

AGA SECTION

American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome



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This document presents the official recommendations of the American Gastroenterological Association (AGA) Institute on the diagnosis and management of Lynch syndrome. Lynch syndrome (previously referred to as hereditary nonpolyposis colorectal cancer syndrome) is the most common heritable colorectal cancer syndrome, accounting for 2% to 3% of colorectal cancers, and has an estimated prevalence in the general population of 1 in 440. Patients with Lynch syndrome have an estimated lifetime cumulative incidence of colorectal cancer up to 80% and endometrial cancer up to 60% and also have increased risks of other cancers, including stomach, small intestine, pancreas, biliary tract, ovary, urinary tract, and brain. The syndrome is often underdiagnosed. This guideline was developed by the AGA Clinical Guidelines Committee and approved by the AGA Governing Board. It focuses on identifying cases of Lynch syndrome and management of risk of colorectal cancer.

The guideline was developed using a process described elsewhere.¹ Briefly, the AGA process for developing clinical practice guidelines incorporates Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology² and best practices as outlined by the Institute of Medicine.³ GRADE methodology was used to prepare the accompanying technical review on focused questions and their related specific population, intervention, comparison, and outcome (PICO).⁴ Optimal understanding of this guideline will be enhanced by reading applicable portions of the technical review. The quality of available evidence on each question was first judged by the technical review panel of content and methodological experts according to the published GRADE process; the interpretations of the categories of quality are shown in Table 1. Reasons justifying grading are detailed in the following text when appropriate. The guideline authors, none of whom have any potential financial or professional conflict of interest on the topic, met with the technical review panel and a patient representative to discuss the evidence. The guideline authors subsequently met privately and drafted recommendations, taking into account the quality of evidence, as well as the balance between benefits and harms, patient preferences, and resource utilization. Such pertinent considerations are also detailed in the following text when relevant. The

strengths of the recommendations were categorized as (1) strong, (2) weak/conditional, or (3) no recommendation according to GRADE terminology (Table 2). The draft recommendations were combined into a clinical decision support tool (Figure 1) and then opened to public comment, edited, and approved by the Governing Board of the AGA (Table 3).

The US Multi-Society Task Force on Colorectal Cancer recently published guidelines on Lynch syndrome, which were endorsed by the AGA.⁵ Although that guideline used the terminology of GRADE for categorizing the quality of evidence, the other aspects of the methods described in the preceding text differed. The motivation for the methodology used in this guideline is that the resulting recommendations can be received by policy makers as the highest-quality recommendations available for swift adoption regarding decisions of coverage and quality metrics. The primary disadvantage of the methods used in this guideline is that the resources and time required for the systematic review and meta-analysis for each PICO in the technical review accompanying this guideline did not permit consideration of the breadth of issues relevant to providers that were addressed by the US Multi-Society Task Force on Colorectal Cancer guidelines, such as screening for noncolorectal cancers or surgical management of colorectal cancer in patients with Lynch syndrome. Thus, the 2 guidelines should be viewed as complementary. The technical review accompanying this guideline include a series of original meta-analyses that provide more precise estimates of summary data of published evidence for some recommendations. These explain any discrepancy in evidence ratings compared with the recent US Multi-Society Task Force on Colorectal Cancer guidelines on Lynch syndrome. Any pertinent explanation for the evidence grading is further specified at the end of related statements, under quality of evidence.

Abbreviations used in this paper: AGA, American Gastroenterological Association; GRADE, Grading of Recommendations Assessment, Development and Evaluation; IHC, immunohistochemistry; MSI, microsatellite instability; PICO, population, intervention, comparator, and outcome.

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Table 1. GRADE Categories of Quality of Evidence

High	We are very confident that the true effect lies close to that of the estimate of the effect.
Moderate	We are moderately confident in the effect estimate. The true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different.
Low	Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.
Very low	We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of the effect.

Recommendations

In patients without a personal history of colorectal or another cancer but with a family history suggestive of Lynch syndrome, the AGA suggests that risk prediction models be offered rather than doing nothing. Conditional recommendation, very low quality of evidence.

Diagnosing Lynch syndrome in patients without a personal history of cancer begins with obtaining a family history of cancers, and health care providers should be prepared to act on that information. If there is a first-degree relative with a known Lynch syndrome mutation, the AGA recommends that the patient be offered germline genetic testing for that mutation (Figure 1). If not, but tumor tissue from an affected relative is available, the screening process should begin with testing of that tumor (see recommendations in the following text).

In the absence of that information, the probability of carrying a Lynch syndrome mutation can be estimated rather quickly and easily using the online model PREMM_{1,2,6} (<http://premm.dfc.harvard.edu/>) or by using free downloadable software that incorporates the MMRpro model (<http://www4.utsouthwestern.edu/breasthealth/cagene/>). MMRpredict is used to predict the presence of a Lynch syndrome mutation in a patient with known cancer and

requires details of the cancer, so it is not relevant for this population. The quality of evidence supporting the use of these tools in this population was judged very low. Indeed, the models are based on observational studies; thus, there is a strong risk of bias. The evidence is further downgraded due to indirectness/poor applicability because the models have primarily been tested in populations of patients with a personal history of cancer. Nonetheless, the AGA recommends use of these models in patients without a personal history of cancer because the sensitivity and specificity of the tools are expected to be reasonably similar in this population, and there is an imperative to improve case finding because most Lynch syndrome kindreds likely remain undiagnosed. The available evidence cannot support the preferential use of PREMM_{1,2,6} or MMRpro over the other. A cost-effectiveness analysis has suggested that a threshold of greater than 5% predicted probability of carrying a Lynch syndrome mutation should prompt germline genetic testing if universally applied to 25-year-old patients.⁶ However, the threshold could be lower in middle-aged adults and as the cost of genetic testing decreases. If the probability is above the threshold, then germline genetic testing for mutations in *MLH1*, *MSH2*, *MSH6*, and *PMS2* should be offered. The question of identifying Lynch syndrome in this population (ie, without a personal history of colorectal or another cancer but a family history suggestive of Lynch syndrome) was not directly addressed by the recommendations in the US Multi-Society Task Force on Colorectal Cancer guidelines on Lynch syndrome.⁵

In patients without a personal history of colorectal or another cancer but with a family history suggestive of Lynch syndrome, the AGA suggests that risk prediction models be offered rather than proceeding directly with germline genetic testing. Conditional recommendation, very low quality of evidence.

When compared with proceeding directly to germline genetic testing, the primary goal of the prediction models is to avoid resource utilization in low-risk individuals. The recommendation in favor of first using prediction models to select patients for genetic testing is therefore conditional on the cost of genetic testing, which could decrease rapidly, and

Table 2. GRADE Categories of Strength of Recommendation

	For the Patient	For the Clinician
Strong	Most individuals in this situation would want the recommended course of action, and only a small proportion would not.	Most individuals should receive the recommended course of action. Formal decision aids are not likely to be needed to help individuals make decisions consistent with their values and preferences.
Weak/conditional	The majority of individuals in this situation would want the suggested course of action, but many would not.	Different choices will be appropriate for different patients. Decision aids may well be useful in helping individuals make decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working toward a decision.

Diagnosis and Management of Lynch Syndrome

Clinical Decision Support Tool

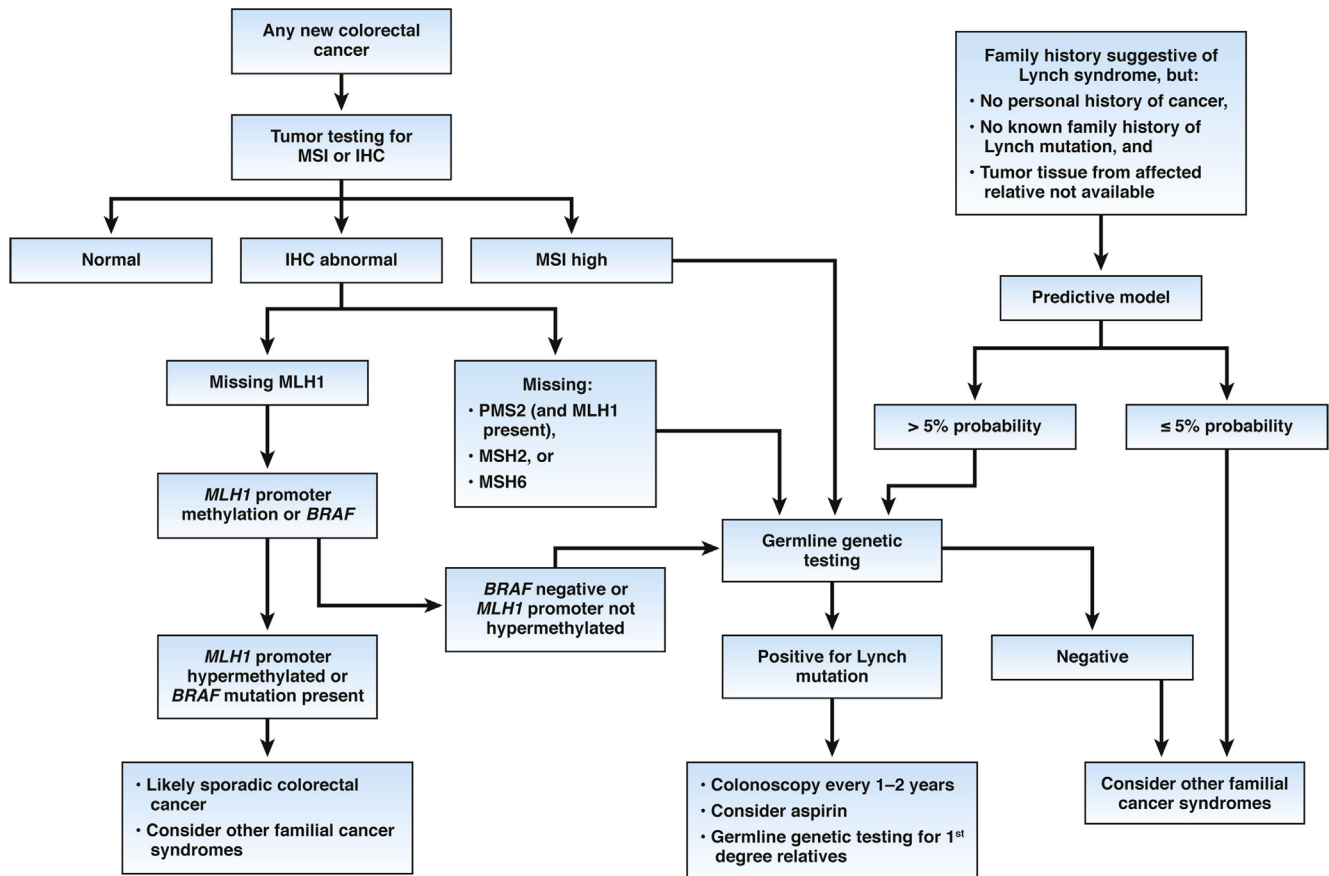


Figure 1. Clinical Decision Support Tool. For newly diagnosed colorectal cancer, begin on the *top left*. For patients with family history suggestive of Lynch syndrome, begin on the *top right*.

is also conditional due to the very low quality of available evidence in this patient population. In patients who are at high risk for Lynch syndrome (for instance, meeting Amsterdam criteria, which are highly specific), risk prediction models are not necessary before proceeding to germline testing.

The AGA recommends testing the tumors of all patients with colorectal cancer with either immunohistochemistry (IHC) or for microsatellite instability (MSI) to identify potential cases of Lynch syndrome versus doing no testing for Lynch syndrome. *Strong recommendation, moderate quality of evidence.*

IHC is performed on tumor tissue to detect the presence or absence of proteins (MLH1, MSH2, MSH6, or PMS2) responsible for DNA mismatch repair. If one of these

proteins is missing, there is an increased risk of Lynch syndrome. Lynch syndrome tumors display high MSI. Variability in recommendations for testing tumors for Lynch syndrome has primarily been based on cost and availability. Traditionally, older patients were excluded from testing because the yield was lower; however, because Lynch syndrome can present in elderly patients and because these findings may have a significant impact on younger family members, older patients with colorectal cancer should also be tested, as supported by cost-effectiveness analyses. The quality of evidence supporting the use of these tests in the population of all cases of colorectal cancer was judged to be moderate. Indeed, the models are based on observational studies, so there is a strong risk of bias; however, the evidence is upgraded due to the strength of the association between the results of the tests and a diagnosis of Lynch syndrome. The strength of the recommendation is further strengthened by some cost data.

Table 3. AGA Recommendations on the Diagnosis and Management of Lynch Syndrome

Population	Intervention	Comparison	Recommendation
Patients with a family history suggestive of Lynch syndrome but no personal history of cancer	Utilization of a risk prediction model (PREMM _{1,2,6} or MMRpro)	Nothing	Conditional
Patients with a family history suggestive of Lynch syndrome but no personal history of cancer	Utilization of risk prediction model (PREMM _{1,2,6} or MMRpro)	Proceeding directly to germline genetic testing	Conditional
Patients with colorectal cancer	Test tumor for MSI or with IHC for MLH1, MSH2, MSH6, and PMS2 proteins	No testing for Lynch syndrome	Strong
Patients with colorectal cancer with IHC absent for <i>MLH1</i>	Test tumor for <i>BRAF</i> mutation or hypermethylation of the <i>MLH1</i> promoter	Proceeding directly to germline genetic testing	Conditional
Patients with Lynch syndrome	Surveillance colonoscopy	Nothing	Strong
Patients with Lynch syndrome	Surveillance colonoscopy every 1–2 y	Surveillance colonoscopy less frequently than every 2 y	Conditional
Patients with Lynch syndrome	Aspirin chemoprevention	Surveillance colonoscopy alone	Conditional

The AGA makes no recommendation regarding the use of IHC versus MSI or the use of both IHC and MSI due to low quality of evidence. Because IHC and MSI testing have comparable sensitivities and specificities, their implementation has varied depending on the level of expertise and availability within a given institution. Although many sites can technically perform IHC, the results must be interpreted with caution; appropriate training and experience of pathologists is required to ensure that they are adept at interpreting the data. Furthermore, a system for systematic follow-up of all positive results must be in place.

The AGA suggests that in patients with colorectal cancer with IHC absent for *MLH1*, second-stage tumor testing for a *BRAF* mutation or for hypermethylation of the *MLH1* promoter should be performed rather than proceeding directly to germline genetic testing. *Conditional recommendation, very low quality of evidence.*

Of those patients with absence of *MLH1* on IHC, approximately 75% will have sporadic cancers rather than Lynch syndrome. Sporadic high MSI colorectal cancers usually show epigenetic loss of the *MLH1* gene protein due to hypermethylation of the *MLH1* promoter; the V600E mutation in the *BRAF* gene in colorectal cancers is associated with this somatic, acquired loss of *MLH1*. This can be determined by testing directly for hypermethylation or a *BRAF* mutation. If either test result is positive, then Lynch syndrome is extremely unlikely. This “second-stage” tumor testing for patients with loss of *MLH1* on IHC is a sensitive and currently less expensive strategy than all patients with loss of *MLH1* undergoing germline testing. For patients with an *MLH1* mutation who do not have hypermethylation or a *BRAF* mutation, germline testing for Lynch syndrome is recommended.

The US Multi-Society Task Force on Colorectal Cancer guidelines on Lynch syndrome include a strong

recommendation in favor of second-step testing for hypermethylation of *MLH1* or *BRAF* mutation.⁵ The recommendation was based on studies that assumed that such testing was 100% specific for sporadic tumors; however, the meta-analysis in the technical review accompanying this guideline found that *BRAF* mutations and hypermethylation of the *MLH1* promoter are also found in some patients with Lynch syndrome.⁴ Therefore, using second-step testing may in fact result in some small proportion of cases of Lynch syndrome being missed (no more than 10%, but likely substantially fewer than that). The evidence in this current AGA guideline was graded as very low because the data originate from observational studies and thus there is a strong risk of bias; the evidence is further downgraded due to imprecision and inconsistency in the data. Furthermore, in determining the grading of the recommendation, the AGA experts considered the cost and anxiety associated with germline genetic testing in all patients with colorectal cancer with absent *MLH1* on IHC, the great majority of whom have sporadic cancers. In light of all these concerns, the AGA conditionally recommends in favor of second-step testing.

The AGA recommends surveillance colonoscopy (versus doing nothing) in persons with Lynch syndrome. *Strong recommendation, moderate quality of evidence.*

The AGA suggests that surveillance colonoscopy should be performed every 1 to 2 years versus less frequent intervals. *Conditional recommendation, low quality of evidence.*

The meta-analysis from the technical review accompanying this guideline found that surveillance colonoscopy in patients with Lynch syndrome was associated with decreased burden of colorectal cancer (odds ratio, 0.23; 95% confidence interval, 0.13–0.41) and decreased colorectal cancer mortality (odds ratio, 0.06; 95% confidence

interval, 0.00–0.93).⁴ A cost-effectiveness model estimating life expectancy and health care costs of frequent colonoscopy surveillance versus no surveillance determined that surveillance of people who are gene carriers for Lynch syndrome increased life expectancy by 7 years and costs of surveillance were less than costs of no surveillance for colorectal cancer. Conventional practice has suggested commencing surveillance at either 20 to 25 years of age or 5 years before the youngest age of diagnosis of colorectal cancer in an affected family member, whichever occurs first.

The best interval for colorectal cancer screening in patients with Lynch syndrome remains unknown, but every 1 to 2 years is most prudent. No identifiable studies have directly compared surveillance intervals, yet most colorectal cancers diagnosed in patients with Lynch syndrome who undergo surveillance are detected in 1- to 2-year intervals and are usually detected at a treatable stage. The various genetic mutations (in *MLH1*, *MSH2*, *MSH6*, and *PMS2*) implicated in the development of Lynch syndrome have different long-term risks, but no data exist to directly guide the choice of screening interval or the age of initiation of screening specific to those mutations.

The AGA suggests that aspirin be offered for cancer prevention in patients with Lynch syndrome. Conditional recommendation, low quality of evidence.

One high-quality randomized controlled trial in adults with Lynch syndrome assessed the antineoplastic effect of aspirin 600 mg daily compared with placebo over a period up to 4 years and showed a decreased incidence of colorectal cancer beyond that with colonoscopy surveillance alone (incidence rate ratio, 0.56; 95% confidence interval, 0.32–0.99) and a trend toward a decreased incidence of other cancers.⁷ Although originating from a randomized controlled trial, the grading of the evidence was downgraded due to imprecision in the estimate. Furthermore, there were no mortality data to support a benefit from long-term aspirin therapy (thus, grading of evidence is very low for this outcome). Adverse risks of aspirin therapy (1% risk of gastrointestinal bleeding and <1% risk of stroke greater than placebo) were not statistically significant. The recommended dose and frequency of aspirin to offer patients with Lynch syndrome for cancer prevention is unknown. Moreover, the dose tested in this trial was high and uncertainties about risks versus benefits remain, so an individualized approach is best, considering the patient's personal risk of adverse events with aspirin therapy. No studies to date have examined the cost-effectiveness of aspirin chemoprevention in adults with Lynch syndrome.

Conclusion

Lynch syndrome is the most common hereditary colorectal cancer syndrome with an identifiable genetic mutation. This guideline used GRADE methodology and follows the best practices outlined by the Institute of Medicine. Although most of the recommendations are conditional, this

should not be confused with making no recommendation. Instead, based on the available evidence, the AGA is able to make recommendations in those scenarios for the current management of patients, but the recommendation could conceivably change in the future in the face of new evidence. The AGA Clinical Guidelines Committee will continue to monitor the field and consider updating the guideline as needed. Areas that should be a priority for future research include the following:

- Validating the calibration of predictive models for Lynch syndrome mutations in a population of patients without a personal history of cancer
- Identifying the threshold predicted probability of carrying a Lynch syndrome mutation that should prompt germline genetic testing
- Identifying germline genetic testing that together provides 100% sensitivity for Lynch syndrome
- Updating cost-effectiveness analyses with new estimates of the accuracy of *BRAF* mutation and *MLH1* promoter hypermethylation testing, and as the cost of germline genetic testing decreases
- Optimizing the time of onset of colonoscopy in patients with Lynch syndrome
- Identifying the optimal dose and frequency of aspirin for chemoprevention; a randomized controlled trial addressing this question is currently enrolling patients.

Given the large incidence of colorectal cancer, one recommendation in particular may be ripe for consideration as a process measure of quality of care: tumor testing in newly diagnosed cases of colorectal cancer to identify cases of Lynch syndrome.

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Reprint requests

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Conflicts of interest

All members were required to complete disclosure statements. These statements are maintained at the American Gastroenterological Association Institute headquarters in Bethesda, Maryland, and none of the disclosures were potentially related to the content of this guideline.