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History, Genetics, and Strategies for Cancer Prevention in Lynch Syndrome

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Abstract

Colorectal cancer (CRC) is the most common gastrointestinal malignancy and the third cause of cancer death in men and women in the United States. The majority of CRC cases diagnosed annually are due to sporadic events, but up to 6% are attributed to known monogenic disorders that confer a markedly increased risk for the development of CRC and multiple extracolonic malignancies. Lynch syndrome is the most common inherited CRC syndrome and is associated with mutations in DNA mismatch repair genes, mainly *MLH1* and *MSH2* but also *MSH6*, *PMS2*, and *EPCAM*. Although the risk of CRC and endometrial cancer may approach near 75% and 50%, respectively, in gene mutation carriers, the identification of these individuals and at-risk family members through predictive genetic testing provides opportunities for cancer prevention including specialized cancer screening, intensified surveillance, and/or prophylactic surgeries. This article will provide a review of the major advances in risk assessment, molecular genetics, DNA mutational analyses, and cancer prevention and management made since Lynch syndrome was first described 100 years ago.

Keywords

Lynch Syndrome; Colorectal Cancer

Colorectal cancer (CRC) is a common malignancy, affecting more than 143,000 new patients each year in the United States and estimated to cause 52,000 deaths in the year 2013.¹ Although the majority of cases are believed to be sporadic, up to 30% are associated with a family history of CRC. Monogenic mutations conferring a high lifetime risk of CRC have been identified in nearly 6% of cases.^{2,3}

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Conflicts of interest

The authors disclose no conflicts.

Lynch syndrome is a highly penetrant, autosomal dominant cancer-susceptibility syndrome implicated in approximately 2%–4% of all CRC cases.^{3,4} It is associated with germline mutations in DNA mismatch repair (MMR) genes, which significantly increase the risk for colorectal, endometrial, and numerous other cancers. Estimates from population-based studies suggest that 1 in every 35 patients with newly diagnosed CRC may have Lynch syndrome, which translates into 4100 individuals annually in the United States.^{5,6} Although lifetime risk for CRC approaches 75% among MMR gene mutation carriers, frequent endoscopic surveillance can decrease this risk. The identification of individuals with Lynch syndrome provides opportunities for cancer prevention through intensified screening, surveillance, and/or prophylactic surgeries.

Historical Perspective

In 1913, Dr Aldred Scott Warthin, a pathologist at the University of Michigan, published the first known case report of a family characterized by a distinct susceptibility to the development of endometrial and gastric cancer.⁷ The pedigree of Warthin's "Family G" has been systematically studied and provided a template for the identification of additional families with similar phenotypes.^{8–11} In 1966, Dr Henry Lynch described 2 large Midwestern kindreds whose members were affected with colon, gastric, and endometrial cancers and proposed that these could be attributed to an autosomal dominant "cancer family syndrome."¹² The term *Lynch syndrome* was coined in 1984 and subdivided as Lynch I and Lynch II to distinguish families with a preponderance of CRC from those with additional endometrial and other noncolonic tumors.^{13,14} The term *hereditary nonpolyposis colorectal cancer* (HNPCC) subsequently emerged to distinguish these cases from those related to the classic presentation of familial adenomatous polyposis (FAP),¹⁵ the more commonly recognized autosomal dominant CRC syndrome associated with hundreds to thousands of colorectal adenomatous polyps.

For nearly a century after Warthin's first description of Family G, the disease was defined by its clinical manifestations.¹⁶ However, in 1993 genome-wide linkage analysis in several large families with autosomal dominant inheritance of CRC led to the discovery of 2 loci on chromosomes 2p and 3p.^{17,18} It was observed that the tumors in these cases had histopathologic features that distinguished them from other nonfamilial cases. The presence of instability at DNA microsatellites provided evidence to implicate errors in MMR in these cancers, which was a novel pathway in CRC development at the time.^{19,20} The association between microsatellite instability (MSI) in colorectal tumors and defects in DNA MMR was made through observations originally described in bacterial and yeast genetics,¹⁶ and these discoveries led to the cloning of the 4 MMR genes most commonly associated with HNPCC, beginning with *MLH1* and *MSH2*, followed by *MSH6* and *PMS2*.^{21–26}

The term *HNPCC* has been criticized for its narrow focus on CRC risk and has fallen out of favor, and the eponymous Lynch syndrome, along with its expanded constellation of malignancies, has been reassigned to denote families affected with germline mutations in DNA MMR genes.

Genetics

Lynch syndrome is associated with germline mutations in *MLH1* (Mut L homologue), *MSH2* and *MSH6* (Mut S homologues), and *PMS2* (postmeiotic segregation, a Mut L homologue). These genes code for proteins integral to complexes involved in MMR, which maintain genomic fidelity by correcting nucleotide mismatches that have “escaped” the normal editing function of DNA polymerase. Errors in single-base mismatches and insertion-deletion loops that form during DNA replication can result in mutations in genes that regulate cell growth and promote neoplasia. In an intact MMR system, proteins bind to nucleotide base mismatches of double-stranded DNA or loops of inaccurately replicated repetitive sequences called microsatellites and target these for repair. A heterodimer complex between MSH2-MSH6 (MutS) recognizes the single nucleotide mispairs and binds to the mismatched sequence, and a second heterodimer complex between MLH1-PMS2 (MutL) binds to MutS to remove several bases from the newly synthesized DNA strand, allowing for resynthesis of DNA with the correct base pairing.^{27,28}

In the majority of individuals with Lynch syndrome, germline mutations can be found in 1 of the 4 DNA MMR genes. An additional somatic event in the wild-type allele is necessary to make both copies of the MMR gene inactive, which predisposes to accumulation of somatic mutations and results in the hypermutable phenotype observed in tumors of mutation carriers. Mutations in the *MLH1* and *MSH2* genes were originally believed to account for more than 90% of all Lynch syndrome cases.⁴ However, recent contributions related to *MSH6* and *PMS2* gene mutations were underestimated in affected families because they display a less striking phenotype. In a population-based study evaluating universal molecular tumor testing on consecutive CRC cases, the prevalence of *MSH6* and *PMS2* gene mutations was as high as 13% and 9%, respectively.⁶ In 2009, germline deletions in the *EPCAM* gene (formerly known as *TACSTD1*) were found in families with presumed Lynch syndrome whose cancers featured loss of MSH2 protein expression without detectable germline *MSH2* mutations.^{29,30} Deletions in the 3' end of *EPCAM* result in epigenetic silencing of the neighboring *MSH2* gene by promoter hypermethylation and may account for up to 6.3% of all Lynch syndrome cases.^{31,32}

Clinical Features and Cancer Risks in Lynch Syndrome

Individuals with Lynch syndrome are at increased risk for developing CRC and other cancers, including those of the endometrium, ovaries, stomach, small intestine, urinary tract, brain, pancreas, and cutaneous sebaceous glands. Colon cancers and polyps in Lynch syndrome typically arise at a young age, although newer data suggest variability in the age of onset. CRC tumors in Lynch syndrome are predominantly right-sided, and the risk of developing metachronous CRC is high, estimated at nearly 30% at 10 years after the first diagnosis.³³ Histologically, Lynch syndrome-associated colorectal tumors are often mucinous, poorly differentiated, and have a large number of tumor-infiltrating lymphocytes, and more than 90% display a high level of MSI, the hallmark feature of cancers that arise in the setting of defective DNA MMR.⁴

Several studies quantify the risks of colorectal, endometrial, and other associated cancers in Lynch syndrome (Table 1).^{34–45} Estimates for lifetime risk of CRC and endometrial cancer have been reported to be as high as 80% and 60%, respectively, although these estimates have been challenged because of the possibility of ascertainment bias. Ascertainment bias can result in overestimates of cumulative cancer risks because calculations are derived from families with unusually striking histories of early-onset CRC, multiple CRCs, or Lynch syndrome–associated cancers enrolled through family cancer registries. Many earlier published data also reported estimates based exclusively on observed genotypes and did not adjust calculations for incomplete testing of the full pedigree. More recent studies that use statistical methodologies to correct for ascertainment bias report lifetime risk estimates ranging from 22% to 66% and 32% to 45% for CRC and endometrial cancer, respectively.^{38–40}

In a prospective cohort comparing cancer risks between unaffected carriers and noncarriers from 284 families with known MMR gene mutations, the risk of CRC was 4% at 5 years and 8% at 10 years of follow-up for carriers compared with 0.4% and 2%, respectively, for noncarriers.⁴³ The 5- and 10-year cumulative risks for endometrial cancer were 2.8% and 9.8%, respectively, in carriers, whereas no endometrial cancers were observed in noncarriers. A prospective study of 764 MMR gene mutation carriers enrolled through multiple family cancer registries reported on the risk of extracolonic cancers after a previous diagnosis of CRC.⁴⁴ The most common cancers were urinary tract cancers, with an estimated 5.2% cumulative risk at 20 years, and small bowel cancer, with a lifetime risk of 4%. In addition, the risk of pancreatic cancer has been estimated to be approximately 4%.^{43,45} Higher risks for other malignancies not typically associated with Lynch syndrome include breast and prostate cancer, which confer a nearly 2-fold increased risk in female and male carriers, respectively, compared with the general population.^{42,43,46}

Cancer risks may vary according to which MMR gene is mutated. Studies that assessed genotype-phenotype correlations have found higher risks for CRC in families with *MLH1* gene mutations, with cases diagnosed at younger ages compared with *MSH2* and *MSH6* carriers.^{47–51} The overall risk of extracolonic tumors appears higher among *MSH2* gene mutation carriers. For *MSH6* gene mutation carriers, risk of CRC appears to be lower and tends to occur at later ages compared with *MLH1* and *MSH2* carriers; however, the risk of endometrial cancer appears to be higher and may be the most prominent tumor in some families.^{52–56} In a large study that evaluated gene-specific risk estimates among 537 French families with identified MMR gene mutations, overall cancer risks were lower for *MSH6* carriers, compared with *MLH1* or *MSH2* gene mutation carriers.⁵⁷ Although risks of CRC were similar among *MLH1* and *MSH2* carriers, endometrial cancer risk was highest in *MLH1* carriers, and the cumulative risks of other Lynch syndrome cancers were highest among *MSH2* gene mutation carriers.

Information regarding cancer risks for *PMS2* gene mutation carriers is limited, but individuals with *PMS2* mutations appear to have a lower overall risk of cancer compared with other MMR gene mutation carriers. Lifetime risk estimates range from 15% to 20% for CRC, 15% for endometrial cancer, and 25% to 32% for any Lynch syndrome–associated cancer up to age 70 years.⁵⁸ Information regarding the tumor spectrum in carriers of the

EPCAM deletions is even more limited. In a recent study of 194 *EPCAM* deletion carriers, the CRC risk was 75% by age 70 years for both men and women. Female carriers had a 12% lifetime risk of endometrial cancer, which is lower than most reports for *MLH1*, *MSH2*, and *MSH6* gene mutation carriers.³² Another study of 77 gene mutation carriers reported no endometrial cancers among 2 large kindreds with *EPCAM* deletions.⁵⁹ Deletions extending close to the *MSH2* promoter region may more efficiently inactivate *MSH2* and are associated with a higher risk of endometrial cancer than those deletions that involve only the termination of *EPCAM* that present with a more colon-specific phenotype.^{32,59} However, additional data are needed to assess whether current recommendations for management of endometrial cancer risk should be altered for *EPCAM* gene mutation carriers.

The high variability in cancer risks observed among Lynch syndrome carriers may be related in part to the influence of modifier genes and/or environmental factors.⁶⁰ Numerous studies on the heterogeneity of age of CRC onset among carriers attribute this to certain modifier genes including variants in the *IGF1*, *RNASEL*, and *HFE* genes.^{61–63} Recent associations have also been made between genes regulating the cell cycle, xenobiotic-metabolizing enzymes, and telomerase and young age of CRC onset in MMR gene mutation carriers.^{64–66}

Management

Screening and Surveillance

Colonoscopy has been shown to decrease CRC incidence and mortality in individuals with Lynch syndrome. A prospective Finnish study found that colonoscopic surveillance was associated with a reduction in CRC incidence and mortality by 63%.^{67,68} Even so, colonoscopy does not offer perfect protection, and there are reports of CRC developing within 3-year intervals between colonoscopic exams.^{69,70} A recent study found that risk of CRC was reduced from 10% to 6% after increasing the frequency of surveillance colonoscopy exams from 3 years to 1–2 years, and 90% of interval cancers were localized, early-stage tumors.⁷¹ In light of this and the accelerated carcinogenesis associated with germline MMR gene mutations, consensus recommendations favor intensive surveillance with colonoscopy every 1–2 years starting at age 20–25 years or 10 years before the youngest age of CRC diagnosis in the family, depending on whichever occurs first (Table 1).^{72–74}

The increased risk of endometrial cancer among women with Lynch syndrome requires personalized screening options for carriers.^{74,75} Screening for gynecologic cancers is debatable because there is limited evidence that transvaginal ultrasound and/or endometrial biopsy results in early detection or improved survival. More than 75% of carriers who develop endometrial cancer are diagnosed with stage I disease, and the 5-year survival rate can be as high as 88%.^{75,76} Some data suggest that screening leads to the detection of early-stage cancers rather than reliance on symptoms, especially in young women with Lynch syndrome who are premenopausal. On the basis of expert consensus, annual endometrial biopsy beginning at age 30–35 years can be offered, and transvaginal ultrasound can assist in evaluating the ovaries in postmenopausal women.⁷² However, the only intervention proven to be effective for preventing endometrial and ovarian cancers in MMR gene

mutation carriers is prophylactic hysterectomy and bilateral oophorectomy and should be considered when childbearing has been completed (Table 1).⁷⁷

Screening for other Lynch syndrome–associated cancers may depend on the specific spectrum of cancers in the family, and recommendations are often individualized. Current recommendations are derived largely from expert consensus because the effectiveness of screening for the majority of Lynch syndrome–associated cancers has not been proven. Although the evidence to support screening for gastric and small bowel cancer is lacking, esophagogastroduodenoscopy with extended duodenoscopy starting at 30–35 years and at 3- to 5-year intervals thereafter may be considered (Table 1).⁷⁴

Surgical Management

There is an increased risk for metachronous CRC in gene mutation carriers, and patients who require surgical resection for CRC or other advanced neoplasia should consider more extensive surgical resection such as subtotal colectomy with ileorectal anastomosis.⁷⁸ If segmental resection is preferred, lifelong annual colonoscopy is required. Because colonoscopy is effective in decreasing CRC incidence and mortality, prophylactic colectomy is not recommended in the absence of a CRC diagnosis, as long as patients comply with lifelong intensive endoscopic surveillance.

Chemoprevention

The Colorectal Adenoma/Carcinoma Prevention Programme 2 (CAPP2), a double-blind randomized chemoprevention trial, tested whether use of aspirin and/or resistant starch had an effect on the incidence of CRC in MMR gene mutation carriers. Although initial findings suggested aspirin had no effect on adenoma or cancer risk after 24 months of treatment,⁷⁹ a 44% reduced incidence of CRC was observed after 56 months of follow-up.⁸⁰ The effect was more pronounced among individuals who had taken aspirin for at least 2 years, with a 63% reduction observed in CRC incidence. Secondary analyses suggested that the incidence of other Lynch syndrome–associated cancers also decreased. Further validation studies are necessary regarding the use of aspirin as chemoprevention in Lynch syndrome.

Strategies for the Identification of Mismatch Repair Gene Mutation Carriers

The early identification of individuals with Lynch syndrome and their at-risk family members is crucial for the implementation of effective cancer prevention strategies. Strategies for identifying carriers include the evaluation of personal and family cancer history, molecular diagnostic testing of tumors, clinical prediction models, and the *sine qua non*, germline DNA mutational analysis.

Clinical Criteria

Historically, assessment of family cancer histories has been the cornerstone for the diagnosis of Lynch syndrome. Because there are phenotypic variations and an extensive spectrum of associated cancers, review of personal and family cancer history involving first-, second-, and third-degree relatives is often necessary. Clinical criteria have been developed to identify individuals at risk and have been modified because of increasing knowledge related

to phenotype and molecular tumor testing (Table 2). The Amsterdam criteria, developed in 1991 to identify families with autosomal dominantly inherited CRC without polyposis, required (1) three or more CRC cases in which 2 of the affected individuals are first-degree relatives of the third, (2) CRC occurring in 2 generations, and (3) one CRC diagnosed before age 50 years.¹⁵ The Amsterdam criteria were instrumental in identifying families with Lynch syndrome, but they have limited sensitivity and specificity because 40% of families with known mutations do not fulfill the Amsterdam criteria, and 50% who do meet these criteria do not have a detectable DNA MMR defect. The latter group, categorized as Familial CRC Type X, can be distinguished from Lynch syndrome because the CRC tumors do not have features of MSI.⁸¹ In addition, the risk for CRC is lower, and there may be no increased risk for extracolonic cancers compared with Lynch syndrome.⁷² On the basis of expert consensus, it may be reasonable in Familial CRC Type X to offer CRC screening initiated 5–10 years before the age of earliest CRC diagnosis, with frequency determined by initial findings but no less often than every 5 years. In a recent study of families with CRC and abnormal immunohistochemistry (IHC) or MSI-high tumors (referred to as Lynch-like syndrome) but no germline MMR mutation, lower cancer risks were observed compared with Lynch syndrome families with identified gene mutations.⁸² However, cancer risks were higher than in families with sporadic CRC, and families with Lynch-like syndrome may benefit from tailored screening and surveillance strategies. Nevertheless, additional research and consensus recommendations are necessary.

With the advent of molecular tumor testing, the Bethesda guidelines were developed in 1997 and updated in 2004 to select those patients with CRC who should undergo MSI testing.^{83,84} The guidelines improved on the Amsterdam criteria's sensitivity by including the expanded spectrum of Lynch syndrome tumors and incorporated the MSI tumor testing results in the identification of carriers. Despite this, up to 28% of MMR gene mutation carriers can be missed when limiting genetic testing to those who meet the Bethesda guidelines.^{33,50}

Reliance solely on the existing clinical criteria presents several problems. Studies suggest health care providers do not systematically apply the complex, cumbersome clinical criteria in their routine evaluation of CRC patients, and lack of time needed to take a comprehensive family history is also a barrier to identifying patients who may benefit from genetic evaluation.^{85,86} As a result, many at-risk individuals and family members go without appropriate cancer preventive care.

Molecular Tumor Testing

The use of molecular testing of CRC tumors in the risk assessment paradigm to identify MMR gene mutation carriers has allowed us to move beyond family history. Routine evaluation of MSI or loss of expression of MLH1, MSH2, MSH6, and/or PMS2 MMR proteins by IHC in all newly diagnosed CRC cases is advocated (Table 2).⁸⁷

MMR-deficient phenotypes are found in more than 90% of colorectal tumors in patients with germline mutations.⁸⁸ MSI is assessed by using a panel of 5–10 microsatellite markers where tumors are MSI-high when 30% or more of the microsatellite sequences are mutated, MSI-low when 1 sequence is mutated, and stable if none is mutated. In addition, the expression of protein products of the MMR genes on IHC staining frequently shows loss of

staining for the antibodies to affected proteins in tumors from patients with Lynch syndrome.

Although the original Bethesda guidelines recommended screening CRC cases diagnosed at younger than 50 years for MSI, more than half of Lynch syndrome cases would be missed by limiting tumor MMR testing to this subset of patients.⁸⁹ To identify the majority of patients with CRC who may have Lynch syndrome, universal tumor testing, rather than a limited approach to testing only those who meet particular criteria (whether on the basis of personal or family history), has been supported.

The universal approach of testing all nonselected, newly diagnosed CRCs is feasible.⁵ The process requires molecular diagnostics laboratories to offer a stepwise series of molecular tests. A common approach is to initially test the tumors for loss of MLH1, MSH2, MSH6, and PMS2 protein expression by IHC testing because it can be more cost-effective in the evaluation of patients with CRC before age 70 years and allows for single-gene germline testing.⁹⁰ In those tumors that have loss of MSH2, MSH6, or PMS2 expression, the likelihood of having a germline mutation is extremely high. However, when tumors display loss of MLH1 protein expression, the evaluation is not as straightforward. Most of these cases have inactivation of the MMR system by somatic epigenetic mechanisms rather than germline mutations. Somatic mutations in *BRAF* V600E, along with hypermethylation of the 5' untranslated region of the *MLH1* gene, silence gene transcription for MLH1, producing an MSI phenotype in the tumor.^{91,92} These epigenetic causes for MMR-deficient tumor phenotypes are frequent in older patients and can account for the 15% of sporadic CRC tumors that show MSI. CRC tumors that display loss of MLH1 expression should also be tested for *BRAF* mutations and/or *MLH1* promoter hypermethylation. The presence of *BRAF* mutations in tumors of patients with epigenetic alterations in *MLH1* can be used to exclude a diagnosis of Lynch syndrome.⁹² IHC testing with *BRAF* analysis can limit unnecessary germline testing and the associated costs for CRC cases that are likely sporadic and not due to MMR deficiency.

Although IHC testing is often helpful, it is not always diagnostic and can provide false-negative results. In some cases, there may be normal staining tumors of truncating-mutation carriers that may be due to the production of an enzymatically inactive but immunologically detectable protein. With missense mutations, there may be a small effect on the protein structure where a stable heterodimer cannot form, and the unstable protein that is present in lower concentrations cannot be recognized properly by the antibody used.⁹³ This is not uncommon in tumors from *MSH6* gene mutation carriers, where up to 28% of tumors may demonstrate normal protein expression on IHC staining.⁹⁴ Because of broad variations in penetrance, some studies have emphasized the concomitant use of both IHC and MSI analysis as a pre-selection tool for *MSH6* DNA analysis.⁹⁵ In addition, studies show a high interobserver variability among pathologists in interpreting results of IHC staining, which may be operator-dependent.^{96,97} As a result, some pathologists suggest that MMR protein immunostaining be restricted to experienced gastrointestinal pathologists in specialized settings to ensure the highest accuracy attainable by molecular tumor testing.

Prediction Models

Prediction models offer an alternative approach to the identification of patients with Lynch syndrome, and the most recently introduced models provide quantifiable estimates of an individual's risk of carrying a MMR gene mutation. These models include MMRPredict, MMRPro, and PREMM_{1,2,6} (Prediction of Mismatch Repair Gene Mutations in *MLH1*, *MSH2*, and *MSH6*).^{98–100} Validation studies have found that these models outperform the Amsterdam and revised Bethesda criteria in identifying carriers, and it has been suggested that they replace the existing clinical criteria as prescreening tools in the risk assessment process for Lynch syndrome.^{101–103} In addition, the risk estimates provided by the prediction models can be particularly useful when evaluating patients without a cancer diagnosis or for those whose tumors are not available for molecular testing. In such scenarios, if a patient's predicted probability of carrying an MMR gene mutation is 5%, direct germline sequencing of MMR genes may be reasonable.⁷⁴

Although the overall purpose of these risk prediction models is similar, they vary in how they were developed and the populations from which they were derived and validated (Table 2). The MMRPredict model was developed by using logistic regression to estimate the overall probability of carrying an MMR gene mutation from CRC patients diagnosed before 55 years of age.⁹⁸ The model includes age at CRC diagnosis, presence of multiple CRC diagnoses, gender, location of tumor (proximal vs distal), presence and age(s) of CRC and/or endometrial cancer diagnosis in first-degree relatives, and molecular tumor testing results. It does not include other Lynch syndrome cancers, and its use is limited to the assessment of only individuals with CRC.

The PREMM_{1,2,6} model was developed by using multivariable polytomous logistic regression and provides an overall estimate in having a MMR gene mutation, as well as individual, gene-specific mutation probabilities for *MLH1*, *MSH2*, and *MSH6*.¹⁰⁰ The model was developed from the largest number of unrelated gene mutation carriers (n = 525) compared with MMRPredict (n = 38) and MMRPro (n = 121, validation cohort). The patient-specific variables include gender, presence and age at CRC diagnosis, endometrial cancer and other Lynch syndrome–associated cancers (including cancers of the ovary, stomach, kidney, ureter, bile duct, small bowel, brain [glioblastoma multiforme], pancreas, or sebaceous gland). Variables related to family cancer history include information of first- and second-degree relatives including the number of relatives with CRC, endometrial cancer, or other Lynch syndrome–associated cancers, and the minimum age at diagnosis of each cancer among relatives. It does not incorporate tumor data in risk prediction.

The MMRPro model was developed by using a Bayesian framework and integrates data on MMR mutation prevalence and penetrance informed by published values to estimate the probability of having any gene mutation, as well as gene-specific mutation probabilities.⁹⁹ Data for the patient being evaluated and for each first- and second-degree relative include age at diagnosis of CRC, endometrial cancer, and current age or age at last follow-up as well as molecular tumor testing results. The model does not incorporate information pertaining to multiple CRC diagnoses or other extracolonic tumors and requires information on the complete pedigree, including ages of family members unaffected by cancer. Both the

MMRPredict and PREMM_{1,2,6} scores can be generated by using online calculators (<http://hnpccpredict.hgu.mrc.ac.uk/> and <http://premm.dfci.harvard.edu>), and software included in the CancerGene package can be used to calculate MMRPro risk scores (<http://astor.som.jhmi.edu/BayesMendel>).

The setting in which patients are evaluated for Lynch syndrome may very well determine which prediction model is most appropriate to use. The MMRPro model accounts for the size of the family and the impact of unaffected relatives on risk prediction that requires data entry from the entire pedigree. Its use is likely more feasible in a specialized, high-risk cancer clinic with genetic counselors who can ensure that a complete pedigree is obtained with information on unaffected family members as well as molecular tumor testing results. The PREMM_{1,2,6} model includes a spectrum of extracolonic cancers associated with Lynch syndrome and evaluates cancer burden among first- and second-degree relatives. In validation studies comparing the models, PREMM_{1,2,6} has been found easy to use and less time-consuming than MMRPro,¹⁰³ which may make it suitable for use in diverse clinical settings where patients are identified for further genetic evaluation or direct predictive testing in certain cases. Last, MMRPredict is best for evaluating young patients with CRC but is likely less accurate in the assessment of families with multiple extracolonic cancers, older individuals with CRC, or patients without a personal history of CRC. Additional collaborative studies are necessary to compare the models' performance in identifying gene mutation carriers among both clinic and population-based cohorts and in diverse patient populations to better promote their systematic use in the routine risk assessment of patients with CRC in clinical practice.

Prediction models for Lynch syndrome may also have applications for CRC risk stratification for patients unaffected by cancer. In a large modeling study of a simulated, population-based cohort of healthy individuals followed through life, the PREMM_{1,2,6} model was used to assess individuals for Lynch syndrome, taking into account the health risks related to the condition and its management.¹⁰⁴ The study reported that it is cost-effective to screen unaffected individuals between the ages of 25 and 35 years for Lynch syndrome by using the PREMM_{1,2,6} model and to proceed directly to clinical genetic testing in those subjects with a 5% or higher risk estimate. This approach reduced colorectal and endometrial cancer incidence in mutation carriers by approximately 12.4% and 8.8%, respectively.

DNA Mutational Analyses

Available clinical genetic testing for Lynch syndrome includes full gene sequencing of *MLH1*, *MSH2*, *MSH6*, and *PMS2*, testing for large rearrangements in these genes, and additional testing for deletions in *EPCAM*. Although germline genetic testing may be considered the gold standard in identifying MMR gene mutation carriers, its use in screening all CRC patients for Lynch syndrome is not feasible because genetic testing is currently too expensive, time-consuming, and difficult to perform in such a setting. Therefore, family history, molecular tumor testing, and/or risk prediction models remain the primary strategies for the clinical identification of individuals at risk for Lynch syndrome. With advances in

DNA sequencing techniques and reductions in the cost of genetic testing, the preferred strategies for identifying patients with Lynch syndrome may indeed change in the future.

Current guidelines recommend that genetic testing for cancer predisposition be offered to at-risk patients when the test will influence their own medical management or that of their at-risk family members.^{72–74} However, the interpretation of genetic tests may sometimes be complicated, and referral to dedicated professionals with expertise in cancer genetics is advised when possible, because results often have important implications on a patient's clinical management for cancer prevention.

The presence of a pathogenic germline mutation identified in 1 of the 4 MMR genes confirms the diagnosis of Lynch syndrome. Once a pathogenic mutation is detected in a family, other at-risk relatives can be tested for the same mutation through single-site, gene-specific DNA mutation analysis; if the mutation is not found, this result can be interpreted as “true negative,” and these individuals are considered average-risk and can be managed as such. When genetic testing fails to detect a pathogenic mutation in a family deemed high-risk or reveals a mutation of uncertain pathogenic significance, this result is “uninformative.” In such cases, individualized recommendations for specialized cancer screening and surveillance are made on the basis of personal and family cancer history, molecular tumor testing results, and/or risk estimates determined through the prediction models.

A Combined Approach for the Identification of Gene Mutation Carriers

A combination of strategies may likely be the best approach to effectively and efficiently distinguish mutation carriers from noncarriers and thereby limit the shortcomings inherent to each individual strategy. Molecular diagnostic testing of CRC tumors is essential in the evaluation for Lynch syndrome, but family cancer risk assessment should not be overlooked, particularly when genetic testing yields results that are clinically uninformative.

In a recent international study of 10,206 population-based CRC cases, the most sensitive strategy in identifying patients with Lynch syndrome was universal MMR tumor testing regardless of CRC age of diagnosis.¹⁰⁵ However, this approach yielded the highest rates of false-positive results. Selective performance of MMR tumor testing in CRC probands diagnosed at 70 years or younger and in patients older than 70 years who met at least 1 criterion of the revised Bethesda guidelines achieved a similar yield to that of universal strategy. The selective approach incorporating age of CRC diagnosis reduced the number of patients undergoing tumor testing and germline genetic testing by 35% and 29%, respectively. Similarly, IHC plus cancer history assessment by using the PREMM_{1,2,6} model provided the best combined approach in identifying MMR gene mutation carriers from noncarriers in a study comparing the performance of PREMM_{1,2,6}, MSI, and IHC testing strategies, individually and in different combinations.⁹⁴ Higher rates of false-positive results on tumor testing were noted mostly in older patients; with every 10-year increase in the age of CRC diagnosis above 50 years, the performance of IHC and MSI testing decreased, with a considerable decrease in the specificity of IHC testing for loss of *MLH1* protein expression in colorectal tumors. In contrast, the performance of PREMM_{1,2,6} increased with every 10-year increase in age of CRC diagnosis compared with both IHC and/or MSI and improved

predictions most when combined with IHC results. In light of these results, a recent approach that incorporates age of CRC diagnosis, molecular tumor results, and cancer history assessment by using PREMM_{1,2,6}, has been proposed in the evaluation of patients with CRC for Lynch syndrome (Figure 1).^{106,107} The algorithm also highlights the importance of identifying individuals without detected MMR gene mutations despite significant personal and family cancer histories (and high prediction scores) or abnormal tumor testing results. Clinical management options still need to be individualized in these patients, and families and additional testing in the future may be considered as novel genes related to familial CRC are discovered.

Challenges in the Identification of Individuals at Risk for Lynch Syndrome

Although multiple strategies are available to identify gene mutation carriers, there is no widely adopted, standard approach in evaluating patients with CRC for Lynch syndrome. There are marked differences and variable clinical practices among U.S. institutions in screening for MMR deficiency, which may be due to limited resources including the availability and costs of molecular diagnostic testing, systems to track and report tumor testing results, and procedures to ensure referral for genetic evaluation.¹⁰⁸

Furthermore, there is increasing concern that despite best attempts in adopting any approach to screening for Lynch syndrome, the uptake of predictive genetic testing may not transcend to at-risk family members of identified gene mutation carriers. This limits the opportunity for effective cancer prevention, particularly among relatives who have yet to be affected by cancer but are at risk for the condition. The key determinant of the cost-effectiveness of any screening strategy for the identification of Lynch syndrome is the number of at-risk relatives unaffected by cancer who ultimately pursue predictive genetic testing.⁹⁰ Current estimates related to the uptake for genetic testing among family members identified as at-risk for Lynch syndrome are low and vary from 34% to 52%.^{90,109,110}

Conclusion

Lynch syndrome was first described 100 years ago, and major advances in risk assessment, molecular genetics, DNA mutational analyses, and cancer prevention have been made. However, efforts are still necessary to standardize the approach in identifying gene mutation carriers and implement strategies that engage unaffected, at-risk family members who would benefit from predictive genetic testing and specialized cancer screening. Because advances in genomic sequencing allow for rapid analysis of multiple CRC-related genes at lower costs compared with traditional sequencing, it is likely that current strategies regarding the identification and management of Lynch syndrome families will need to be revisited. Furthermore, the discovery of novel genetic factors associated with familial CRC will provide opportunities to expand genetic evaluation and testing beyond Lynch syndrome.

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Abbreviations used in this paper

CRC	colorectal cancer
FAP	familial adenomatous polyposis
HNPCC	hereditary nonpolyposis colorectal cancer
IHC	immunohistochemistry
MMR	mismatch repair
MSI	microsatellite instability

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Figure 1.

MSS, microsatellite stable. §PREMM_{1,2,6} score can be calculated at <http://premm.dfci.harvard.edu/>. ¶Other models (MMRpro, MMRpredict) may also be used with their own specified cut-off scores. *BRAF testing: (+), mutation present; (-), mutation absent/wild type. **Surveillance recommendations based on personal and family history. ‡Gene-specific germline mutational analysis.

Table 1**Lifetime Cancer Risks and Screening Recommendations in Lynch Syndrome**

Cancer site	Lifetime cancer risk (%)	Screening recommendations	Initiation age (y)
Colorectum	22–75	Colonoscopy every 1–2 years	20–25
Endometrium	30–60	Consider transvaginal ultrasound ± endometrial biopsy annually vs prophylactic TAH/BSO	30
Ovarian	9–12		
Stomach	1–13	Consider EGD every 3–5 years	30–35
Urinary tract	4–5	There is currently no evidence to support screening	
Small bowel	1–4		
Pancreas	3–4		
Biliary tract	2–7		
Central nervous system ^a	1–3		

EGD, esophagogastroduodenoscopy; TAH/BSO, total abdominal hysterectomy/bilateral salpingo-oophorectomy.

^a Glioblastoma multiforme.

Table 2

Strategies in the Evaluation for Lynch Syndrome Among Individuals With CRC

Strategy	Features	Strengths	Limitations
Molecular tumor testing			
MSI	MSI-H tumors: hallmark feature of LS Panel consists of 5 microsatellite markers Phenotype is defined by proportion of microsatellite sequences that show instability within the tumor DNA MSI-H if ≥30% of microsatellite sequences are mutated	MSI-H tumors characterize the majority of LS associated CRCs	Sporadic cases of CRC may display MSI-H phenotype Should consider additional IHC testing of MSI-H tumors to further evaluate for LS
IHC	Loss of protein expression of MMR genes LS: <i>MLH1</i> , <i>MSH2</i> , <i>MSH6</i> , <i>PMS2</i> Heterodimer complexes form between <i>MLH1</i> - <i>PMS2</i> and <i>MSH2</i> - <i>MSH6</i> , which cause concomitant loss of staining in both proteins of each complex when the primary defect is in <i>MLH1</i> or <i>MSH2</i> , respectively Isolated loss of <i>MSH6</i> or <i>PMS2</i> protein expression may occur when the primary defect is in the <i>MSH6</i> or <i>PMS2</i> gene, respectively	May direct single MMR DNA mutational analysis Cost-effective approach when used as first-line screening in patients with CRC <70 y, along with BRAF testing when indicated	Sporadic cases may display loss of <i>MLH1</i> protein expression BRAF or <i>MLH1</i> methylation testing recommended with loss of <i>MLH1</i> protein expression IHC testing may be falsely negative in tumors from <i>MSH6</i> carriers Universal IHC screening may yield high false-positive results
Prediction models			
PREMM _{1,2,6}	Derived by using polytomous logistic regression analysis Derived from cohort of high-risk individuals including 525 gene mutation carriers Validated in population and clinic-based cohorts Data for proband include gender, presence and ages of cancer diagnoses for CRC, endometrial, and LS related tumors, ^a presence of multiple CRCs Data for FDRs and SDRs include number of affected relatives, youngest ages of CRC, endometrial cancer and other LS tumors ^a	Extensively validated Provides gene-specific risk estimates Provides clinical applicability at different cutoff values Online calculator: http://premm.dfci.harvard.edu/ Easy to use; time efficient	Molecular tumor data not included Developed from cohort with heightened risk Family size and unaffected individuals not considered in prediction
MMRPro	Derived by using Mendelian and Bayesian analyses Derived by using published MMR mutation prevalence and penetrance data Validated among clinic-based cases including 121 MMR gene carriers Data for proband, FDRs, and SDRs include presence and ages of CRC and endometrial cancer Current age or age at last follow-up required on all unaffected relatives MSI and IHC testing results included	Provides gene-specific risk estimates Incorporates tumor testing results Offers pre- and post-DNA sequencing risk estimates Accounts for unaffected relatives and family size Requires software accessible at http://astor.som.jhmi.edu/BayesMendel	Requires extensive data entry from pedigree, including unaffected family members Time-consuming History of multiple CRC diagnoses not included LS associated tumors other than endometrial cancer not included
MMRPredict	Developed by using logistic regression analysis Derived from population-based CRC cases diagnosed <55 y including 38 gene mutation carriers Data for proband include gender, age of CRC diagnosis, presence of multiple CRCs, location of CRC Data for FDRs include presence and ages of CRC and/or endometrial cancers MSI and IHC testing results included	Derived from population-based cohort Provides clinical applicability at different cutoffs Online calculator available: http://hnpccpredict.hgu.mrc.ac.uk/	Application limited to only individuals with CRC Developed in individuals with CRC <55 y Validated in high-risk cohort: CRC <45 y LS associated tumors other than endometrial not included
Clinical criteria			

Strategy	Features	Strengths	Limitations
Amsterdam criteria ^a	3 relatives with CRC where all of the following apply: One is FDR of the other two Two successive generations affected At least one relative diagnosed <50 y FAP is excluded	Developed to identify families with high CRC risk	Limited sensitivity and specificity ~40% of families with LS will be missed because they do not meet criteria ~50% of families who meet criteria do not have MMR gene mutations
Bethesda guidelines	Requires one of the following: CRC diagnosed <50 y Synchronous or metachronous CRC or other LS cancers diagnosed at any age CRC in patient with MSI-H histology ^a at age <60 y CRC in patient with 1 FDR with any LS related cancer (at least 1 diagnosis <50 y) CRC in patient with 2 FDRs or SDRs with LS-related cancers regardless of age	Developed to identify CRC cases to be screened for MSI Includes LS associated cancers Improves on Amsterdam criteria's sensitivity	Complex criteria to apply May miss up to 25% of carriers

FDR, first-degree relative; LS, Lynch syndrome; SDR, second-degree relative.

^a Presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.