Clinical Actionability of Multigene Tests for Hereditary Breast and Ovarian Cancer

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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) risk is now well documented, the clinical validity and clinical impact of these tests is not yet fully understood.

We sought to measure how often and in which ways non-BRCA1/2 findings from multigene panels could change patient management recommendations in a representative clinical cohort. We further analyzed the analytic and clinical validity of multigene testing by comparison with traditional 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.

Clinical Actionability

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.

Validation Study

If multigene 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. In a companion study, panel test results for the MGH and Stanford patients (adding in BRCA1/2 positives and individuals with familial mutations) were compared to traditional genetic tests performed on the same patients.

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

Analytic concordance

Sensitivity 100.0%
Specificity 100.0%
Agree 99.8%
Disagree 0.2%

Clinical interpretation: Positive vs. not positive

Finding a PALB2 mutation makes this proband (black triangle), who is already a candidate for enhanced (MRI) breast screening, a possible candidate for prophylactic surgery. It also makes the sister, two daughters and potentially other paternal relatives candidates for testing that may alter their recommended screening and prevention options.

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