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

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Introduction

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 Non-Polyposis Colorectal Cancer Syndrome, HNPCC) is the most common heritable colorectal cancer syndrome, accounting for 2-3% of colorectal cancers, and has an estimated prevalence in the general population of 1 in 440. Individuals 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 for other cancers, including stomach, small intestine, pancreas, biliary tract, ovary, urinary tract, and glioblastoma multiforme. The syndrome is often underdiagnosed. This guideline was developed by the AGA’s Clinical Guidelines Committee and approved by the AGA Institute Governing Board. It focuses on identifying cases of Lynch Syndrome and management of risk of colorectal cancer.

The guideline was developed utilizing a process described elsewhere. Briefly, the AGA process for developing clinical practice guidelines incorporates GRADE methodology and best practices as outlined by the Institute of Medicine. GRADE methodology was utilized to prepare the accompanying technical review on focused questions and their related specific Populations, Interventions, Comparisons, and Outcomes (PICO). 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 (Table 1). Reasons justifying grading are detailed below, 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 below, when relevant. The strength of the recommendations were categorized as strong, weak/conditional, or 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 U.S. Multi-Society Task Force on Colorectal Cancer recently published guidelines on Lynch Syndrome which were endorsed by the AGA. While that guideline utilized some aspects of GRADE methodology for categorizing the quality of evidence and strength of recommendations, the other aspects of the methods described above differed. One of the advantages of the methodology of 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 addressing the breadth of issues relevant to providers that were addressed by the Multi-Society Task Force guideline. Thus, the two guidelines should be viewed as complementary. We highlight below the areas where the two guidelines differ; in those rare areas, the recommendation of this guideline supersedes the AGA endorsement of the Multi-Society Task Force guidelines.

**AGA Recommendations on the Diagnosis and Management of Lynch Syndrome**

<table>
<thead>
<tr>
<th>Population</th>
<th>Intervention</th>
<th>Comparison</th>
<th>Recommendation</th>
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Patients with colorectal cancer with IHC absent for MLH-1 | Test tumor for BRAF mutation or hypermethylation of the MLH-1 promoter | Proceeding directly to germline genetic testing | Conditional

Patients with Lynch Syndrome | Surveillance colonoscopy | Nothing | Strong

Patients with Lynch Syndrome | Surveillance colonoscopy every 1 to 2 years | Less frequent intervals | Conditional

Patients with Lynch Syndrome | Aspirin chemoprevention | Surveillance colonoscopy alone | Conditional

**Recommendations**

*In patients without a personal history of colorectal or another cancer, but with a family history suggestive of Lynch Syndrome, the AGA recommends 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 family history of a known Lynch mutation, or tumor tissue from an affected relative is available, the screening process should be guided by that information (Figure 1). 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.dfci.harvard.edu/), or by using free downloadable software that incorporates the MMRpro model (http://www4.utsouthwestern.edu/breasthealth/cagene/). 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, there thus exists a strong risk of bias. The evidence is further downgraded due to indirectness/poor applicability since the models have primarily been tested in populations of patients with a personal history of cancer. Nonetheless, the AGA recommends the 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 as most Lynch Syndrome kindreds likely remain undiagnosed. The available evidence cannot support the preferential use of the PREMM1,2,6 or MMRpro over the other. The MMRpredict is not relevant to this population, as it requires personal history of cancer. A cost-effectiveness analysis has suggested that a threshold of greater than 5% predicted probability of carrying a Lynch 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. The question of identifying Lynch Syndrome in this population was not directly addressed by the recommendations of the U.S. 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 recommends 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 is also conditional due to the very low quality of available evidence in this patient population.

| The AGA recommends testing the tumors of 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, MSSH6 or PMS2) responsible for DNA mismatch repair. If one of these proteins is missing there is an increased risk for 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. With the reduction in the cost of both IHC and MSI testing, it is reasonable to consider testing on all colorectal
cancers. Traditionally, older patients were excluded from testing since the yield was lower; however, as Lynch Syndrome can present in the elderly, and since these findings may have significant impact on other younger family members, older patients with colorectal cancer should be tested. The quality of evidence supporting the use of these tests in this population was judged moderate. Indeed, as the models are based on observational studies, there thus exists a strong risk of bias; however, the evidence is upgraded due to the strength of 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.

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. Since 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 recommends that in patients with colorectal cancer with IHC absent for MLH-1, 2nd stage tumor testing for a BRAF mutation or for hypermethylation of the MLH-1 promoter should be performed rather than proceeding directly to germline genetic testing. Conditional recommendation, very low quality of evidence.

Of those patients with only the absence of MLH1 on IHC, only approximately 25% will have Lynch Syndrome. Sporadic MSI-H colorectal cancers usually demonstrate 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 is positive, then Lynch Syndrome is extremely unlikely. This ‘second-stage’ tumor testing for MLH1 patients is a sensitive and less expensive strategy than all patients undergoing germline testing. For patients with a MLH1 mutation who do not have hypermethylation or a BRAF mutation, germline testing for Lynch Syndrome is recommended.
The Multi-Society Task Force on Colorectal Cancer guidelines on Lynch Syndrome made a strong recommendation in favor of 2\textsuperscript{nd} step testing for hypermethylation of MLH-1 or BRAF mutation.\textsuperscript{5} The recommendation was based on studies that made the assumption 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 MLH-1 promoter are also found in some individuals with Lynch Syndrome.\textsuperscript{4} Therefore, utilizing 2\textsuperscript{nd} step testing will in fact result in some small proportion of Lynch Syndrome cases being missed (< 10%). The evidence in this current AGA guideline was graded as very low as the data originate from observational studies, there thus exists 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 colorectal cancer patients with absent MLH-1 on IHC, the great majority of whom have sporadic cancers. In light of all these concerns, the AGA conditionally recommends in favor of 2\textsuperscript{nd} step testing.

The AGA recommends surveillance colonoscopy (versus doing nothing) in persons with Lynch Syndrome. \textit{(Strong recommendation, moderate quality of evidence)}. The AGA suggests that surveillance colonoscopy should be performed every 1 to 2 years versus less frequent intervals. \textit{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).\textsuperscript{4} A cost-effectiveness model estimating life expectancy and healthcare costs of colonoscopy surveillance every 2 to 3 years versus no surveillance determined that surveillance of persons who are gene carriers for Lynch Syndrome increased life expectancy 7 years and costs of surveillance were less than costs of no surveillance for colorectal cancer. Conventional practice has suggested commencing surveillance at either age 20 to 25 years or 5 years before the youngest age of colorectal cancer in an affected family member, whichever occurs first.
The Multi-Society Task Force on Colorectal Cancer guidelines on Lynch Syndrome made a strong recommendation for both surveillance and the interval of surveillance, but the AGA finds that the available data only supports a conditional recommendation for the interval of surveillance.5

The evidence in the current AGA guideline originates from observational studies for these recommendations; there thus exists a strong risk of bias. The grading of evidence is upgraded because of the magnitude of effect relating to the effectiveness of colonoscopic surveillance in lowering CRC incidence and mortality. The latter, however is not true for the data comparing different surveillance intervals, leading to the lower grading of evidence and strength of recommendation. The best interval to recommend colorectal cancer screening in persons with Lynch Syndrome remains unknown. No identifiable studies have directly compared surveillance intervals, yet most colorectal cancers diagnosed in persons 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 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 persons with Lynch Syndrome.**
*Conditional recommendation, low quality of evidence.*

One high-quality randomized controlled trial in adults with Lynch Syndrome assessed the anti-neoplastic effect of aspirin 600mg daily compared to 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 trend toward decrease incidence in 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 was no mortality data to support a benefit from long-term aspirin therapy (grading of evidence thus is very low for this outcome). Adverse risks of aspirin therapy (3% risk of gastrointestinal bleed and 1% risk of stroke over 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. No studies to date have examined 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. These guidelines utilize GRADE methodology and follow the best practices outlined by the Institute of Medicine. Areas that should be a priority for future research include:

- Validating the calibration of predictive models for Lynch mutations in a population of patients without a personal history of cancer.
- Identifying the threshold predicted probability of carrying a Lynch mutation that should prompt germline genetic testing.
- Updating cost-effectiveness analyses with new estimates of the accuracy of BRAF mutation and MLH-1 promoter hypermethylation testing, and as the cost of germline genetic testing decreases.
- 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.
REFERENCES


### Table 1. GRADE Categories of Quality of Evidence

<table>
<thead>
<tr>
<th>Category</th>
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<td>High</td>
<td>We are very confident that the true effect lies close to that of the estimate of the effect.</td>
</tr>
<tr>
<td>Moderate</td>
<td>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.</td>
</tr>
<tr>
<td>Low</td>
<td>Our confidence in the effect estimate is limited. The true effect may be substantially different from the estimate of the effect.</td>
</tr>
<tr>
<td>Very Low</td>
<td>We have very little confidence in the effect estimate. The true effect is likely to be substantially different from the estimate of effect.</td>
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### Table 2. GRADE Categories of Strength of Recommendation

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<th>For the Clinician</th>
</tr>
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<td>Strong</td>
<td>Most individuals in this situation would want the recommended course of action and only a small proportion would not.</td>
<td>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.</td>
</tr>
<tr>
<td><strong>Weak/Conditional</strong></td>
<td>The majority of individuals in this situation would want the suggested course of action, but many would not.</td>
<td>Different choices will be appropriate for different patients. Decision aids may well be useful helping individuals making decisions consistent with their values and preferences. Clinicians should expect to spend more time with patients when working towards a decision.</td>
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<td>Patients with Lynch Syndrome</td>
<td>Aspirin chemoprevention</td>
<td>Surveillance colonoscopy alone</td>
<td>Conditional</td>
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Any new colorectal cancer

Tumor testing for MSI or IHC

Normal  IHC abnormal

 MSI high

Missing MLH-1  Other IHC abnormal

BRAF or MLH-1 methylation testing

Negative

MLH-1 promoter hypermethylated or BRAF mutation present
- Likely sporadic colorectal cancer
- Consider other familial cancer

Predictive model

>5% probability

<5% probability

Family history suggestive of Lynch syndrome, but:
- no personal history of cancer,
- no known family history of Lynch mutation,
- and tumor tissue from affected relative not available.

Positive for Lynch mutation
- Colonoscopy every 1-2 years
- Consider aspirin
- Genetic counseling for 1st degree relatives

Negative

Consider other familial cancer syndromes
BRAF: somatic mutations in the BRAF gene at codon 600,

IHC: immunohistochemistry utilizing antibodies against the mismatch repair gene proteins MLH1, MSH2, MSH6, and PMS2 assessing for loss of expression,

MSI: microsatellite instability