Large panel genetic testing produces more questions than answers in breast cancer

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While large genetic testing panels promise to uncover clues about patients' DNA, a team of researchers from Penn Medicine's Abramson Cancer Center (ACC)has found that those powerful tests tend to produce more questions than they answer. In a study of 278 women with early onset breast cancer who did not have the BRCA genes, the researchers found that only 2.5 percent of the patients had inherited mutations that were actually clinically actionable. Experts don't yet know how to interpret most of the mutations discovered by the test—known as massively parallel gene sequencing.

Results of the study, led by author Kara Maxwell, MD, PhD, a fellow in the division of Hematology-Oncology in the Perelman School of Medicine at the University of Pennsylvania, will be presented during the annual meeting of the American Society of Clinical Oncology (ASCO) in Chicago in early June (Abstract #1510).

Large genetic testing panels sometimes reveal mutations in genes that are associated with an increased risk in developing cancer. BRCA 1 and BRCA 2 genes are prime examples, where women can opt for mastectomies and ovary removal surgery—which research shows slashes their risk of developing those cancers). However, there is not yet guidance for clinicians on how to care for patients who exhibit other types of mutations, such as CHEK2 and ATM. These are known as variants of unknown significance (VUS).

"We're in a time where the testing technology has outpaced what we

know from a clinical standpoint. There's going to be a lot of unknown variants that we're going to have to deal with as more patients undergo large genetic testing panels," said Maxwell. "It's crucial that we figure out the right way to counsel women on these issues, because it can really provoke a lot of anxiety for a patient when you tell them, 'We found a change in your DNA and we don't know what it means.'"

The team, which includes Susan Domchek, MD, the Basser Professor in Oncology and director of the Basser Research Center for BRCA in Penn's ACC, and Katherine Nathanson, MD, an associate professor in the division of Translational Medicine and Chief Oncogenomics Physician for the ACC, studied 278 patients who had been diagnosed with breast cancer under the age of 40, were not carriers of the BRCA1 or BRCA2 mutations, and had no family history of ovarian cancer.

The researchers performed massively parallel gene sequencing to detect 22 known or proposed breast cancer susceptibility genes in each woman. Though the testing did reveal multiple variants of genes that are known to confer increased risk of breast cancer in patients who develop the disease young, only 2.5 percent of patients tested were found to have mutations that are actionable under current treatment guidelines, including TP53, CDKN2A, MSH2, and MUTYH.

In all, the sequencing revealed reportable variants in over 30 percent of the patients.

"Knowing there is a mutation may not help us any more than knowing that the person has a positive family history – which we already know," Nathanson said. "We don't know yet what to do with the information on an individual basis, and there certainly are no clinical standards."

This field of research is especially important when dealing with families who appear to have genetic predisposition to breast or other cancers but

don't carry BRCA1/2 mutations, Maxwell said.

"We need to be very careful with how we use this data," Maxwell said. "You could be taking someone who thinks they're not at risk and making them at risk, or taking someone who is believed to be at risk and relieving them of that risk, but we don't know enough yet to be confident in our assessments of these findings."

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