Title: Importance of Genetic Testing for Patients with Multiple Colorectal Cancer Primaries

Authors: Caroline Elsas, Holly LaDuca, Jessica Profato, Bryan Mak

Background: Individuals with hereditary colorectal cancer (CRC) may be at increased risk for a second primary CRC. Therefore, a personal history of multiple CRCs may be considered an indication for genetic testing.

Methods: Multi-gene panel test (MGPT) results and age at CRC diagnoses were reviewed for 7046 CRC patients who underwent testing from March 2012 to June 2016. Depending on the panel ordered, analysis of up to 49 genes associated with CRC and/or other cancers was performed. The diagnostic yield and age at CRC diagnoses were compared between patients with a history of one CRC (n=6739) and those with two or more CRCs (n=307).

Results: Individuals with a history of multiple CRCs had an overall positive rate of 23.8% (n=73), as compared to 12.4% (n=836) in those with a history of one CRC (OR=2.2; p=1.1E-7; 95%CI [1.653,2.907]). In the multiple CRCs group, 77 mutations were identified as follows: *MLH1* (n=29), *MSH2* (n=18), *MSH6* (n=5), *PMS2* (n=5), biallelic *MUTYH* (n=5), *CHEK2* (n=5), *APC* (n=2), *BRCA2* (n=3), *RAD50* (n=1), *BRIP1* (n=1), *BRCA1* (n=1), *ATM* (n=1), and *PTEN* (n=1). Four patients carried mutations in two different genes. Of the mutation-positive patients with multiple CRCs, 72.6% were diagnosed with their first CRC before age 50, as compared to 59.3% of mutation-positive patients with one CRC. Consequently, the mutation-positive rate increased to 36.3% in patients with multiple CRCs whose first CRC was diagnosed before age 50; whereas it was 12.4% for patients diagnosed with both CRCs at age 50 or above.

Conclusions: Overall, individuals with multiple CRCs were approximately twice as likely to be mutation-positive than those with a history of one CRC. This data highlights the importance of genetic testing for those with multiple CRCs, particularly in cases where the first CRC is diagnosed before age 50. Additionally, genetic testing of patients with early onset CRC at the time of diagnosis has the potential to capture patients who may benefit from consideration of additional options to reduce their risk of developing a secondary CRC. Furthermore, mutations were identified in various genes associated with extra-colonic cancers, presenting additional opportunities for cancer risk reduction in patients and their relatives.