Title: Paired Tumor/Germline Analysis for Early Onset Colorectal Cancer: Resolution for High Risk Patients

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Background: Molecular germline testing confirms the diagnosis of Lynch syndrome (LS) in 83-95% of patients with early onset mismatch repair-deficient (MMRd) colorectal cancer (CRC), depending upon the age cut-off used, family cancer history, and genes analyzed.[1,2] Individuals with early onset CRC pose a unique challenge for clinicians regarding screening and management, especially in the absence of a germline mutation in one of the LS genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) following abnormal immunohistochemistry (IHC) or microsatellite instability (MSI) results. The aim of this study is to assess the ability of paired tumor/germline testing to diagnose or rule out LS in patients with early onset CRC.

Methods: We retrospectively reviewed a consecutive series of early onset CRC patients (diagnosed $\leq$40 years) undergoing paired tumor/germline analysis of the LS genes at a clinical diagnostic laboratory from December 2016 to February 2018 (N=47). MSI, *MLH1* promoter hypermethylation (MPH), and germline testing of additional cancer susceptibility genes were performed, if ordered. We report overall results of paired tumor/germline testing in the context of clinical histories and prior tumor screening and/or germline testing.

Results: Demographic information, clinical features, and results of prior tumor screening are presented in Table 1. Overall results of paired tumor/germline testing based on IHC staining pattern are provided in Table 2. Germline LS mutations were identified in 28% (13/47) of cases, and somatic causes were confirmed in 30% (14/47). Additionally, nine cases (19%) yielded negative results and were MSS/MSI-L. Approximately 19% (9/47) of cases remained inconclusive, mainly due to identifying a single somatic mutation. When taken in context with IHC and/or MSI results, paired tumor/germline testing resolved the diagnosis of LS in 81% of patients with early onset CRC.

Conclusions: Paired tumor/germline testing offers an opportunity to resolve the diagnosis of LS in patients with early onset CRC and provides the necessary information to clinicians to manage these high-risk patients. LS was diagnosed in 28% of early onset CRC patients undergoing paired tumor/germline testing. Moreover, this testing allowed 53% (n=25) of patients to consider foregoing LS screening, resulting in potential cost savings for families and the healthcare system overall.

References:

1. Antelo M et al. 17th Annual Meeting of the CGA-ICC; October 6-8, 2013; Aneheim, CA.
2. Perea J et al. *J Mol Diag.* 2014 Jan;16(1):116-126.