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.