Individuals with Lynch Syndrome and Colon Polyps Identified by Multi-Gene Panels

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Background: Lynch syndrome, the most common cause of hereditary colorectal cancer, is typically considered a "nonpolyposis" hereditary colorectal cancer syndrome and individuals are generally expected to have less than 10 colorectal polyps. Familial Adenomatous Polyposis (FAP) and *MUTYH*-Associate Polyposis (MAP) are typically associated with 100s-1000s of gastrointestinal adenomas, but more recent data has shown that some families with FAP and MAP have a milder phenotype associated with fewer polyps and that there is clinical overlap between MAP and Lynch syndrome. Next-generation sequencing (NGS) multi-gene panels allow clinicians to test for all potential genes of interest for a particular patient at once, saving time and money. The use of NGS multi-gene panels for hereditary cancer has led to the identification of mutations in unexpected genes and is providing emerging data on more expanded phenotypes for some well-established syndromes. This study aims to explore and describe the polyp load in individuals with Lynch syndrome identified through NGS multi-gene panels.

Methods: Our sample consisted of 112 individuals who tested positive for a mutation in one of the mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or *EPCAM*, identified via an NGS multi-gene panel between March 2012 and March 2014. We conducted a retrospective review of clinical and family history data obtained from test request forms, pedigrees, and clinical notes submitted by the ordering clinician.

Results: Of the 112 individuals with Lynch syndrome, 38 (33.9 %) had colorectal polyps: 35 (31.3%) had at least 1 adenoma, 3 (2.7%) had only polyps of another histology (most were hyperplastic), and 10 (8.9%) had both adenomatous and other polyps. Overall, 10 of the 112 (8.9%) had $\geq$10 adenomas, including two with 20-99 adenomas, and one with a "heavy" polyp load who was found to have Constitutional Mismatch Repair Deficiency (CMMRD). Three others in the cohort were found to have a second mutation, two in *CHEK2*, and another with CMMRD. All of these had less than 5 adenomas. Of the 35 with adenomas, 15 (42.8%) met the Revised Bethesda Guidelines, 9 (25.7%) met the Amsterdam I or II criteria, 13 (37.1%) reported a family history of polyps, and 3 had a personal or family history suggestive of Cowden syndrome. All individuals with $\geq$10 polyps were identified through a panel that included *APC* and *MUTYH* and no mutations were identified in those genes.

Conclusions: In this cohort of individuals with Lynch syndrome, 8.9% had $\geq$10 colorectal adenomas. While this included one individual with CMMRD where polyposis is typical, polyposis syndromes would likely have been on the list of differentials for this and many of the other cases with $\geq$10 adenomas, and none would have been detected with traditional single gene testing for *APC* and *MUTYH*. These data provide additional support for the benefit of multi-gene panels in individuals with multiple differential diagnoses, and in identifying those with hereditary cancer risk that have an atypical phenotype and may have been missed by traditional methods. Further studies and a larger sample size are needed to better define the level of polyposis seen in individuals with Lynch syndrome and determine whether it is due to the mismatch repair gene defect or other factors.