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When Should Patients Undergo Genetic Testing for Hereditary Colon Cancer Syndromes?

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Identifying Individuals With Hereditary Colorectal Cancer is an Opportunity to Deliver High-Value Care

Hereditary colorectal cancer (CRC) syndromes account for 5%–10% of all CRC cases. Identification of mutation carriers and their families offers potential to provide life-saving cancer surveillance and prevention strategies, and represents an opportunity to deliver high-value care. Potential detection strategies include (1) screening all individuals with CRC for Lynch syndrome (LS), (2) careful evaluation of individuals with high adenoma burden or unusual polyps, and (3) identifying individuals with high-risk personal and/or familial history of cancer.

High-Value Care Advice

Screen all individuals with CRC for LS

LS is the most common inherited predisposition to CRC, caused by a mutation in 1 of the 4 DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) or *EPCAM*, a promoter for the MSH2 gene. LS confers 15%–82% lifetime risk of CRC; up to 60% risk of endometrial cancer; and increased risks for ovarian, gastric, small bowel, brain, hepatobiliary, urinary tract, sebaceous gland, and pancreatic cancer.[1] Many, but not all, families with LS have multiple family members across multiple generations impacted by LS cancers because inheritance is autosomal-dominant. Preventive interventions, such as frequent surveillance colonoscopy or prophylactic hysterectomy, may improve outcomes.[2] Readily available clinical tests can identify suggestive molecular “signs” within LS cancers, including failure to express ≥1 DNA mismatch repair proteins as measured by immunohistochemistry, and presence of high-frequency microsatellite instability.[3] Both features are easily assessed with clinically available tests. Screening all patients with CRC for either abnormal absence of DNA mismatch repair protein expression or microsatellite instability is referred to as

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Conflicts of interest

The authors disclose no conflicts.

"universal screening," and has been shown to maximize sensitivity for identifying individuals with LS compared with selection based on age at presentation and/or family cancer history.[4] The American Gastroenterological Association, National Comprehensive Cancer Network, and others have recommended universal screening for all newly diagnosed patients with CRC for LS, regardless of age at presentation or cancer family history.[3,5] Recommendations are supported by evidence that universal screening, coupled with mutation testing and surveillance in the index patient and relatives, has potential to reduce CRC morbidity and mortality.[6] Moreover, subsequent analyses have suggested this strategy is cost-effective.[7]

Evaluate all individuals with >10 adenomas or multiple hamartomatous polyps for potential genetic syndromes

Several polyposis syndromes that present with high adenoma burden or unusual polyps are associated with high CRC risk (Table 1).[8] Because patients with these conditions may be offered frequent surveillance colonoscopy and even prophylactic colectomy if cancer or an unmanageable polyp burden is present, identification offers potential to improve CRC outcomes. Work-up should be triggered based on presence of >10 adenomas, multiple hamartomatous polyps, or suggestive extracolonic manifestations (Table 1), and should include a careful assessment of number and type of polyps, and detailed family history.[9] Those with concerning features (eg, >20 adenomas, hamartomatous polyps, or >10 adenomas plus any concerning extracolonic manifestation and/or family history of cancer) should move on to referral to a genetics specialist and be considered for genetic testing.

Identify individuals with high-risk personal and/or familial history of cancer

Potential high-risk history includes early age onset of CRC or endometrial cancer (younger than 50 years of age), presence of multiple CRCs or other LS cancers, history of multiple family members with CRC or LS cancers (especially young onset), or known hereditary syndrome in the family. For identifying individuals at risk for LS, probability models, such as PREMM5 (http://premm.dfci.harvard.edu/), based on personal and family history have been developed.[10] Consensus guidelines recommend genetic evaluation for those with a ≥5% model-predicted chance of having LS, personal or familial history of young-onset CRC, and/or when multiple family members are affected by cancer.

Implementation

Risk assessment and referral for hereditary CRC syndromes in usual practice is underutilized. Furthermore, physicians have difficulty in obtaining an accurate family history and recognizing potential hereditary CRC syndromes.[11] Implementation of universal screening for LS has been slow.[12] Because gastroenterologists are at the forefront of CRC diagnosis and prevention, they are uniquely positioned to recognize individuals at increased risk based on phenotype and family history, but must develop and implement standardized protocols to ensure assessment. One approach recommended by the National Colorectal Cancer Roundtable is to implement a simple 3-question tool for identifying individuals at potentially increased risk meriting more detailed assessment of personal and family history that includes the following 3 questions[18]:

1. Do you have a first degree relative with CRC or LS-related cancer diagnosed before age 50?
2. Have you had CRC or polyps diagnosed before age 50?
3. Do you have ≥3 relatives with CRC?

Conclusions

We recommend 3 strategies for finding individuals with hereditary CRC syndromes: (1) screening all individuals with CRC for LS, (2) careful evaluation of individuals with high adenoma burden or unusual polyps, and (3) identifying individuals with high-risk personal and/or familial history of cancer. Finding individuals and families with hereditary CRC syndromes presents an underutilized opportunity for delivery of high-value care.

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Table 1.

Clinical Features and Lifetime CRC Risk Associated With >10 Adenomas or Hamartomatous Polyps

Syndrome	Genes	Clinical features	Lifetime CRC risk
Familial adenomatous polyposis	*APC*	Adenomas, thyroid cancer, desmoid tumors, duodenal adenomas, mandibular osteomas, and congenital hypertrophic pigmentary lesions of the retina	100%[13]
MYH-associated polyposis	*MUTYH* (biallelic)	Adenomas, thyroid cancer, colorectal cancer	43%–100%[14]
Peutz-Jeghers	*STK11*	Mucocutaneous melanin spots, hamartomas, breast, gastrointestinal, pancreatic, ovarian sex cord tumors with annular tubules, testicular large calcifying Sertoli cell tumors	39%[15]
Cowden/PTEN hamartoma	*PTEN*	Hamartomas, dermatologic lesions (trichilemmomas, and papillomatous papules), macrocephaly, breast, thyroid, and endometrial cancers	9%[16]
Juvenile polyposis	*BMPR1A, SMAD4*	Hamartomas, colon cancer, some with *SMAD4* have hemorrhagic hereditary telangiectasia	50%[17]

CRC, colorectal cancer.

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