Risk Assessment, Genetic Testing, and Management of Lynch Syndrome

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Abstract
Of the estimated 150,000 colorectal cancer (CRC) cases diagnosed annually, approximately 30% have a familial basis and 3% to 5% are from high-penetrance inherited cancer syndromes. Lynch syndrome, or hereditary nonpolyposis colorectal cancer, caused by inherited germline mutations in mismatch repair (MMR) genes, is the most commonly inherited CRC syndrome. It is characterized by young-onset CRC and an increased risk for extracolonic tumors, including gynecologic, urinary tract, and other gastrointestinal cancers. Commercial testing is available for mutations in the MMR genes, but testing all patients with CRC would be economically prohibitive. Therefore, a comprehensive evaluation of a multigenerational family cancer history is essential for the identification of at-risk individuals. The presence of tumors diagnosed at a young age, multiple first- and second-degree relatives with cancer, or 2 or more primary cancers may be indicative of an inherited cancer syndrome and these individuals should undergo genetic evaluation. Genetic test results, when conclusive, can guide management for patients and their families. However, indeterminate test results may provide false reassurance to patients who should be managed as being at higher-than-average risk. Online risk assessment tools and commercial genetic testing offer the potential to identify a greater number of at-risk individuals at an earlier age. However, for these measures to improve outcomes, patients must receive screening recommendations and counseling appropriate for their cancer risk. (*JNCCN* 2010;8:98–105)

Colorectal cancer (CRC) is the second leading cause of cancer death in the United States. Approximately 65% of all CRC cases are sporadic, and may be associated with environmental factors or polygenic in inheritance from multiple low-penetrance susceptibility genes and do not exhibit familial clustering of cancer.

Nearly 30% of CRC cases arise from moderately penetrant, inherited susceptibility genes, possibly interacting with environmental factors.[1,2] In families with moderately penetrant, inherited susceptibility genes there is a clustering of CRC cases in excess of that expected by chance.[3] Studies have shown that the risk for CRC is 2- to 3-fold higher than expected in the general population if a first-degree relative is diagnosed with CRC. This risk increases to 3-fold or higher if 2 first-degree relatives have CRC or a single first-degree relative is diagnosed with CRC prior to 50 years of age. An individual's risk for developing CRC is also increased if a second- or third-degree relative has CRC or a first-degree relative has a colorectal adenoma.[4,5]

Among CRC cases, 3% to 5% are caused by highly penetrant inherited syndromes, including Lynch syndrome or hereditary nonpolyposis colorectal cancer (HNPCC), familial adenomatous polyposis (FAP), *MYH*-associated polyposis (MAP), and rare hamartomatous polyposis syndromes. This article focuses on the diagnostic features, evaluation, and management of Lynch syndrome, and includes a brief discussion of other inherited CRC syndromes.

Background

Lynch syndrome, the most common familial CRC syndrome, results from a mutation in one of the mismatch repair genes: *MLH1, MSH2, MSH6,* or *PMS2*. After Aldred Warthin[6] initially described it in a family with endometrial cancer and CRC, Henry Lynch later

broadened the syndrome to include a spectrum of malignancies.[6,7] Lynch syndrome is now known to be associated with early onset of CRC and a predisposition to cancers of the endometrium, ovary, stomach, small bowel, biliary tract, urinary tract, and brain.

Clinical Features

Individuals with Lynch syndrome have a 60% to 80% lifetime risk for developing CRC.[8–11] Cancer risk varies based on gender and the mismatch repair mutation.[8,11–14] CRCs in Lynch syndrome arise from adenomatous polyps. Although individuals with Lynch syndrome develop adenomas more frequently than controls,[15] they do not present with hundreds to thousands of polyps, as seen in classic FAP. A large proportion of adenomas in individuals with Lynch syndrome show advanced histology. In addition, the progression from adenoma to carcinoma may occur over a shorter interval of 2 to 3 years, in contrast to 8 to 10 years in sporadic CRC cases.[16,17]

CRC in Lynch syndrome has an early age of onset, with an average age of 45 years at diagnosis. Individuals with Lynch syndrome are at risk for both synchronous and metachronous CRC.[16] These CRCs are frequently located in the proximal colon (70%) and on histology have an intense Crohn's-like lymphocytic reaction, a mucinous component, or are poorly differentiated.[18] After adjusting for stage, patients with Lynch syndrome who have CRC have a better prognosis than sporadic cases; however, the reasons for the better prognosis remain unclear.[19–21]

Individuals with Lynch syndrome are also at risk for several extracolonic malignancies. Among women, endometrial cancer is the second most common malignancy, with an estimated lifetime risk of 40% to 60%. Women also have a 10% to 12 % lifetime risk for developing ovarian cancer.[10,13,22] Brain tumors are the third leading cause of cancer death in individuals with Lynch syndrome.[23] The Turcot variant of Lynch syndrome is associated with astrocytomas, glioblastomas, and oligodendrogliomas of the brain.[24] Sebaceous neoplasms of the skin, including sebaceous adenoma, sebaceous epithelioma, basal cell epithelioma with sebaceous differentiation, sebaceous carcinoma, and squamous cell cancer (keratoacanthoma type), are associated with Muir-Torre syndrome.[25] The spectrum of Lynch-associated malignancies is also known to include stomach, small intestine, biliary tract, and urothelial carcinoma of the renal pelvis and ureter.

Genetics

Lynch syndrome is inherited in an autosomal dominant pattern. Germline mutations in mismatch repair (MMR) genes MLH1 and MSH2 account for 90% of cases.[16] Mutations in MSH6 have been found in 6% to 10% of families with a history of Lynch syndrome, and mutations in PMS2 have been identified in 1%.

The MMR system is responsible for correcting errors that occur during DNA replication. Slippage of DNA occurs frequently during the replication of short mononucleotide or dinucleotide repeat sequences (microsatellites), resulting in too few or too many copies. These errors are normally corrected by DNA polymerase. Errors not corrected by DNA polymerase are corrected by the MMR mechanism. In individuals with Lynch syndrome, errors in microsatellite repeat sequences are not corrected because of failure of the MMR mechanism. This phenomenon is referred to as *microsatellite instability* (MSI). Tumorigenesis results when the second copy of the affected MMR gene is somatically mutated and microsatellites are located in the coding regions of genes involved in tumor initiation and progression.

Genetic Evaluation

Genetic evaluation confirms the suspected clinical diagnosis of Lynch syndrome in individuals and helps stratify family members according to risk. Initial evaluation in families with no known mutation should begin with molecular analysis of the colorectal tumor.

Tumor Molecular Evaluation

MSI Testing: MSI is usually assessed using a panel of 5 microsatellite markers recommended by the National Cancer Institute. The MSI phenotype is defined by the number of markers that show instability.[26] Tumors are considered microsatellite high (MSI-H) if 2 or more of the 5 microsatellite sequences are mutated, microsatellite low (MSI-L) if 1 sequence is mutated, and microsatellite stable if none of the sequences in tumor DNA are mutated.

Immunohistochemistry Testing: Immunohistochem-

istry (IHC) testing analyzes the expression of MMR proteins. Tumors in Lynch syndrome frequently show loss of staining for the antibodies to MMR proteins.[27] Loss of expression of a MMR protein according to IHC is an alternate marker of MMR mutations.[28] Guidelines recommend germline testing for MMR mutations in individuals with abnormal MSI or IHC results.

Both MSI and IHC testing have limitations. IHC analysis is a faster, less expensive test than MSI analysis, but mutations associated with immunoreactive, although nonfunctional, proteins can result in false-negative IHC results. Studies have also shown slightly lower sensitivity of IHC compared with MSI testing.[29–32]

With regard to MSI testing, although 90% of Lynch-related cancers show MSI, up to 15% of sporadic CRCs may have MSI abnormalities because of epigenetic mechanisms (i.e., inactivation of *MLH1* by promoter methylation).[33] Therefore, in tumors that show loss of MLH1 staining on IHC, it may be reasonable to perform *BRAF* mutation analysis for the p.V600E mutation associated with sporadic *MLH1* promoter methylation before performing germline testing.

Germline Testing

The presence of a pathogenic/deleterious germline mutation in 1 of 4 MMR genes identifies individuals positive for Lynch syndrome or true positive. Once a pathogenic mutation is identified in the proband, at-risk relatives can be tested for the same mutation. If the identified family mutation is not found, the results are considered true negative and these individuals can be managed as average-risk. When no family mutation is identified and no pathogenic mutation detected, or a mutation of unclear pathogenic significance is found, genetic test results are considered indeterminate or uninformative. Individuals with indeterminate results are still considered at higher-than-average risk, and recommendations for surveillance must be based on personal and family cancer history.

Identification of Individuals at Risk

Clinical Criteria

In 1991, the Amsterdam criteria were proposed to identify individuals who were likely to be mutation carriers. They required the presence of young-onset CRC, in addition to a family history of 3 CRCs involving 2 successive generations. Because these criteria are stringent, they are limited in sensitivity.[19] The Amsterdam II criteria include other Lynch-associated malignancies,[34] and therefore have a higher sensitivity than the Amsterdam criteria. With the introduction of tumor molecular analysis for Lynch syndrome, the Bethesda guidelines were proposed to help identify patients for MSI testing.[35] Studies evaluating the performance of clinical criteria in populations at high-risk for Lynch syndrome have shown that the Bethesda guidelines have a higher sensitivity than the Amsterdam I and II criteria.[36]

Recently, revised Bethesda guidelines were proposed to improve the accuracy of identifying patients with Lynch syndrome.[37] However, Hampel et al.[38] highlighted the limitations of these criteria, noting that in a population-based cohort of 1066 patients with CRC, 5 of 23 mutation carriers did not meet the Bethesda or revised Bethesda criteria and would otherwise have been missed if genetic evaluation was limited to individuals who met these criteria. In light of these limitations, an alternative strategy involving universal MSI/IHC testing of all individuals with CRC was proposed. Even if this strategy were found to be cost-effective, it may still fail to identify cases in which MMR mutations disrupt MMR function but do not result in MSI, as seen with *MSH6* mutations or when IHC results are normal despite a nonfunctional MMR protein.

Prediction Models

Prediction models have been developed to identify individuals at risk for Lynch syndrome and to quantify the risk for germline MMR mutations. Three models are noteworthy: the Barnetson et al.[21] model, the PREMM$_{1,2}$,[39] and the MMRpro.[40]

Barnetson et al.[21] analyzed a population-based cohort of 870 patients diagnosed with CRC before 55 years of age. They developed a 2-stage model to predict *MLH1, MSH2*, and *MSH6* mutations using multivariable regression analysis. The model included patient age, gender, tumor location, presence of synchronous and metachronous CRCs, family history of endometrial cancer and CRC, age of the youngest relative with CRC (stage 1), and tumor MSI and IHC results (stage 2). The model was then validated in 155 patients with CRC diagnosed before 45 years of age.

The model sensitivity of 62%, specificity of 97%,

and positive predictive value of 80% were superior to the performance of the Bethesda and Amsterdam criteria. The ability of the model to separate mutation carriers from those without an MMR mutation (model discrimination) was similar between the derivation and validation cohorts. However, this model was developed and validated in patients with young-onset CRC and did not include Lynch-associated cancers other than endometrial cancer.

The $PREMM_{1,2}$ model (Prediction of mutations in *MLH1* and *MSH2*) was developed using a cohort of 1914 individuals at moderate risk for Lynch syndrome.[39] Clinical data from 898 probands were used for model derivation. The model was then validated in 1016 unrelated probands. The final multivariable logistic regression model included proband diagnosis of CRC, colonic adenomas, extracolonic Lynch-associated cancers, and a family history of Lynch cancers. The $PREMM_{1,2}$ model showed good discrimination with an area under the receiver operating curve of 0.80. It has also been validated in a large population-based cohort.[41] Strengths of the model include its ability to incorporate extracolonic Lynch-associated neoplasms and provide individualized risk prediction using an easy-to-use web-based calculator. However, the $PREMM_{1,2}$ model does not consider family size or unaffected family members.

The MMRpro model uses estimates of mutation prevalence and the penetrance of MMR genes to estimate the probability of carrying a deleterious mutation in *MLH1*, *MSH2*, and *MSH6* genes.[40] The model can also estimate the probability of developing CRC or endometrial cancer in unaffected relatives. In the validation group, the MMRpro model performed better at identifying mutation carriers than the Bethesda guidelines, although it slightly overpredicted the number of carriers. Advantages of the MMRpro model include its ability to account for family size by including unaffected relatives and to incorporate MSI data. For individuals with indeterminate or uninformative genetic testing results, the MMRpro model can provide postsequencing probability of a deleterious mutation. These estimates are particularly valuable given that genetic testing has limitations in sensitivity and that uninformative results may lead to false reassurance and poor adherence to recommended cancer screening.[42]

Studies have shown that these 3 prediction models have comparable sensitivities to the revised Bethesda criteria. They can also provide quantitative risk assessment and streamline genetic testing by identifying the family member with the highest probability of being a mutation carrier. But before prediction models can be widely incorporated into more advanced management decisions, such as deciding the extent of surgical resection in an operative setting, external validation studies are needed to assess the transportability of model cutoffs in population-based and high-risk cohorts. An approach to the genetic evaluation for Lynch syndrome is outlined in Figure 1.

Management

Screening and Management of CRC

Among individuals with Lynch syndrome, screening for CRC has been shown to decrease CRC incidence and mortality.[43,44] In a prospective screening study that followed individuals over 15-years, colonoscopies at 3-year intervals decreased CRC mortality by 63%.[44] Observational studies have, however, reported interval cancers in individuals undergoing colonoscopies at 3-year intervals.[45] Therefore, current screening guidelines take into account the early age of CRC onset, predisposition to proximal and metachronous cancer, rapid progression from adenoma to carcinoma, and incidence of interval cancers. Individuals with Lynch syndrome are recommended to undergo CRC screening with colonoscopy every 1 to 2 years beginning at 20 to 25 years of age.[46,47]

In patients with Lynch syndrome who develop CRC, given their risk for synchronous CRCs, evaluation of the entire colon is necessary before surgical resection. Microsatellite stability may affect the response to chemotherapy. Patients who have MSI-H cancers are less likely to respond to alkylating agents or 5-FU[48,49] but are more likely to respond to irinotecan than patients who have MSI-L CRCs.[50] In patients undergoing surgery, subtotal colectomy should be considered because the cumulative risk for detecting a second CRC at 10-year follow-up is significantly higher after a partial colectomy (3.4% and 15.7%, respectively).[51]

Screening for Endometrial Cancer

Guidelines recommend that women at risk for Lynch syndrome undergo endometrial cancer screening with annual transvaginal ultrasound and endometrial
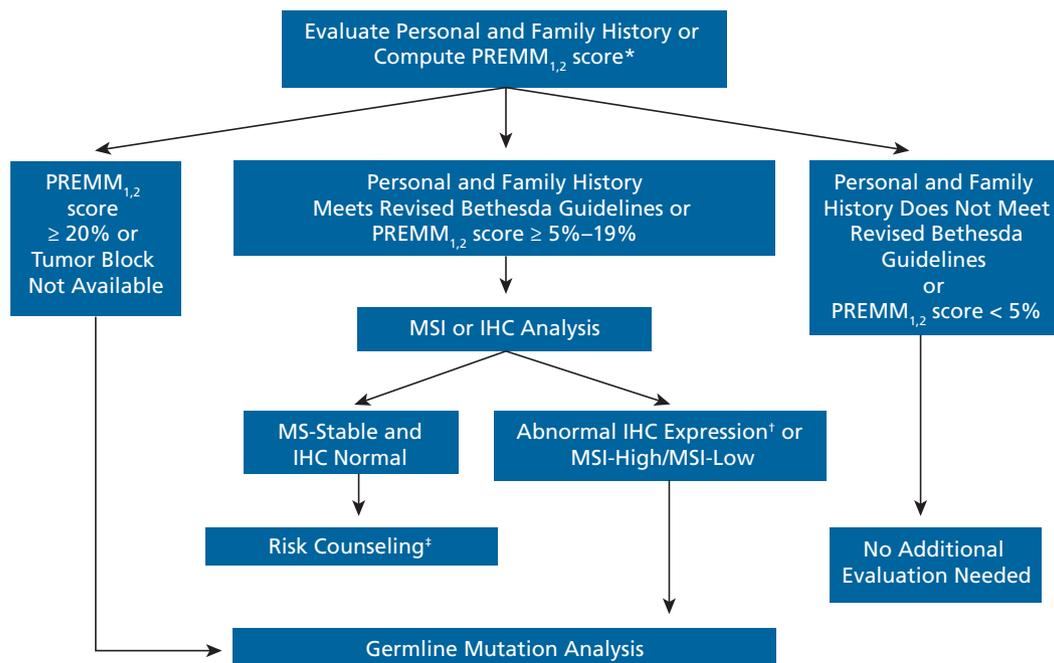
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Figure 1   Algorithm for genetic evaluation of individuals with colorectal cancer based on revised Bethesda guidelines and $PREMM_{1,2}$ score.

Abbreviations: IHC, immunohistochemistry; MSI, microsatellite instability.

*Other models may be used. Each model has its own prespecified cutoff ($PREMM_{1,2}$: http://www.dana-farber.org/pat/cancer/gastrointestinal/crc-calculator/default.asp; Barnetson: https://hnpccpredict.hgu.mrc.ac.uk/; MMRpro: http://astor.som.jhmi.edu/Bayes-Mendel/).

[†]If loss of MLH1 expression, *BRAF* analysis should be performed.

[‡]Surveillance recommendations based on personal and family history.

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biopsy beginning at 25 to 35 years of age. Although screening for endometrial cancer has not been shown to improve survival in women with Lynch syndrome, data suggest that screening may lead to the detection of premalignant lesions or of endometrial cancer at an early stage.[52]

An alternative strategy to endometrial cancer screening is prophylactic hysterectomy and bilateral salpingo-oophorectomy. In a case-control study, Schmeler et al.[53] examined the occurrence of endometrial and ovarian cancer in women with Lynch syndrome who had undergone prophylactic hysterectomy alone or with bilateral salpingo-oophorectomy, compared with controls. No endometrial cancers occurred in the 61 women who underwent hysterectomy compared with 69 endometrial cancers in 210 controls. In addition, no ovarian or peritoneal cancers were diagnosed in the 47 women who had undergone bilateral salpingo-oophorectomy, compared with 12 of 223 controls. Although this study

supported prophylactic surgery to reduce the risk for endometrial and ovarian cancer, the protective effect against ovarian cancer after surgery was not statistically significant. Therefore, discussion of prophylactic hysterectomy and bilateral salpingo-oophorectomy should be part of management, particularly when childbearing is complete.

Screening for Other Cancers

Annual physical examinations with total body dermatologic examinations are recommended for individuals with Lynch syndrome.[9] The incidence of brain tumors and cancers of the small bowel, stomach, and biliary tract are too low to warrant routine screening.[54] However, experts have suggested that if the family shows a clustering of gastric cancers or there is a high incidence of gastric cancer in the individual's country of origin, screening for gastric cancer with esophagogastroduodenoscopy can be considered. Screening for urothelial cancers starting at 30 to 35 years using annual urine analysis with cytol-

ogy and renal ultrasounds in families with clustering of these tumors has been proposed, but no data exist on the effectiveness of these approaches. Therefore, screening for these cancers is generally approached on a family-by-family basis and individualized based on the specific spectrum of tumors.

Differential Diagnosis

"Familial colon cancer type X" has been used to describe families that meet Amsterdam criteria due to clustering of CRCs, but with no DNA mismatch repair mutation. Studies have suggested that the incidence of CRC may be lower in these families as compared with those with Lynch syndrome, and these individuals may not be at an increased risk for extra-colonic cancers.[55]

Attenuated FAP (AFAP) and MAP should also be considered in the differential diagnosis. FAP is caused by an inherited mutation in the adenomatous polyposis coli (APC) gene. FAP follows an autosomal dominant pattern of inheritance, but approximately one third of cases arise from de novo mutations. Unlike patients with classic FAP who may present with greater than a thousand polyps, those with AFAP have an average of 30 polyps and can present in the fourth or fifth decade. These patients have a 70% to 80% lifetime risk for developing CRC and are at risk for polyps in the upper gastrointestinal tract.

MAP should be considered in patients with colorectal adenomas and CRC whose family history is suggestive of an autosomal recessive inheritance. Biallelic pathogenic mutations in the MYH gene may account for 30% of families with multiple adenomas who do not have a pathogenic APC mutation.[56] As with Lynch syndrome, genetic testing for AFAP and MAP allows for assessment of the patient's cancer risk and identification of at-risk and affected family members. Although no clear guidelines exist for the frequency of endoscopic surveillance in MAP, current recommendations include upper endoscopy and colonoscopy, the frequency of which should be based on the size, number, and pathology of polyps.[57]

Conclusions

A comprehensive assessment of an individual's family history of cancer is essential in determining risk for developing CRC. More frequent screening is recommended for patients with familial cancer risk than for average-risk individuals. For patients with a family history of cancer who meet criteria for an inherited cancer syndrome (based on clinical criteria or with a score higher than the prespecified prediction model cutoff), genetic testing should be performed. As other low penetrance genes that contribute to familial risk are identified and gene–gene and gene–environment interactions are more clearly defined, the interpretation and estimation of cancer risk is likely to become more complex. Testing should therefore be performed in a specialized setting so that risk counseling and recommendations for future screening can be made in accordance with an individual's cancer risk.

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