Background and Objectives

The practice of genetic testing is rapidly evolving with the recent introduction of multigene panels. While the prevalence of non-BRCA1/2 mutations in patients with suspected hereditary breast and ovarian cancer (HBOC) is now well documented, the clinical validity and clinical utility of these tests is not yet fully understood. We sought to measure how often and in which ways non-BRCA1/2 findings from multigene tests could change patient management in a representative clinical cohort. We further analyzed the analytic and clinical validity of multigene testing by comparison with traditional genetic tests on the same patients.

Study Design/Methods

We tested up to 29 genes in over 1000 BRCA1/2-negative patients, all of whom were enrolled prospectively at three academic medical centers and all of whom met NCCN guidelines for HBOC evaluation. We established a uniform algorithm based on current practice guidelines to recommend management actions for the non-BRCA1/2 positive individuals, and we evaluated which of these actions would represent a change in management over and above any recommendations based on personal and family history alone.

Prevalence and Clinical Relevance

63 patients were identified with mutations in non-BRCA1/2 genes.

- 74% of the cancer-affected patients had a syndromic cancer for the gene they were found to carry, 26% did not.
- However, in 92% of cases, the patient’s personal and/or family history was consistent with the syndromic effects of the gene they carry.

Clinical Management

We found that the majority of these findings would result in consideration of additional screening and/or prevention measures for the patient. Moreover, testing of first-degree family members would also be warranted given the potential management changes in these individuals if found to be mutation positive.

Clinical Interpretation: Positive vs. not positive

Analytic concordance

Sensitivity: 100.0%
Specificity: 100.0%

Analytic concordance: 97/97 directly comparable patients in 1125 individuals. All of these TSK were copy number deletions or otherwise technically challenging sequencing alterations.

Clinical Interpretation: Positive vs. not positive

Clinical actionability for alterations in BRCA1/2 in 1125 directly comparable cases. Positive result means pathogenic or likely pathogenic variants identified. Two positive means any VUS, family history, or benign variants identified.

Conclusions

In appropriately referred patients, multigene panel testing yields valid and clinically relevant findings with potential management impact for substantially more patients than does BRCA1/2 testing alone. Additional results and discussion are available in our recent publications from this multicenter study:

- Desmond et al., JAMA Oncology 2015
- Swisher, JAMA Oncology 2015 (Commentary)
- Lincoln et al., J Molecular Diagnostics 2015