Title: Increased identification of hereditary breast cancer mutations by utilizing a multi-gene test approach

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Category: Category 1
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Objectives:
Specific clinical management and genetic testing guidelines are recognized for four additional genes beyond BRCA1 and BRCA2 in hereditary breast cancer susceptibility: CDH1, PTEN, STK11 and TP53. Although these genes were initially identified in families with classically defined genetic syndromes, testing criteria have broadened in scope as non-classic families and patients have recently been found to harbor mutations. For example, in 2013, the National Comprehensive Cancer Network (NCCN) increased the early-onset breast cancer testing criterion in its TP53 testing guideline from under age 30 to under age 36. We aimed to study whether analyzing these additional genes in individuals at risk for hereditary breast cancer would increase the likelihood of identifying a gene mutation in high-risk families.

Methods:
All individuals identified who tested positive, that is were found to carry a pathogenic mutation or likely pathogenic variant (referred to herein as 'mutations') in BRCAplus, a multi-gene panel created by Ambry genetics consisting of BRCA1, BRCA2, CDH1, PTEN, STK11, and TP53, between June 17, 2012-January 17, 2014 were included in the analysis.

Results:
Of 4,323 individuals tested, 202 (4.7%) individuals tested positive for a disease-causing mutation. The breakdown of the positive mutation carriers was as follows: BRCA1 accounted for 44.5% (90/202), BRCA2 accounted for 42% (85/202), TP53 accounted for 9.4% (19/202), PTEN accounted for 2.5% (5/202), CDH1 accounted for 1% (2/202) and STK11 accounted for .5% (1/202). In addition, of all mutation types identified 7.4% (15/202) of individuals were large deletions or duplications: nine in BRCA1, four in BRCA2, and two in TP53.

Conclusions:
Testing for mutations in CDH1, PTEN, STK11 and TP53 in addition to BRCA1 and BRCA2, increases the likelihood of finding a mutation in a high risk breast cancer family by 15.4%. If only BRCA1 and BRCA2 were considered in this patient population, at least one in ten individuals with a clinically actionable mutation would have not been identified. Additionally, performing sequencing alone would have failed to identify a significant number of pathogenic mutations. These findings highlight the importance of considering multiple genes when assessing an individual for hereditary breast cancer risk and clearly demonstrate the importance of performing comprehensive molecular testing for all genes.