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Results of Next-Generation Sequencing Panels in a Large Community-Based Hereditary Cancer Risk Program

Background: Next-generation sequencing (NGS) allows for broader germline genetic testing for hereditary cancers. Since the Supreme Court decision of AMP v. Myriad on June 13, 2013, hereditary cancer multi-gene panels can now include *BRCA1* and *BRCA2*, making these panels an option for first-tier testing. However, questions have been raised about the clinical utility and implications of extended panels for medical management given the inclusion of unknown to moderate penetrant genes.

Methods: We reviewed all patients who underwent multi-gene panel testing from July 1, 2013 through May 23, 2014. The indications for testing included personal and/or family history of breast or ovarian cancer. The panels were ordered in a single genetic counseling clinic within a large community-based cancer center.

Results: A total of 136 patients underwent panel testing via a single commercial laboratory. We identified 12 (8.8%) patients who were positive for a pathogenic or likely pathogenic mutation in a cancer susceptibility gene; 4 had prior negative *BRCA1* and *BRCA2* sequencing and deletion/duplication testing. These positive results included 4 *BRCA2* mutations, 2 *TP53* mutations, 1 *CDH1* mutation, 2 *ATM* mutations, and 1 patient each with a *CHEK2, NBN*, or *PALB2* mutation. Of the patients found to have a positive test result, 100% met the National Comprehensive Cancer Network (NCCN) guidelines for Hereditary Breast and Ovarian Cancer (HBOC) genetic testing. The *CDH1* mutation carrier did not meet NCCN guidelines for hereditary diffuse gastric cancer testing and only one of the *TP53* mutation carriers met NCCN guidelines for Li-Fraumeni syndrome. Within our cohort (136), 21 (15.4%) patients had a total of 25 variants of uncertain significance (VUS) and 103 (75.7%) patients had negative test results.

Conclusion: Testing through NGS panels identified 7/12 (58%) patients with a mutation which led to changes in current medical management and 3/7 (43%) had a mutation in a gene other than *BRCA1* or *BRCA2*. Our findings suggest that there is clinical utility of NGS panels for use in this patient population despite the inclusion of unknown to moderate penetrant genes and a higher rate of VUS than single gene testing.