Title: Multi-gene panel testing results prompt frequent and guideline adherent changes to cancer risk management recommendations based on clinician report

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Background: Utilization of multi-gene panel testing (MGPT) as a first line test marks a paradigm shift in the clinical approach to hereditary cancer testing. In order to better understand the clinical utility of MGPT, data are needed to determine how often MGPT results prompt changes to risk management recommendations, how closely those recommendations align with clinical practice guidelines, and the extent to which gene penetrance and intervention type influence guideline adherence.

Methods: Clinicians were invited to participate in an IRB-exempt study using an online survey to assess cancer risk management recommendations before and after MGPT. Management recommendations pertaining to surveillance, risk-reducing surgery, chemoprevention, clinical trial eligibility, and education/counseling were evaluated. Changes in cancer risk management recommendations were compared across test result status (positive, inconclusive, negative) and personal history of cancer using multivariate logistic regression. Positive results were stratified such that genes specifically designated as high-risk (HR) and/or those with surgical recommendations according to National Comprehensive Cancer Network & copy; guidelines were categorized as HR and remaining genes were categorized as moderate-risk (MR).

Results: Paired pre- and post-test responses were received for 2172 patients and post-test-only responses in 168 additional patients with positive MGPT results. Clinicians reported one or more change in risk management recommendations for 76.6% of patients who tested positive for a pathogenic or likely pathogenic variant (PV) in categories as follows: surveillance (71.1%), surgical (33.6%), chemoprevention (15.1%) and clinical trial participation (9.4%). Clinicians recommended risk-reducing interventions more often for patients with PVs in HR than MR genes (surgery: OR 6.2, 95% CI 4.0-9.6; p=<0.001; chemoprevention: OR 4.1; 95% CI 2.3-7.3; p=<0.001, and clinical trials: OR 5.5; 95% CI 2.5-12.3; p=<0.001); whereas the rate of new surveillance recommendations did not differ between patients with PVs in HR and MR genes. Guideline adherence was high for surveillance (86.3%) and surgical (79.6%) recommendations. As was observed for rate of new surveillance introductions, there was also no difference in adherence rates for breast surveillance guidelines between HR and MR genes. Changes to recommendations occurred in 8.8% of patients with an uncertain result and 7.6% with a negative result (OR 1.2; 95% CI 0.84-1.7; p=0.32).

Discussion: Clinicians report frequent and appropriate changes to cancer risk management recommendations based on positive MGPT results in both HR and MR genes. Reported introduction of recommended interventions in patients with inconclusive and negative results is rare and adherence to practice guidelines is high for patients with positive results, suggesting a low probability of harm resulting from MGPT. Continued study of MGPT utilization and outcomes is needed to optimize the clinical utility of this technology and inform practice guideline development.