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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) methodology[2] 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.dfci.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.