



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

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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

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