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Multi-Gene Panel Testing Provides Broader Information About Breast Cancer Risk

More Data May Pose New Questions

Abstract: Multi-Gene Panel Testing Detects Equal Rates of Pathogenic BRCA1/2 Mutations and Has a Higher Diagnostic Yield Compared to Limited BRCA1/2 Analysis Alone in Patients at Risk for Hereditary Breast Cancer

April 30, 2015, Orlando--For women with a family history of breast cancer, new multi-gene panel testing yields greater information about cancer risk while assessing deleterious BRCA 1/2 mutations as accurately as BRCA testing alone, according to a new study presented this week at the American Society of Breast Surgeons (ASBrS) Annual Meeting. Lead researcher Dr. Nimmi Kapoor of Breastlink noted that until recently, genetic testing involved an initial evaluation for deleterious BRCA mutations only, followed as needed by testing for other breast cancer-related genetic abnormalities--with greater cost and time delays.

"BRCA testing can now be incorporated in single broader genetic tests offered by a wide range of vendors, as a result of recent patent law rulings," explained Dr. Kapoor. "But some concern exists about the precision of these newer panel tests in detecting all deleterious BRCA mutations. Additionally both patients and physicians face a rapidly changing landscape of testing that may find mutations whose significance is not understood. Through our study, we hoped to address some of this confusion."

Researchers retrospectively analyzed data for 966 patients who underwent genetic testing at three sites at a single institution. All met National Comprehensive Cancer Network guidelines testing criteria and had no history of prior BRCA 1/2 testing. Full panel testing was performed on 337 patients, while 629 received limited BRCA testing. In addition to BRCA1/2 mutations, panel tests focused on PTEN, TP53, CDH1 and up to 28 additional cancer-related genes.

No statistical difference (3.6% vs. 4.0% respectively) was found for positive deleterious BRCA mutations between the panel and limited BRCA testing groups. Similarly, no statistical differences were found between the two groups for variants of uncertain significance (VUS) in BRCA genes (3.3% vs. 4.0% respectively).

For the panel group, 3.9% were found to have non-BRCA mutations, while 13.4% had non-BRCA VUS. Mutations in PALB2, CHEK2, MUTYH, and ATM were the most common non-BRCA mutations identified. The most frequent non-BRCA VUS was in the ATM gene.

"The door has been opened. With today's new panel tests, women at risk for hereditary breast cancers will benefit from more timely and efficient multi-gene testing, without compromising BRCA accuracy," said Dr. Kapoor. "Test results may help women with other known breast cancer-related genetic abnormalities take preventive measures. Newer tests are also increasingly being covered by insurance. Both panel and BRCA limited tests are as simple as sampling saliva with a swab."

Dr. Kapoor notes, however, that women should be aware that recently discovered genetic variants may pose unanswered questions about cancer risk. "Scientists do not yet understand the significance of many of these mutations and protocols for dealing with them do not exist," she said. "Further, negative findings for known mutations do not necessarily reduce a woman's cancer risk based on factors such as family history. Cancer genetics are complex. But tests can certainly rule out certain genetic problems and add to the picture of a woman's overall chance of being diagnosed with breast cancer."

Dr. Kapoor also noted that patients undergoing genetic testing also will be contributing vital information to enhance the understanding of breast cancer development for future generations of scientists and women. "We are not only gaining useful clinical information, but also enhancing our understanding of breast cancer biology with multi-gene panel testing. This is an essential step towards developing and utilizing better, targeted therapy."

Abstract

Presenter: Nimmi Kapoor
Institution: Breastlink

Title: Multi-Gene Panel Testing Detects Equal Rates of Pathogenic BRCA1/2 Mutations and Has a Higher Diagnostic Yield Compared to Limited BRCA1/2 Analysis Alone in Patients at Risk for Hereditary Breast Cancer

Objective: After the Supreme Court ruling of *Association for Molecular Pathology v. Myriad Genetics,* patients at risk for hereditary breast and ovarian cancer were able to undergo expanded multi-gene panel testing with BRCA1 and BRCA2 (BRCA1/2) primarily, rather than in sequence after initial BRCA1/2 testing. Concerns with newer panel testing include inability to detect all deleterious mutations in BRCA1/2 and high rates of genetic variants of uncertain significance (VUS). The purpose of this study is to evaluate the rate of pathogenic BRCA1/2 mutation detection and VUS detection between previous restricted methods of gene testing and newer multi-gene panel testing.

Methods: Data were collected retrospectively from patients who underwent genetic testing between January 2008 and September 2014 at 1 of 3 sites from a single institution. Patients were evaluated by a breast surgeon and/or a risk assessment counselor at time of visit if they met criteria for genetic testing based on National Comprehensive Cancer Network (NCCN) guidelines. Patients were excluded from the study if they underwent only targeted genetic testing for a known family mutation. Patients who underwent multi-gene panel testing were excluded if they had prior BRCA1/2 testing. Genetic testing results were compared between patients who underwent limited BRCA1/2 testing, including multisite testing (Ashkenazi panel) or full BRCA sequence testing with or without large rearrangement testing (limited testing group), to patients who underwent multi-gene panel testing consisting of a minimum of 5 breast cancer–related genes, including BRCA1, BRCA2, PTEN, TP53, CDH1, and up to 28 cancer-related genes (panel testing group).

Results: A total of 973 patients underwent genetic testing; 355 patients underwent panel testing and 618 underwent limited BRCA1/2 testing only. Deleterious BRCA1/2 mutations were identified in 34 patients (3.5%). There was no difference in the rate of detecting BRCA1/2 mutations between limited and panel testing groups (3.6% vs 3.4%, respectively; p = 1.0). Thirty-nine patients (4.0%) were found to carry a VUS in a BRCA1/2 gene and this was similar between limited and panel testing groups (4.0% vs 3.9%, respectively; p = 1.0). Of patients undergoing panel testing, an additional 3.9% (n = 14) were found to harbor non-BRCA pathogenic mutations and an additional 10.1% (n = 36) had non-BRCA VUS. Mutations in PALB2, CHEK2, MUTYH, and ATM accounted for some of the more common additional non-BRCA mutations identified (n = 10, 2.8%). The most frequent non-BRCA VUS was in the ATM gene (n = 11, 3.1%).

Conclusion: In this series, multi-gene panel testing detected pathogenic BRCA mutations at equivalent rates as limited BRCA1/2 testing and led to increased diagnostic yield. Multi-gene panel testing does increase the rate of detecting VUS; however, variant genes are more likely to be non-BRCA genes. Patients at risk for hereditary cancer syndromes can benefit from upfront, more efficient, multi-gene panel testing without any sacrifice to BRCA testing capability.