Title: *MSH6* and *PMS2* Carriers Identified by Multi-Gene Testing May Have a Breast-Ovarian Cancer Phenotype

Holly LaDuca, MS, CGC[1], Carin R. Espenschied, MS, CGC[1*], Shuwei Li, PhD[1], Rachel McFarland, BS[1], Chia-Ling Gau, PhD[1], and Heather Hampel, MS, CGC[2]

1. Ambry Genetics, Aliso Viejo, CA

2. The Ohio State University Comprehensive Cancer Center, Columbus, OH

*Corresponding author email: cespenschied@ambrygen.com

Objectives: To date, Lynch syndrome research has primarily been performed on cohorts that meet the Amsterdam criteria or Bethesda guidelines and population-based colorectal cancer (CRC) and endometrial cancer (EC) cohorts, possibly biasing results. To further evaluate the full phenotypic spectrum of mismatch repair (MMR) gene mutations, we performed a retrospective phenotype analysis of MMR and *EPCAM* mutation carriers ascertained through multi-gene panel testing (MGPT).

Methods: 35,214 patients underwent MGPT including the MMR and *EPCAM* genes between March 2012 and June 2015. Clinical histories of those who tested positive for an MMR gene mutation (MMR+) were retrospectively reviewed and pairwise comparisons were performed for the various MMR genes using Fisher's exact test and logistic regression multivariate analysis.

Results: Overall, 621 MMR+ patients (1.8%) were identified. Patients with a second mutation in an MMR or other cancer gene (n=35) and those without personal and/or family history of cancer indicated (n=51) were excluded from subsequent analyses. Of the remaining 535, 74 (13.8%) had breast cancer (BC) only (no CRC or EC) and 49 (9.2%) had ovarian cancer (OC) only (no CRC or EC). Nine of these had both BC and OC, seven of which had *MSH6* or *PMS2* mutations. When comparing those with BC only to those with CRC but not BC, *MSH6* and *PMS2* mutations were more frequent than *MLH1* and *MSH2* mutations after controlling for age, ethnicity, gender, and family history of CRC and EC (p=2.36e-07). Similarly, when comparing those with OC only to those with CRC but not BC or OC, *MSH6* and *PMS2* mutations were more likely than *MLH1* and *MSH2* mutations after controlling for age, ethnicity, gender, and family history of CRC and EC (p=5.19e-04). In this cohort, 22.4% met only the National Comprehensive Cancer Network (NCCN) hereditary breast and ovarian cancer (HBOC) testing criteria and 5% met neither HBOC nor Lynch syndrome testing criteria. *MSH6* and *PMS2* mutations were more frequent than *MLH1* and *MSH2* mutations among cases that met NCCN HBOC testing criteria, but did not meet NCCN Lynch syndrome testing criteria (p=5.14e-08).

Conclusions: Results from this study support the association of an HBOC phenotype with *MSH6* and *PMS2* mutations and highlight the need for further investigation of BC and OC risks for these mutation carriers. These data also support the inclusion of Lynch syndrome in the differential diagnosis for patients with an HBOC phenotype and highlight the limitations of current testing criteria in identifying these cases.