.

Case Study 2

O.B., a 48-year-old Caucasian, nulliparous female of Ashkenazi Jewish ancestry, presented to the breast center with a palpable left breast mass. She noted that her father had tested positive for the *BRCA2* 5946delT (6174delT) mutation with the Multisite 3 *BRCA* panel. In addition, O.B.'s older sister died of pancreatic cancer at age 38 years and did not undergo genetic testing. Her 44-year-old younger sister had several precancerous polyps removed at age 38 years and also had not undergone genetic testing. O.B.'s father was diagnosed with prostate cancer at age 72 years and with gallbladder cancer at age 81 years. Her paternal aunt was unaffected and died

at age 81 years, whereas her paternal grandfather died from pancreatic cancer at age 70 years (see Figure 2).

O.B.'s mother was cancer free at age 78 years and tested negative for the Ashkenazi Jewish *BRCA* panel. Her mother had one sibling who died from a cutaneous angiosarcoma at age 79 years. O.B.'s maternal grandfather was diag-

nosed with breast cancer at age 60 years, and her maternal grandmother died from gastric cancer at age 83 years. In addition, O.B.'s maternal grandmother had a sister who died from pancreatic cancer at age 70 years. Several cancers (e.g., breast cancer, ovarian cancer, lymphoma) occurred in the offspring of these third-generation maternal relatives.

O.B. tested positive for *BRCA2* at 5946delT, which is the mutation for which her father also tested positive. Because extensive familial phenotypic cancers exist in the maternal lineage, a large multigene panel containing 28 genes associated with cancer risk was performed. O.B. also tested positive for *APC* at p.I1307K. She was diagnosed with left breast invasive ductal carcinoma, ER and PR positive, HER2/neu negative.

The p.I1307K mutation, which carries a moderate risk of colorectal cancer, is located in coding exon 15 of the *APC* gene. This alteration is present in 6%–7% of the Ashkenazi Jewish population and has been reported at even higher frequencies in cohorts of those of Ashkenazi Jewish ancestry with colorectal cancer or adenomatous polyps (Gryfe, Di Nicola, Lal, Gallinger, & Redston, 1999; Stern et al., 2001; Syngal et al., 2000). The risk of colorectal cancer associated with the p.I1307K mutation has been debated in the literature; however, a meta-analysis of data from numerous

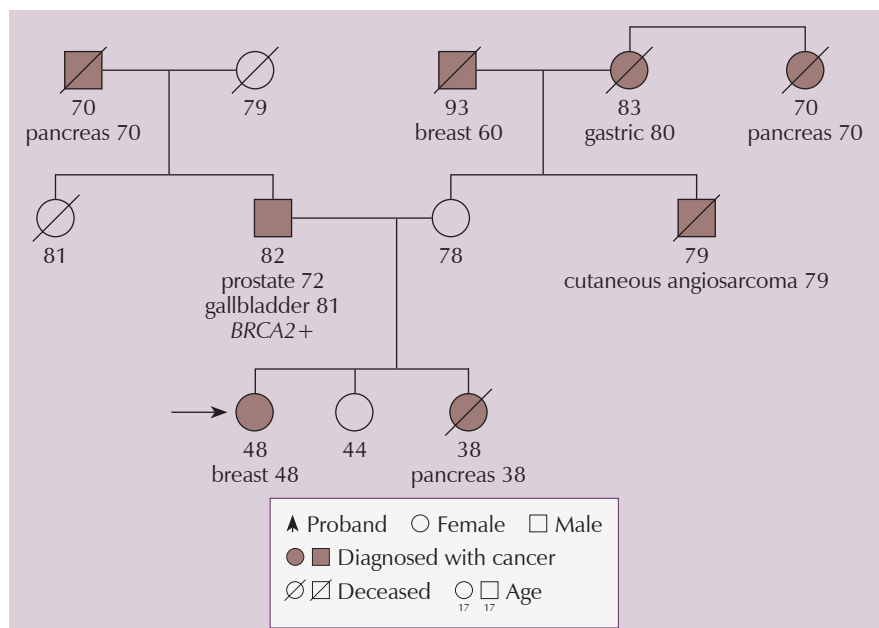


Figure 2. Case Study 2 Pedigree: Ashkenazi Jewish

independent studies found that the p.I1307K mutation confers a moderate increase in lifetime colorectal cancer risk in the Ashkenazi Jewish population (Liang et al., 2013).

Whether this mutation is inherited from the maternal or paternal lineage is uncertain; it is not known to account for the male breast cancer, angiosarcoma, or other cancers in O.B.'s maternal lineage. Because of the increase in colorectal cancer risk, O.B. should receive medical management recommendations regarding colonoscopy screening. In addition, whether a gene interaction affects risk, given O.B.'s status as a carrier of two genetic mutations, is unknown.

Case Study 3

F.A., a 71-year-old Caucasian woman, was referred to the genetics clinic for hereditary cancer risk assessment; she has a personal history of bilateral breast cancer (diagnosed at age 48 years and at age 70 years), as well as a history of one adenomatous colon polyp. Pathology of F.A.'s first breast cancer was not available, but the physician's dictation noted estrogen-positive adenocarcinoma of the right breast. Pathology of F.A.'s second breast cancer revealed estrogen- and progesterone-positive, low-grade ductal carcinoma in situ of the left breast. Family history included a daughter diagnosed with breast cancer at age 46 years, as well as a maternal aunt and a niece diagnosed with breast cancer (see Figure 3).

F.A. was determined to have an elevated risk of HBOC syndrome, as well as several other syndromes, because of a personal history of bilateral breast cancer. She also had a family history of breast cancer, including two diagnoses at younger than age 50 years. Other significant cancers noted in F.A.'s family history were colon cancer in her brother, who was diagnosed at age 30 years, and stomach cancer in her maternal grandmother. F.A. met the NCCN guidelines, as well as Medicare criteria, for HBOC syndrome testing. Gene panel analyses were recommended; these can simultaneously evaluate a large number of genes known to be associated with multiple syndromes, such as HBOC, Lynch, Cowden (a syndrome characterized by multiple noncancerous, tumor-like growths and an increased risk of developing certain cancers, including breast, uterine, and thyroid cancer), and Peutz-Jeghers (caused by a mutation in the

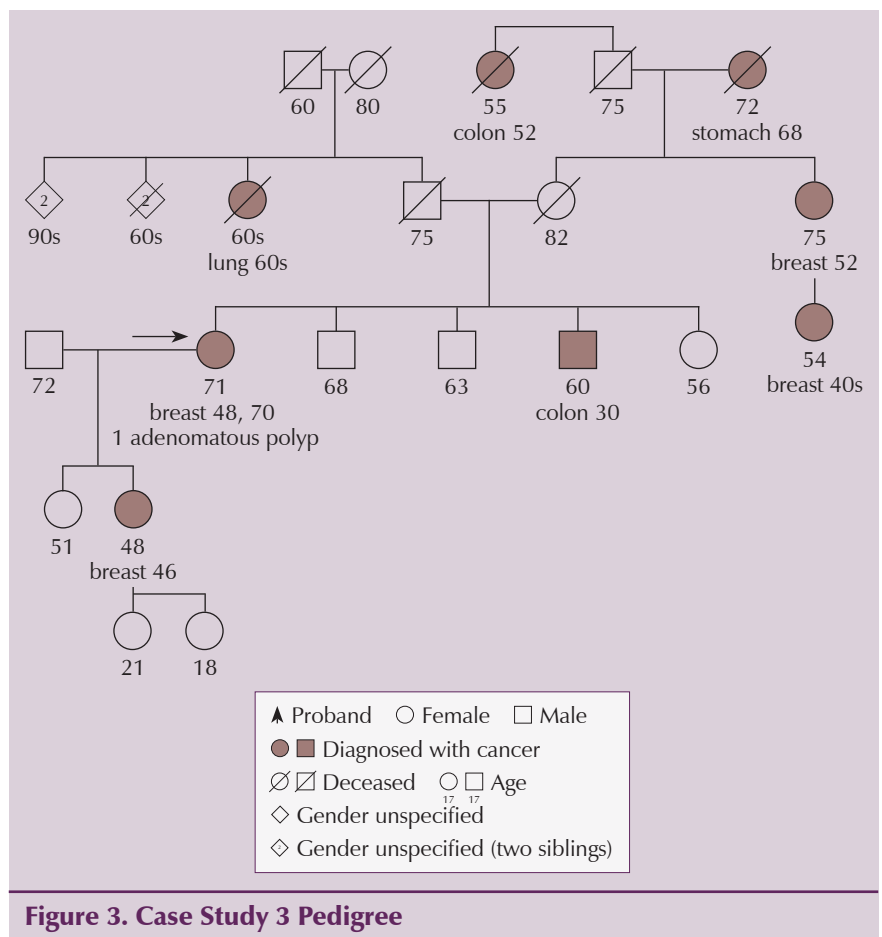


Figure 3. Case Study 3 Pedigree

STK11 gene, the syndrome is associated with the development of hamartomatous polyps in the gastrointestinal [GI] tract and an increased risk of cancers of the GI tract, pancreas, ovary, cervix, and breast). F.A. underwent testing with a 25-gene panel.

The results returned positive for a deleterious mutation in the *NBN* gene. *NBN* mutations are associated with an elevated risk of female breast cancer—as much as 30% by age 80 years as compared to the general population risk of 10%. The risk of prostate cancer is also elevated. Although the data are not conclusive at this time, an association between *NBN* mutations and pediatric leukemia and lymphoma has been reported (Seemanová et al., 2007).

No specific medical management guidelines are available to address breast cancer risk in mutation carriers. However, the possibility of an increased risk of breast cancer warrants consideration of individualized breast cancer risk reduction strategies (e.g., modification of standard population screening recommendations by starting screenings at younger ages, performing screenings

at greater frequency) (NCCN, 2015a). Parents, siblings, and children each have a 50% chance of carrying an *NBN* mutation and should consider undergoing testing. Those found to have the mutation can benefit from surveillance and early intervention.

In rare instances, an individual may inherit mutations in both copies of the *NBN* gene if both parents are carriers of an *NBN* mutation. This can lead to Nijmegen breakage syndrome, which is associated with growth retardation, immunodeficiency, and an increased risk of multiple cancers often diagnosed at a young age (Chrzanowska, Gregorek, Dembowska-Baginska, Kalina, & Digweed, 2012).

Implications for Nursing and Conclusion

The three case studies discussed in the current article clearly illustrate the challenges that accompany multigene panel testing for cancer susceptibility. Although each case suggested the possibility of HBOC syndrome and a *BRCA1* or *BRCA2* familial mutation, the genetic nurses recognized the importance of exploring

beyond *BRCA1* and *BRCA2*, given patients' personal and family histories. If these patients had undergone only *BRCA1* and *BRCA2* analysis, other familial mutations would have been missed; depending on insurance, further testing may not have been covered. Pretest counseling to help patients understand and choose the most appropriate genetic test, as well as post-test counseling to assess, interpret, and communicate the complex information gathered by these tests, requires a genetics professional (Hall et al., 2015). Nurses must be aware of resources, such as genetics counselors (National Society of Genetic Counselors, www.nsgc.org) and genetics nurses (International Society of Nurses in Genetics, www.isong.org), to help their patients find appropriate genetics services.

In addition, oncology nurses need to obtain a three-generation pedigree and assess a thorough family history to identify individuals who could benefit from a comprehensive genetic assessment (Powers & Stopfer, 2014) and refer their patients to the applicable resources. The information gained from these multigene panels can help to inform risk and treatment for patients, as well as provide potentially life-saving information to their families.

Sylvia S. Estrada, DNP, MSN, MSHCM, WHNP-BC, CBCN[®], is a nurse practitioner in the Saul and Joyce Brandman Breast Center at Cedars-Sinai Medical Center in Los Angeles, CA; Bridget LeGrazie, RN, MSN, APN-C, AGN-BC, AOCN[®], is the director of oncology services at Virtua Cancer Program in Voorhees, NJ; Tammy McKamie, RN, MSN, OCN[®], GCN, is a clinical oncology nurse navigator and cancer genetic educator for the CHRISTUS St. Michael Health System in Texarkana, TX; and Susan Montgomery, RN, BSN, OCN[®], GCN, is a genetics nurse navigator at Fox Chase Cancer Center in Philadelphia, PA. No financial relationships to disclose. Estrada can be reached at estradas@cshs.org, with copy to editor at ONFEditor@ons.org.

Key words: family history; genetic assessment; multigene panel testing

References

- Antoniou, A.C., Casadei, S., Heikkinen, T., Barrowdale, D., Pylkäs, K., . . . Tischkowitz, M. (2014). Breast cancer risk in families with mutations in *PALB2*. *New England Journal of Medicine*, *371*, 497–506. doi:10.1056/NEJMoa1400382
- Chrzanowska, K.H., Gregorek, H., Dembowska-Baginska, B., Kalina, M.A., & Digweed, M. (2012). *Orphanet Journal of Rare Diseases*, *7*, 13. doi:11.86/1750-1172-7-13
- Domchek, S.M., Bradbury, A., Garber, J.E., Offit, K., & Robson, M.E. (2013). Multiplex genetic testing for cancer susceptibility: Out on the high wire without a net? *Journal of Clinical Oncology*, *31*, 1267–1270. doi:10.1200/JCO.2012.46.9403
- Gryfe, R., Di Nicola, N., Lal, G., Gallinger, S., & Redston, M. (1999). Inherited colorectal polyposis and cancer risk of the APC I1307K polymorphism. *American Journal of Human Genetics*, *64*, 378–384. doi:10.1086/302262
- Hall, M.J., Forman, A.D., Montgomery, S.V., Rainey, K.L., & Daly, M.B. (2015). Understanding patient and provider perceptions and expectations of genomic medicine. *Journal of Surgical Oncology*, *111*, 9–17. doi:10.1002/jso.23712
- Liang, J., Lin, C., Hu, F., Wang, F., Zhu, L., Yao, X., . . . Zhao, Y. (2013). APC polymorphisms and the risk of colorectal neoplasia: A HuGE review and meta-analysis. *American Journal of Epidemiology*, *177*, 1169–1179. doi:10.1093/aje/kws382
- National Comprehensive Cancer Network. (2015a). *NCCN Clinical Practice Guidelines in Oncology: Breast cancer screening and diagnosis* [v.1.2015]. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/breast-screening.pdf
- National Comprehensive Cancer Network. (2015b). *NCCN Clinical Practice Guidelines in Oncology: Genetic/familial high-risk assessment: Breast and ovarian* [v.2.2015]. Retrieved from http://www.nccn.org/professionals/physician_gls/pdf/genetics_screening.pdf
- Powers, J., & Stopfer, J.E. (2014). Risk assessment, genetic counseling, and clinical care for hereditary breast cancer. *Journal of Obstetric, Gynecologic, and Neonatal Nursing*, *43*, 361–373. doi:10.1111/1552-6909.12304
- Seemanová, E., Jarolim, P., Seeman, P., Varon, R., Digweed, M., Swift, M., & Sperling, K. (2007). Cancer risk of heterozygotes with the NBN founder mutation. *Journal of the National Cancer Institute*, *99*, 1875–1880. doi:10.1093/jnci/djm251
- Stern, H.S., Viertelhausen, S., Hunter, A.G., O'Rourke, K., Cappelli, M., Perras, H., . . . Lagarde, A.E. (2001). APC I1307K increases risk of transition from polyp to colorectal carcinoma in Ashkenazi Jews. *Gastroenterology*, *120*, 392–400. doi:10.1053/gast.2001.21170
- Syngal, S., Schrag, D., Falchuk, M., Tung, N., Farraye, F.A., Chung, D., . . . Garber, J.E. (2000). Phenotypic characteristics associated with the APC gene I1307K mutation in Ashkenazi Jewish patients with colorectal polyps. *JAMA*, *284*, 857–860. doi:10.1001/jama.284.7.857

Genetics & Genomics

This feature aims to educate oncology nurses about the emerging role of genetics and genomics in cancer care. Possible submissions include, but are not limited to, application of genetics and genomics in clinical practice, screening and surveillance, case studies to present new ideas or challenge current notions, and ethical issues. Manuscripts should

clearly link the content to the impact on cancer care. Manuscripts should be 1,000–1,500 words, exclusive of tables and figures, and accompanied by a cover letter requesting consideration for this feature. For more information, contact Associate Editor Lisa B. Aiello, RN, MSN, AOCNS[®], APN-C, at lba34@drexel.edu.