Tailoring Colorectal Cancer Surveillance in Lynch Syndrome: More Is Not Always Better

Short Title: Tailoring Surveillance in Lynch Syndrome

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Lynch syndrome (LS) is one of the most common hereditary colorectal cancer (CRC) syndromes, affecting 1 in 279 individuals in the general population\(^1\) and contributing to 3% of all CRCs\(^2\). Inherited in an autosomal dominant pattern, LS is caused by pathogenic germline mutations in the DNA mismatch repair (MMR) genes, *MLH1*, *MSH2*, *MSH6*, *PMS2*, and deletions in *EPCAM*. Loss of expression of MMR proteins causes defective DNA mismatch repair, leading to changes in the length of nucleotide repeat sequences, or microsatellite instability (MSI).\(^3\) In addition to CRC, LS is also associated with endometrial, ovarian, urothelial (renal, pelvis, ureter, bladder), gastric, pancreatic, biliary tract, and small bowel cancers along with brain tumors, and sebaceous neoplasms. Personal and/or family history of these gastrointestinal and extraintestinal malignancies can be used to identify at-risk individuals (i.e., Amsterdam criteria, Bethesda guidelines).\(^4\) For those with a history of CRC and endometrial cancers, universal testing for MMR deficiency by MSI and/or loss of MMR protein expression by immunohistochemical (IHC) analysis, is recommended regardless of age.\(^5\) Based on clinical suspicion or the presence of MSI and/or loss of MMR protein expression, referral for genetic counseling and germline testing for mutations in MMR genes can then be performed to confirm diagnosis of LS.

Although CRC is the most common cancer in LS regardless of underlying genetic mutation involved, previous studies show variable penetrance of MMR genes with regard to CRC risk.\(^6\)–\(^8\) Pathogenic variants of *MLH1* and *MSH2* are associated with greater lifetime CRC risk with earlier age of CRC onset compared to *MSH6* and *PMS2* variants. Previously, CRC screening was recommended to start between 20-25 years of age for all LS patients and continued every 1-2 years, regardless of gene involved.\(^9\) Recently, the National Comprehensive Cancer
Network\textsuperscript{®} recommended the following CRC prevention strategies in LS: high-quality colonoscopy starting between the ages of 20-25 for \textit{MLH1} and \textit{MSH2} carriers, and starting at the age of 30-35 for \textit{MSH6} and \textit{PMS2} carriers, continued every 1-2 years.\textsuperscript{5} 

In this issue of \textit{Gastroenterology}, Kastrinos and colleagues present a cost-effective analysis using a Markov simulation model to investigate the impact of varying age of CRC surveillance initiation and frequency on CRC incidence and mortality, quality-adjusted life years (QALYs), and cost for each MMR gene in order to determine optimal gene-specific surveillance strategies.\textsuperscript{10} A cohort of 25-year-olds were cycled annually until age 75 years or death. The authors varied surveillance initiation between ages 25 and 40, and surveillance intervals ranging from 1 to 5 years, resulting in a total of 20 strategies for each gene-specific scenario. The primary endpoint was the optimal strategy for each gene, which they defined as the greatest QALYs with an incremental cost-effectiveness ratio (ICER) below a willingness-to-pay threshold of $100,000/QALY. Many of the strategies were dominated (meaning they were both more expensive and less beneficial than competing strategies), but the pattern of which strategies were dominated and which was optimal differed by gene. For \textit{MLH1}, the authors found that the optimal strategy was annual colonoscopy starting at age 25 resulting in cumulative CRC incidence of 17% compared to 53% with colonoscopy every 5 years beginning at age 40. For \textit{MSH2}, biennial colonoscopy starting at age 25 was optimal (CRC incidence 17% compared to 42% with colonoscopy every 5 years beginning at age 40). For \textit{MSH6}, surveillance every 3 years starting at age 35 was found to be optimal (CRC incidence 7% compared to 16% with colonoscopy every 5 years beginning at age 40). Finally, for \textit{PMS2}, surveillance every 3 years
starting at age 40 was optimal (CRC incidence 3% compared to 8% with colonoscopy every 5 years starting at age 40).

Consistent with previously established gene-specific CRC risk estimates, optimal strategies for \textit{MLH1} and \textit{MSH2} were more aggressive in terms of starting age and frequency as compared to optimal strategies for \textit{MSH6} and \textit{PMS2}. Notably however, even with the most aggressive strategy of annual colonoscopy starting at the age of 25, CRC incidence for \textit{MLH1} was 17%. To reduce CRC incidence further, frequent and early colonoscopy might need to be paired with chemoprevention (for instance with daily aspirin\textsuperscript{11}), though such an approach was not studied by Kastrinos, et al. Similarly, the optimal strategy for \textit{MSH2} (colonoscopy every 2 years, starting at the age of 25) also resulted in a CRC incidence rate of 17%. But compared to \textit{MLH1}, increasing the frequency of colonoscopy to annually in \textit{MSH2} led to lower incremental benefit (due to lower risk of cancer in \textit{MSH2}) and greater incremental cost (likely due to less resources saved related to averting fewer cancers), resulting in a very expensive ICER of $2,009,850/QALY compared to biennial colonoscopy. For \textit{PMS2}, beginning surveillance at age 35 actually resulted in fewer QALYs than beginning at age 40, due to decrements in quality of life related to colonoscopy and/or rare complications rather than fewer life years saved. Depending on how burdensome an individual values colonoscopy and its complications, screening at age 35 might be reasonable.

This modelling study is very useful since testing all of these surveillance strategies in a timely manner using the gold standard of a randomized controlled trial would not be practical. However, a few limitations of the study are worth noting. First, the study assumes perfect adherence to surveillance and high-quality exams, conditions that are unlikely to hold in real-
world settings. In addition, there are other individual-level factors that likely modify CRC risk in LS and could impact the age at which to start, or continue surveillance, such as the age at which a relative is diagnosed with CRC, male sex, and presence of adenoma on index colonoscopy.\textsuperscript{12}

Despite these limitations, this study highlights an important, cost-effective, gene-specific approach to CRC surveillance in patients with LS with less aggressive strategies for individuals with \textit{MSH6} and \textit{PMS2} variants who may otherwise undergo more than 50 colonoscopies in their lifespans. As evidence to support tailored cancer surveillance strategies among individuals with LS grows, future studies are needed to understand the acceptability and feasibility of implementing these strategies.
References


