Germline mutation likelihood in breast cancer patients: Navigating the nuances of multi-gene panel testing

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Background: Risk assessment tools providing clinicians with the mutation likelihood based on clinical presentation of testing candidates have not evolved to accommodate the multi-gene panel testing (MGPT) landscape. Here we aimed to determine the mutation likelihood in individuals with female breast cancer (BC) undergoing MGPT to better inform clinicians' expectations of finding clinically actionable results for their patients.

Methods: We retrospectively reviewed clinical histories and MGPT results (5-49 genes) for 86,660 female BC patients tested from June 2012 through December 2016 at our clinical laboratory to assess whether National Comprehensive Cancer Network (NCCN) 2.2017 *BRCA1/2* genetic testing guidelines pertaining to individuals with a personal history of BC were met. Mutation likelihood per test was calculated based on each criterion.

Results: Positive rates increased for individual criteria with increased panel size, with the exception of the TNBC criterion and the family history of male BC criterion. Likewise, compared to a 5-gene high risk BC panel, positive rate increased by 25.08% on an 8-gene BC panel, by 44.39% on a 17-gene BC panel, by 69.47% on a 24-gene OC panel, and by 82.71% on a 49-gene comprehensive tumor panel. Individuals with triple negative BC (TNBC) ≤60y had the highest positive rate in the 5-gene high risk breast panel (14.77%), individuals with BC ≤50y and an additional breast primary had the highest positive rate in larger panels targeted for BC (12.39% and 13.57%) and ovarian cancer (OC) (16.35%), and individuals with BC ≤50y and ≥1 relative with pancreatic cancer had the highest positive rate in the largest comprehensive tumor panel (17.93%).

Conclusions: Our findings that mutation likelihood based on clinical presentation differ by panel highlight the need to tailor risk assessment for MGPT rather than relying on tools designed for single gene testing. An accurate family history can influence test selection, as shown by the finding that individuals with a family history of pancreatic cancer had the highest positive rate on a comprehensive panel that included genes beyond the breast/ovarian spectrum. Continued exploration of panel and phenotype-specific detection rates will improve risk counseling in the MGPT setting.