A new breast cancer susceptibility gene on the market: When to put PALB2 in your cart

Genetics and Your Practice
Mary Pritzlaff, MS, CGC
Moncrief Cancer Institute and UT Southwestern Medical Center

Although the BRCA1 and BRCA2 genes account for a large percentage of hereditary breast cancers, we know that there are other breast cancer susceptibility genes yet to be discovered. It is likely that most of the other genes involved will have more moderate risks associated with them compared to the risks associated with BRCA1 and BRCA2. Recently, such a gene was made commercially available. This gene was discovered, in part, because of its association with the BRCA2 gene, and is named PALB2 for its role as a partner and localizer of the BRCA2 gene. PALB2 is part of the same DNA repair pathway as the BRCA2 gene, and promotes the stability and function of the BRCA2 protein. Although PALB2 works hand in hand with BRCA2, mutations within these two genes have different implications. This article will review the potential applications and limitations of clinical PALB2 testing.

Like BRCA2, mutations in the PALB2 gene have been associated with breast and pancreatic cancer, but the risks conferred by the two genes are different. Women with PALB2 mutations have a 2-4 fold increased risk for developing breast cancer, compared to the general population risk (1, 2, 3). Although this represents a significant increase in risk, it is not as high as the estimated 57-84% risk for breast cancer associated with the BRCA1 and BRCA2 genes. Also, unlike with BRCA1 and BRCA2, women with PALB2 mutations do not appear to have a significantly younger age of diagnosis than the general population. The risk for pancreatic cancer associated with PALB2 is increased, but the magnitude of the risk is unknown. Unlike with BRCA2, there does not appear to a significant increase in risk for other types of cancer associated with PALB2.

Given that what we know about the risks associated with PALB2, the $2,000 question is when to put it in our cart. A recent study of 1144 women in the U.S. with familial breast cancer (women with breast cancer and at least two first or second degree relatives with breast cancer) found 3.4% of women with familial breast cancer who tested negative for BRCA1 and BRCA2 mutations have a PALB2 mutation (4). Most women who have BRCA1 and BRCA2 testing do not meet these family history criteria, so the likelihood of finding a PALB2 mutation in the average BRCA negative patient would be much lower than 3%. PALB2 testing would be a better option for BRCA negative patients that clearly have a striking family history of breast cancer, although the yield will still be low. Likewise, families with pancreatic cancer have a similar risk for PALB2 mutations. Approximately 3-4% of familial pancreatic cancer has been associated with PALB2 mutations, compared to 5% associated with BRCA2 mutations (5, 6). A recent study found that 2% of 94 BRCA negative patients with breast cancer and a personal or family history of pancreatic cancer had a PALB2 mutation (7). It is important for patients to understand that 80% of familial pancreatic cancer is not explained with current genes, including PALB2 and BRCA2. When considering testing for PALB2, it is important to consider the limitations to applying this test in clinical practice. Currently, there are no clinical guidelines for breast cancer risk management for individuals with PALB2 mutations. Screening with breast MRI may be a reasonable choice, but there is no data yet to establish its clinical utility in this group of women, and it is uncertain if insurance will cover the costs. It is less clear if chemoprevention or prophylactic mastectomy will be established for women with PALB2 mutations. Likewise, there
are currently no guidelines for the management of pancreatic cancer risk. There is some promise that PARP inhibitors may play a role in treatment for pancreatic cancers in individuals with \( PALB2 \) mutations, and more research is being done in that arena. There are also several studies that are currently investigating the clinical utility of pancreatic screening for high risk individuals. The complexities of applying these results clinically highlight the importance of using a shopping assistant (i.e. your local friendly genetic counselor) to help decide when to choose \( PALB2 \). As always, if we can assist you with questions about \( PALB2 \), or any other genetic questions, please contact us at 817-838-4874.

References: