

# Screening for Lynch Syndrome: Optimal Strategies and Performance Remain a Moving Target

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In the past decade, implementation science has emerged as a transdisciplinary research approach to enhance the systematic uptake and integration of evidence-based guidelines across real-world practice settings. It is estimated that it takes up to 17 years for only 14% of published evidence to be incorporated into clinical practice (1,2). Given this notable time lag, the barriers and facilitators of implementation have often been explored and found to vary by practice setting, provider and patient characteristics, and overall healthcare systems.

For individuals with colorectal cancer (CRC), universal screening for Lynch syndrome, the most common form of inherited CRC syndrome, involves tumor testing for mismatch repair deficiency (MMRd) by either microsatellite instability (MSI) or immunohistochemistry (IHC) for loss of protein expression of the MMR genes associated with the condition. Universal screening was first recommended in 2009 by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) group (3), followed by the US Multi-Society Task Force on Colorectal Cancer (4) in 2014 and the National Comprehensive Cancer Network. Results from the implementation of tumor screening programs and their impact have been variable and have often been related to practice setting or type of cancer center.

In this study, Stone et al. (5) reported the outcomes of MMRd tumor testing, notably IHC, in Manitoba, the first Canadian provincial program to implement universal screening of all CRCs diagnosed in patients younger than 70 years. Nearly a decade following the recommendations and guidelines to pursue MMRd, Stone et al. provided results from a large study of over 3,000 CRC specimens analyzed between 2018 and 2020. The investigators evaluated predictors of MMRd testing and referral rates for germline testing.

Stone et al (5) found a high level of compliance with reflex testing, where 89.4% of patients 70 years and younger with CRC had tumor IHC testing. This is higher than previous reports of reflex MMRd tumor testing for CRC (6–10), and factors predictive of an increased rate of reflex testing were patient age (<54 years vs 66–70 years), laboratory site, and most notably, individual pathologist. Pathologists with rates of testing higher than the mean (and therefore low miss rates) were 17 times more likely to conduct IHC testing than those with high miss rates. The primary finding that individual pathologist was the most important predictor of universal testing completion has been suggested in previous studies that found variable performance and

uptake of tumor MMRd testing based on cancer center (6,9,10). This finding highlights the potential use of MMRd testing in CRC as a quality performance metric; the investigators are developing a feedback process to alert pathologists of their rates of MMRd testing to mitigate the missed opportunities to screen for Lynch syndrome.

However, universal tumor screening for Lynch syndrome is only successful (and cost-effective) if patients who screen positive by tumor MMRd undergo germline genetic testing where the identified carriers can benefit from targeted cancer treatment, and their family members can also benefit from screening programs and other risk-reducing surgeries (11). This Canadian province's healthcare system allowed for a standardized program for genetic counseling referral and testing, provided multigene panel testing through next-generation sequencing, insurance coverage for tumor testing and germline testing and counseling for screen positive cases. Such a system eliminates a number of common barriers related to access to care and varied insurance coverage encountered in other healthcare systems. Under these close-to-ideal conditions, approximately 76% of patients with MMRd tumors were referred for genetic services, where pathologists were the major driver of referrals in 53.4% of cases and 22.4% were referred by other healthcare providers. When offered, uptake of genetics services was high and 84% of patients attended a counseling visit. Unfortunately, 24% of screen-positive cases were not referred. Although suboptimal, it is a marked improvement from most studies reporting less than 50% referral for genetic evaluation after positive tumor testing. A potential solution to help close this gap relates to the recent paradigm shift in genetic counseling service delivery models; upfront germline genetic testing for some malignancies is performed at the time of diagnosis (point-of-care), predominantly to guide treatment options, and genetic referral is reserved for post-test counseling in those with identified pathogenic variants. With a growing appreciation for the benefits of universal germline testing for all solid tumors, screening patients with CRC in this manner would facilitate the potential identification of all individuals with Lynch syndrome (12,13).

Stone and colleagues also reported the uptake of cascade testing, the process of offering genetic counseling and testing to at-risk family members of the proband diagnosed with Lynch syndrome. They reported that 21.1% of first-degree relatives underwent cascade testing, which is lower than prior reports

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ranging from 34% to 52% (14), despite full insurance coverage of cascade testing for relatives by the provincial universal healthcare plan. Similar to other genetics programs and current practice, probands were provided letters for family members and printed material to facilitate family communication, but studies report that the role of the provider is critical in the process of cascade testing and that the nature of provider engagement with patients and their relatives could be optimized (15,16). As the investigators conclude, gastroenterologists may not only facilitate genetic referral but also improve cascade testing and the identification of previvors. Because gastroenterologists are involved in the care continuum of Lynch syndrome carriers with frequent presence during annual/biennial endoscopic surveillance, they have the opportunity to often engage and/or facilitate communication with at-risk family members about cascade testing and its implications. Evaluation of novel strategies to improve the uptake of cascade testing warrant attention and a tracking system and/or other interventions to ensure program success may be an additional, critical component of Lynch syndrome screening.

Clinical practice guidelines for Lynch syndrome screening require continued development and updating, even within healthcare systems or practice settings that have already implemented screening programs, given the rapid pace with which genomic medicine can affect therapeutic decision making. Manitoba's program has made an investment in the necessary infrastructure to successfully implement universal tumor MMRd testing for Lynch syndrome screening. It may also be well-poised to assess future strategies for the optimal identification of Lynch syndrome through universal germline testing of all CRC cases and in those eligible for cascade testing, who can benefit most from cancer prevention.

## CONFLICTS OF INTEREST

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