Multigene Panel Testing Increases the Detection of Clinically-Actionable Mutations in Ovarian Cancer Patients
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Objectives: Beyond BRCA1/2, there are a number of genes associated with an increased risk for ovarian and/or other cancers. The majority of these genes have associated National Comprehensive Cancer Network (NCCN®) guidelines for cancer risk management. We aimed to determine the frequency of pathogenic germline mutations in genes, other than BRCA1/2, among women with ovarian cancer undergoing multigene panel testing (MGPT).

Methods: All cases of ovarian, Fallopian tube or primary peritoneal cancer submitted to a clinical diagnostic laboratory for MGPT targeting breast and/or ovarian cancer genes between 2012 and 2016 were included (n=12,806). Genetic test results and clinical histories (as provided on test requisition forms or via clinical documentation) were retrospectively reviewed. Frequencies of pathogenic mutations/likely pathogenic variants (herein referred to as pathogenic mutations) were calculated for each gene (ATM, BARD1, BRIP1, CDH1, CHEK2, EPCAM, MLH1, MRE11A, MSH2, MSH6, MUTYH, NBN, NF1, PALB2, PMS2, PTEN, RAD50, RAD51C, RAD51D, SMARCA4, STK11, and TP53) and then summed to determine the combined mutation frequency.

Results: Most patients self-identified as Caucasian (71.3%, N=9136). The average age at ovarian cancer diagnosis was 49 years and 26.2% (n=3351) had a history of ≥ one additional primary cancer. The combined frequency of pathogenic mutations in breast and/or ovarian cancer risk genes beyond BRCA1/BRCA2 was 8.3%. Pathogenic mutations were most commonly detected in Lynch syndrome genes (1.7%), CHEK2 (1.6%), ATM (0.9%), BRIP1 (0.9%), and RAD51C (0.8%). 92.9% (762/820) of pathogenic mutations were identified in genes for which there are NCCN® cancer risk management guidelines. 47.3% (388/820) of mutations occurred in genes where prophylactic oophorectomy should be considered (Lynch syndrome genes, BRIP1, RAD51C, and RAD51D) and 68.4% (561/820) of mutations occurred in genes where increased screening (and prophylactic surgery in some cases) is recommended for other cancers such as breast, colorectal, or endometrial cancer.

Conclusions: Testing beyond BRCA1/2 with MGPT can significantly increase detection of clinically-actionable mutations in ovarian cancer patients, allowing for more personalized management recommendations of patients and their at-risk relatives.