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Overview of Multi-Gene Panels for Hereditary Cancer

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Background: Genetic testing for several hereditary cancer genes, such as *BRCA1* and *BRCA2*, has been available in the United States since the 1990's. Historically, many patients and families with histories suggestive of hereditary cancer predisposition tested negative for mutations in these well-described genes. Multi-gene panel tests can provide an answer for a proportion of these families, and have been available in the United States since 2012. There is an ongoing discussion among providers regarding the benefits and limitations of panel tests. The identification of a causative mutation allows patients and families to be aware of additional cancer risks, and therefore pursue appropriate management for risk reduction. Additionally, panel testing is a more time and cost-effective approach. However, many of the genes on the panels do not have published management guidelines or cancer risk estimates for mutation carriers, which can lead to difficulty in recommending appropriate screening for patients and families.

Objectives: We aim to briefly describe the overall panel results, and discuss the utility of multi-gene testing for hereditary cancer.

Methods: Ambry Genetics offers ten cancer panels, from a 5 gene high risk breast cancer panel, to a 49 gene pan-cancer panel. We assessed the overall results of these panels from March 2012 to March 2015.

Results: Over 50,000 individuals underwent testing through a multi-gene panel at Ambry Genetics. The overall positive rate is 8.6%, and the overall inconclusive rate is 17.92% across all panels. The two most frequently ordered panels are BRCAPlus, a panel assessing 5 genes associated with a high risk for breast cancer, and BreastNext, an expanded panel assessing 17 genes associated with moderate to high breast cancer risk. Without accounting for the total cases tested for each gene, most mutations were identified in *BRCA1*, *BRCA2*, *CHEK2*, and *ATM*, respectively. The vast majority of patients tested were Caucasian, while 3.4% were Asian.

Conclusions: Based on our review of a large number of cases submitted for panel testing, we found several genes that are commonly mutated that may provide an explanation for a portion of hereditary cancer families. However, testing more genes increases the number of variants of uncertain significance, which can potentially lead

to confusion and anxiety in patients. Appropriate genetic counseling and education for patients about the substantial benefits and limitations of multi-gene panel testing is necessary so that patients and their providers can make informed choices about the most appropriate testing option.

Keywords: *oncology, hereditary, panel*