Title: Patients with Multiple Pathogenic Mutations Detected by Multi-gene Panel Testing in a Lynch Syndrome Cohort

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Purpose: The aim of this study was to determine the clinical and molecular characteristics of individuals in whom multi-gene panel testing resulted in identification of a pathogenic mutation in one of the mismatch repair (MMR) genes as well as an additional pathogenic mutation.

Methods: Multi-gene panel tests including analysis of the MMR genes performed from March 2012 to March 2014 were reviewed. Clinical histories of individuals who tested positive for two pathogenic mutations/likely pathogenic variants, of which at least one mutation was in a MMR gene, were assessed.

Results: Seven percent (8/112) of MMR mutation carriers in this cohort were identified to carry a second pathogenic mutation/like pathogenic variant. Of these eight cases: one harbored a *PTEN* likely pathogenic variant, two harbored *ATM* mutations, three harbored *CHEK2* mutations, one harbored a *RAD51C* mutation and one harbored two *MSH6* mutations, consistent with a diagnosis of Constitutional Mismatch Repair Deficiency syndrome (CMMRD). Four cases met Amsterdam I, Amsterdam II, or revised Bethesda criteria and four did not meet any of these criteria. In addition, several cases met National Comprehensive Cancer Network (NCCN) testing criteria (version 1.2014) for other hereditary cancer syndromes: two met criteria for *APC* and *MUTYH*-associated polyposis testing and five met criteria for hereditary breast and ovarian cancer syndrome (HBOC) testing. Two of the *CHEK2* mutation cases and the *RAD51C* mutation case had a personal and/or family history of breast cancer. Of the cases that also harbored an *ATM* mutation, one had a personal and family history of pancreatic cancer.

Conclusion: Our data demonstrate that the clinical history associated with a MMR gene mutation and an additional pathogenic mutation can be extremely variable. Our data also highlight the importance of detecting multiple pathogenic mutations in patients and conducting further research on these individuals, as this can result in more complex counseling about inheritance, co-segregation with disease phenotype, and risk management.