Title: Comparison of non-breast and ovarian cancer phenotypes of *BRCA1/2* mutation carriers across multi-gene panels.

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Background: *BRCA1/2* germline mutations account for the majority of hereditary breast and ovarian cancers. Until 2013, the only way to identify individuals with BRCA mutations was through single gene testing. With multi-gene panel testing (MGPT) including *BRCA1/2*, BRCA mutations are being identified at an increased rate. To date, the phenotype of *BRCA1/2* mutation carriers includes an increased prevalence of breast, ovarian, prostate, and pancreatic cancer, as well as melanoma. The phenotype, however, of mutation carriers identified by panel testing is not well understood.

Methods: All sequential cases submitted to our laboratory for MGPT including *BRCA1/2* between June 2013 and June 2015 and *BRCA1/2* single gene testing between June 2013 and February 2015 were retrospectively reviewed. Data from 77,345 test request forms were reviewed; probands with a *BRCA1* or *BRCA2* mutation were selected and analyzed. Probands with no personal history of cancer/not provided (n=528) were excluded.

Results: Of 2,967 *BRCA1/2* positive probands, 2,439 (82.2%) had a personal history of cancer, with 2,794 cancers reported. On all tests completed, with the exception of a pancreatic cancer focused panel, breast and/or ovarian cancer were the most commonly observed cancer types (n=2,364, 84.6%). On single gene testing (n=739), prostate (n=16, 2.2%), colorectal (n=8, 1.1%), and pancreatic (n=7, 0.9%) cancers were the other most frequent cancers reported. Across all MGPT cases (n=1,700), additional observed cancers included uterine (n=48, 2.8%), colorectal (n=46, 2.7%), pancreatic (n=37, 2.2%), melanoma (n=29, 1.7%), and thyroid (n=27, 1.6%). For breast cancer-specific gene panel cases (n=934), additional cancers included thyroid (n=12, 1.3%) and uterine cancer (n=10, 1.1%). For gynecologic cancer gene panel cases (n= 482), additional cancers included uterine (n=21, 4.4%), colorectal (n=11, 2.3%), and melanoma (n=11, 2.3%). Cases tested via a pancreatic cancer gene panel (n=25,) had pancreatic cancer (n=17, 68%) reported most frequently, followed by breast (n=6, 24%), colorectal (n=3, 12%), and melanoma (n=3, 12%). For comprehensive cancer gene panel cases (n=254), colorectal (n=28, 11.0%), uterine (n=17, 6.7%), pancreatic (n=14, 5.5%), prostate (n=10, 3.9%), thyroid (n=10, 3.9%), and a variety of rare tumor types (n=15, 5.9%) were among the additional cancers reported.

Discussion: As expected, the majority of cancers reported on almost all tests were breast and/or ovarian cancer. More specifically, the observed cancers for tumor specific cancer panels, matched the relevant cancer type (i.e. pancreatic cancer most commonly reported in those tested via a pancreatic cancer panel). However, on the comprehensive cancer panels, other than breast and ovarian cancer, there appears to be a more even distribution of various cancer types, including rare tumors, in probands who have a *BRCA1* or *BRCA2* mutation. Further studies should be conducted to examine the phenotypes of BRCA mutation carriers identified via comprehensive cancer panels to determine the association and prevalence of unexpected cancer types with *BRCA1/2* mutations. This could have important implications for determining the most appropriate genetic test and management of BRCA mutation carriers.