PRECISION ONCOLOGY NEWS

ACMG Suggests Docs Evaluate All Breast Cancer Patients for Genetic Risk Test Suitability

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NEW YORK – The American College of Medical Genetics and Genomics said today that all breast cancer patients should be evaluated to determine if they should receive germline genetic testing for assessing their inherited risk for the disease.

However, the medical genetics professional organization doesn't recommend testing all breast cancer patients for germline pathogenic or likely pathogenic variants in BRCA1, BRCA2, and other breast cancer-linked genes.

"Clinicians should be aware that there is currently insufficient evidence to support genetic testing for all patients with breast cancer, especially with multigene panels that include genes without evidence to guide follow-up care," said Tuya Pal from the Vanderbilt University Medical Center, lead author of the ACMG's "Points to Consider" statement, published in *Genetics in Medicine*, the organization's official journal.

Pal clarified in an interview that the statement is not a guideline and doesn't reflect a change in recommendations. ACMG experts issued the statement to communicate to clinicians the evidence supporting germline genetic testing in breast cancer, and presented information that they should consider when making the decision about which patients to test.

The take home point, Pal said, is that the group has not found sufficient evidence supporting universal genetic testing for all women with breast cancer. "What we are saying, though, is that all women with breast cancer should be evaluated for the need for genetic testing based on existing clinical criteria," she added.

Moreover, the group emphasized that it "considers germline genetic information to be critical to the management of patients with genetic conditions," and acknowledged the need to improve test access for individuals who do meet current consensus guidelines. "We as a medical community haven't even done a good job of testing those at high risk, where the yield of positive results is much higher," Pal said.

The ACMG cited estimates that less than 10 percent of adults with BRCA1/2 pathogenic or likely pathogenic variants in the US have been identified, and less than 20 percent of breast and ovarian cancer patients who should receive testing according to guidelines are actually receiving it. This access gap is particularly pronounced among racial and ethnic minorities.

When deciding which test to order for assessing inherited breast cancer risk, the ACMG urged clinicians to pick a lab that is certified under the Clinical Laboratory Improvement Amendments and accredited by the College of American Pathologists, and to choose testing that involves sequencing full genes, analyzing deletions and duplications, and detecting known pathogenic and likely pathogenic intronic variants.

The ACMG said that patients should receive genetic counseling to help them understand the implications of testing, and that this counseling should be provided by trained genetics professionals or healthcare providers with cancer genetics expertise. Individuals who have pathogenic or likely pathogenic variants in a

breast cancer-linked gene with evidence-based follow up recommendations should also be educated about cascade testing of family members to assess their inherited risk of cancer, the group said.

Pal and colleagues suggested that clinicians look to the National Comprehensive Cancer Network, which recently updated its genetic testing guidelines for assessing the risk of breast, ovarian, and pancreatic cancers. For breast cancer patients, the group continues to recommend using patients' own cancer history and family history to determine the appropriateness of testing. Previously, the NCCN focused its recommendations around high-penetrance genes, such as BRCA1/2, TP53, and PTEN, but in updated guidelines, the group discusses evidence-based follow up actions for when patients have pathogenic or likely pathogenic variants in other breast-cancer linked high-penetrance genes, such as PALB2, and additional moderate-penetrance genes.

"Currently breast cancer penetrance data are used to guide follow-up care after positive results (i.e., identification of [a] pathogenic or likely pathogenic variant). Follow-up may include either enhanced screening or risk-reducing mastectomy for genes with the highest penetrance," the ACMG authors wrote. "In contrast, only heightened screening (but not risk-reducing mastectomy) is recommended for other moderate penetrance genes that reach the threshold for it, based on a 20 percent or more lifetime risk."

The NCCN's recommendations and the ACMG statement are in sync since a number of clinical genetics experts were involved in drafting both, including Pal and Fox Chase Cancer Center's Mary Daly. However, in its new statement, the ACMG takes a more conservative stance than the American Society of Breast Surgeons (ASBrS), which updated its consensus statement earlier this year and recommended that all breast cancer patients receive genetic testing for BRCA1/2 and PALB2, and if appropriate based on clinical factors and family history, for other genes as well.

Susan Domchek, director of the Basser Center for BRCA at the University of Pennsylvania, wrote in an accompanying editorial in *Genetics in Medicine* that the debate over whether to test all breast cancer patients is caught up in the competing pressures in healthcare. On one hand, the US Preventive Services Task Force, in its latest recommendations on mammograms for average-risk women starting at age 50, the focus is on doing less based on clinical utility evidence, knowing that a low number of women who go on to develop cancer will be missed. On the other hand, there are efforts underway to do more, with the aim of increasing diagnostic yield. She noted, for example, that several states have mandated insurance coverage for supplemental imaging for women with dense breast tissue, despite a lack of data showing that such interventions would improve breast cancer mortality.

In genetic testing, the proliferation of multigene panels has made it possible to increase diagnostic yield. However, for many of the genes on these panels the evidence is not yet clear as to whether acting on pathogenic mutations would actually extend patients' lives.

Pal estimated that recommending that all breast cancer patients have genetic testing would result in a fivefold increase in the number of individuals being tested compared to a risk-based approach. However, the yield of positive results in high-penetrance genes "would be minimal," she said. The ACMG experts estimated that less than 1 percent of breast cancer patients with a high-risk genetic mutation would not meet current NCCN guidelines.

Moreover, expanding testing before there is evidence could lead to inappropriate management and cause patients harm, experts cautioned. One study, for example, found that some patients with a variant of unknown significance in BRCA1/2 received bilateral mastectomy, despite guidelines recommending against making clinical decisions based on VUS.

"There is a concern that misinterpretation of these types of results could potentially lead to unnecessary imaging or surgery," Domchek wrote. In addition, "there is a strong argument for careful gene selection on multi-gene panels. More is not necessarily better."

The ACMG experts noted that additional evidence is needed on the cost effectiveness of cancer risk management strategies and cascade family variant testing, and the field needs to have a better understanding of what to do with moderate penetrance and incompletely characterized genes. They urged professional societies to work together to advance harmonized, evidence-based recommendations and reduce barriers to care. "Testing alone will not improve outcomes but rather implementation of appropriate care following testing is required," they wrote.

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