Reducing Unnecessary Screening in Lynch-Like Syndrome with Tumor Sequencing

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Background: While there is widespread adoption of universal screening for Lynch syndrome (LS) in the US, 20-84% of patients with mismatch repair-deficient (MMRd) colorectal and endometrial cancers (CRC/EC) still have uninformative germline testing ('Lynch-like syndrome'). Biallelic somatic MMR gene mutations are thought to explain at least half of such cases; however, the impact of tumor sequencing on healthcare provider management recommendations for patients with Lynch-like syndrome has not been evaluated.

Methods: Healthcare providers were invited to participate in a web-based survey assessing their intent to modify management recommendations for four hypothetical Lynch-like patients and their first degree relatives, based on results of somatic MMR gene sequencing.

Results: In total, 123 surveys were completed (Table 1). Compared to cases with no tumor sequencing performed, respondents were less likely to recommend increased screening/risk-reducing measures when biallelic somatic MMR mutations were identified in patients with young-onset CRC/EC with no family history (Figures 1A/1B) or early onset EC in an Amsterdam II positive family (Figure 1C). Knowledge of biallelic somatic mutations in older onset EC (Figure 1D) was less likely to impact management, however a reduction in screening recommendations was still observed. Respondents were also less likely to recommend increased screening/risk-reducing measures for first-degree relatives in all four scenarios (data not shown). Additionally, most healthcare providers treated *MLH1* hypermethylation the same as biallelic somatic MMR mutations.

Conclusions: Providers consider tumor MMR sequencing results as an important factor when determining management recommendations for CRC/EC patients with Lynch-like syndrome and their first-degree relatives. As such, tumor sequencing may substantially reduce the number of costly and unnecessary screening procedures and risk-reducing surgeries recommended for both patients and their relatives. Prospective studies aimed at assessing patient outcomes are needed to verify the utility of tumor sequencing in Lynch-like syndrome and to determine the optimal timing of tumor sequencing in the diagnostic algorithm for LS.