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CRC SCREENING

Tumor-based screening for Lynch Syndrome: Check Every Colorectal Cancer

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STRUCTURED ABSTRACT

Question: What is the adherence to a universal colorectal cancer (CRC) tumor screening program for Lynch Syndrome and what are factors associated with non-adherence?

Study Design: Retrospective population-based cohort.

Setting: Manitoba, Canada.

Participants: Individuals aged 18-70 diagnosed with colorectal adenocarcinoma based on pathology records between March 2018 and December 2020.

Intervention: Manitoba implemented a universal tumor screening program in 2013, and as of December 2017, the program recommends that the primary diagnostic pathologist order immunohistochemistry (IHC) for mismatch repair (MMR) proteins in all patients diagnosed with colorectal

adenocarcinoma under age 70. These specimens are interpreted by 8 trained pathologists who are responsible for interpreting results and placing referrals for patients that have deficient MMR (dMMR) to the Program of Genetics and Metabolism. Genetic testing through this program is funded by universal health care plan. For those diagnosed with LS, genetic testing for at-risk family members living in Manitoba is offered at no cost to the family member.

Outcomes: The proportion of all CRCs that had appropriate IHC, the proportion of dMMR patients who were referred to the Program of Genetics and Metabolism, the proportion who completed germline genetic testing and the number of family members who completed genetic testing.

Results: Of the 1,692 unique patients diagnosed with colorectal adenocarcinoma during the study period (57% male, mean age 69), 936 were <70 and eligible for IHC screening. Eighty-eight percent of eligible specimens were screened (48% via biopsy specimen, 35% via surgical specimen and 5% via both) and 43 (5%) patients <70 were dMMR. Of the 58 dMMR patients in the entire cohort (all ages), 53% were referred to genetics by the pathologist and an additional 22% were referred by another physician (total referral rate of 75%, n=44). Of those referred, 84% accepted the appointment and of those who accepted the appointment, 87% (n=32) accepted genetic testing. Thirteen of these patients (40%) had a pathogenic or likely pathogenic germline variant in a Lynch Syndrome gene, 5 (16%) had a variant of uncertain significance. Among those with a pathogenic or likely pathogenic variant, 38 at-risk first-degree relatives living in Manitoba were identified and 21% (n=8) completed genetic testing. Individual pathologist (odds ratio 17.51, 95% confidence interval (CI) 6.05-50.67) and age <54 (odds ratio 0.53, 95% CI 0.30-0.97) were independently associated with completion of IHC for MMR proteins.

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COMMENTARY

Why Is This Important?

Lynch syndrome is the most common hereditary cancer syndrome with an estimated prevalence of 1/279 individuals,[1] accounting for 3-5% of all colorectal cancers. It also increases risk of multiple other cancers. There are effective cancer risk reduction strategies for Lynch Syndrome patients, including more intensive endoscopic surveillance, chemoprevention and risk reduction surgery that can significantly decrease the burden of cancer in these patients and their family members.[2] Unfortunately, Lynch Syndrome is grossly underdiagnosed with less than 10% of Lynch Syndrome patients being aware of their diagnosis in the United States.[3] An approach to improving identification of these patients is to screen all CRC patients for dMMR or microsatellite instability (MSI), the hallmarks of Lynch. Though this has been recommended by multiple professional societies, a minority of health systems in the US have successful universal screening programs.[4-7] Successful population-based implementation of a LS screening program can be an example to other health systems.

Key Study Findings

This study demonstrates that a protocolized universal tumor screening program where there is clear designation of who is responsible for ordering, performing, interpreting and conducting follow up on testing results in high adherence to tumor-based screening for Lynch Syndrome where 88% of eligible specimens are screened.

Unfortunately, there is successive drop off in appropriate referral to genetics, patient acceptance of referral, and patient acceptance of genetic testing, such that only 55% of patients who qualify for genetic testing based on tumor screening complete germline testing. Even when offered as a covered benefit, only 21% of family members of those with newly diagnosed syndromes complete germline genetic testing. The individual pathologist responsible for ordering the tumor-based IHC screening was the strongest predictor of whether the screening was completed.

Caution

Though health systems can use the results of this study to model programs within their systems, it is important to acknowledge several limitations to tumor-based screening. It requires multiple steps: (1) ordering/completing dMMR or MSI testing, (2) conducting any follow up tests (for instance *braf* or hypermethylation testing to exclude sporadic cancers in those with absence of *MLH1*/*PMS2* on IHC0, (3) interpreting results, (4) placing referral to genetics, (5) completion of genetic testing, and (6) disclosure of results to patients and clinical providers. Even when there is clear designation of who is responsible for completing, interpreting and following up on the testing, there is drop off at each level. This study also reinforced how these programs are still vulnerable to variabilities in practice among individual clinicians. Furthermore, the tumor testing approach does not screen for other hereditary syndromes, which account for 50% of all pathogenic/likely pathogenic variants among CRC patients,[8] and can even miss patients with Lynch Syndrome[9] . Thus, to try to simplify the process and optimize yield, there is movement in the field towards offering all CRC patients direct multigene panel germline genetic testing with the National Comprehensive Cancer Network asking clinicians to consider this approach for the first time in 2022.

My Practice

I recommend all CRC patients undergo hereditary risk assessment with three simple steps. First, we should be thinking about a possible hereditary syndrome in all patients we diagnose with CRC, regardless of age at diagnosis, family history or tumor characteristics. Second, I recommend ensuring that our pathology colleagues are performing tumor-based screening for dMMR on our CRC biopsy specimens instead of waiting until resection, since surgical management can change based on presence of a hereditary syndrome. Third, and finally, I recommend all patients with CRC be referred to a genetic counselor who can interpret tumor-based testing, collect multi-generation cancer family history and review the indications, benefits and expected yield of multi-gene panel testing for all CRC patients. I always

emphasize the importance of communicating genetic testing results to all family members so they may benefit from relevant cancer risk reduction interventions.

For Future Research

As we move towards direct germline genetic testing in CRC patients, more research will need to be done to determine exactly which genes should be included on a panel and how best to ensure equitable access to genetic testing and appropriate follow up care for newly diagnosed patients and their family members.

Conflict of Interest

Dr. Patel has no disclosures.

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