**Clinical Actionability of Multigene Tests for Hereditary Breast and Ovarian Cancer**

**Andrea Desmond**, Allison Kuriyan, Michelle Gabren, Meredith Mills, Michael Anderson, Yuya Kobayashi, Shan Yang, Kristen Shannon, Nadine Tung, James Ford, Stephen Lincoln and Leif Ellis

1. Massachusetts General Hospital, Boston, MA 2. Stanford University Medical Center, Palo Alto, CA 3. Invitae, San Francisco, CA 4. Beth Israel Deaconess Medical Center, Boston, MA

**Background and Objectives**

The practice of genetic testing is rapidly evolving with the recent introduction of multiplex 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 multiplex gene tests could change patient management in a representative clinical cohort. We further analyzed the analytic and clinical validity of multiplex gene 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 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.

**Mutation 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 syndrome effects of the gene they carry.

**Clinical Management Impacts**

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 based on the potential management changes in these individuals if found to be mutation positive.

**Validation Study**

If multiplex panels are to replace traditional tests in appropriate situations, then it is important to understand the analytic and clinical performance of these new tests in comparison with the previous standard of care. Panel test results for the MGH and Stanford patients, adding in the BRCA1/2 positives, were compared to traditional (sanger) genetic tests performed on the same patients by another laboratory.

**Conclusions**

In appropriately referred patients, multiplex gene 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