Multi-gene panel testing increases yield of surgically-actionable results among breast cancer patients

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Background: Genetic testing for *BRCA1/2* is widely accepted following a breast cancer diagnosis to assist with impending surgical management decisions. With multigene panel tests (MGPT) becoming more common place, National Comprehensive Cancer Network (NCCN) guidelines have evolved to include surgical management considerations for additional breast cancer susceptibility genes due to significantly increased cancer risks. This study aims to determine the likelihood of a surgically actionable result based on NCCN guidelines beyond *BRCA1/2* when using a breast cancer-specific MGPT at one commercial laboratory.

Methods: We performed a retrospective analysis in our cohort of female patients with a breast cancer diagnosis who had testing with a 17-gene breast cancer-specific MGPT (*ATM, BARD1, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, MRE11A, MUTYH, NBN, NF1, PALB2, PTEN, RAD50, RAD51C, RAD51D, TP53*) between June 2012 and December 2016. The frequency of likely pathogenic and pathogenic variants was calculated for each gene. NCCN guidelines (Version 1.2018) were used to determine surgically-actionable findings for breast and other cancers.

Results: Of 29,568 breast cancer cases tested, 9.14% (n=2702) were identified to carry a likely pathogenic or pathogenic variant (excluding *MUTYH* carriers). 2.69% (n=794) of patients were positive for either *BRCA1* or *BRCA2*. 1908 patients (6.45%) tested positive for mutation(s) in genes beyond *BRCA1/2*. Based on these results, risk reducing mastectomy (RRM) could be considered for an additional 83 patients based on identification of a mutation in *PTEN* or *TP53* (3.07% of mutation carriers). As indicated by NCCN, RRM could be considered for an additional 1465 patients (54.22% of mutation carriers) with mutations in *ATM, PALB2, CHEK2, CDH1, NF1* or *NBN* in the context of a significant family history of breast cancer. Importantly, an additional 194 patients (7.18% of mutation carriers) had a surgically actionable finding for sites beyond breast, including consideration of risk-reducing Salpingo-Oophorectomy (n=159, *BRIP1, RAD51C, RAD51D*), gastrectomy (n=18, *CDH1*), and hysterectomy (n=17, *PTEN*).

Conclusions: Expanding testing beyond *BRCA1/2* for breast cancer patients with clinical histories suggestive of inherited cancer predisposition increased the identification of surgically-actionable mutations for breast and other cancers. These findings highlight MGPT as an efficient and effective approach to identify more patients for whom discussion of cancer risk management options is warranted, including the risk and benefits of various cancer prevention options.