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American Gastroenterological Association Technical Review on the Diagnosis and Management of Lynch Syndrome

Uri Ladabaum,[1] James M. Ford,[2] Myriam Martel,[3] and Alan N. Barkun[3,4]

[1]Division of Gastroenterology/Hepatology, [2]Division of Oncology, Department of Medicine, Stanford University School of Medicine, Stanford, California; and [3]Division of Gastroenterology, [4]Division of Epidemiology and Biostatistics and Occupational Health, McGill University Health Center, McGill University, Montreal, Quebec, Canada

Hereditary syndromes account for a small but important fraction of all cases of colorectal cancer (CRC). Approximately 30% of people with CRC have a family history of the disease, and 5% to 6% have mutations that are diagnostic of a known hereditary cancer syndrome.[1] Even though most CRCs are sporadic and most familial CRCs do not arise in the context of a recognized genetic syndrome, it is critical to identify families with hereditary CRC syndromes for 2 reasons: (1) those with a hereditary syndrome and a personal history of CRC have an elevated risk of other noncolorectal cancers as well as a higher risk of metachronous CRC than people without a hereditary syndrome and (2) relatives without a personal history of CRC or other cancers have an elevated risk of CRC and other cancers starting at relatively young ages. Awareness of these risks can be coupled with risk management strategies (screening, surveillance, prophylactic surgery, and possibly chemoprevention) that can substantially improve patient outcomes.

This technical review focuses on questions faced in routine clinical practice related to the identification and management of risk of CRC in patients with Lynch syndrome, which is the most common inherited CRC predisposition syndrome. The process behind the development of this technical review, our conceptual framework regarding hereditary CRC syndromes, and questions related to other hereditary CRC syndromes (including the polyposis syndromes) are discussed in Appendix 1.

When this technical review was conceived, the leadership of the American Gastroenterological Association (AGA) and the authors were aware that the US Multi-Society Task Force on Colorectal Cancer had begun work on a consensus statement on the genetic evaluation and management of Lynch syndrome.[2] We worked to ensure that these documents would be parallel and complementary but not duplicative efforts. Our specific aims were to systematically review the published evidence on a selected set of focused questions related to Lynch syndrome and perform meta-analyses when possible. This technical review (which informs the accompanying guideline) includes a series of original meta-analyses that provide more precise summary estimates of published evidence than have been available previously for some recommendations. This explains any discrepancy in evidence ratings compared with the recent US Multi-Society Task Force consensus statement.[2] Any pertinent explanation for the evidence grading is further specified at the end of related statements (under quality of evidence).

Lynch syndrome, previously referred to as hereditary nonpolyposis colorectal cancer (HNPCC), is an autosomal dominant cancer predisposition syndrome caused by mutations in DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, *PMS2*) or a gene (*EPCAM*) near the *MSH2* gene.[3–10] Lynch syndrome accounts for approximately 2% to 3% of cases of CRC; the population prevalence is estimated at 1 in 440,[11,12] although some authorities believe this estimate is conservative. Lynch syndrome–associated tumors usually display high microsatellite instability (MSI-H) as a consequence of replication errors due to deficient DNA MMR and/or abnormal immunohistochemistry (IHC) for the MMR gene products.[3,12] The risk of cancer in patients with Lynch syndrome depends on the affected MMR gene. The reported risk of CRC by 70 years of age ranges from 15% to 20% for *PMS2* mutation carriers,[13,14] from 30% to 69% for *MSH6* mutation carriers,[15] and from 40% to 80% for *MLH1* or *MSH2* mutation carriers.[2,12,16,17] The age of onset is often younger than 50 years, which is earlier than the typical age to start average-risk CRC screening. The risk of endometrial cancer in patients with Lynch syndrome can be as high as 60% to 70% by 70 years of age, depending on the gene affected.[12,16,17] There is also elevated risk of other cancers in patients with Lynch syndrome, including ovarian, gastric, hepatobiliary, small intestine, urinary tract, sebaceous skin, and brain cancer.[2,12,16,17] Frequent colonoscopy with polypectomy decreases the incidence and mortality of CRC in patients with Lynch syndrome.[18,19] Prophylactic hysterectomy and oophorectomy after childbearing is complete nearly eliminates the risk of endometrial and ovarian cancer in women with Lynch syndrome.[20]

HNPCC was originally defined by clinical criteria that emphasized early-onset CRC in multiple first-degree relatives. The Amsterdam II criteria for a clinical diagnosis of HNPCC include having at least 3 relatives with an HNPCC-associated cancer, with at least one being a first-degree relative of the other 2 relatives and at least 2 successive

Abbreviations used in this paper: **AFAP, attenuated familial adenomatous polyposis; AGA, American Gastroenterological Association; AUC, area under the curve; CI, confidence interval; CRC, colorectal cancer; FAP, familial adenomatous polyposis; HNPCC, hereditary nonpolyposis colorectal cancer; IHC, immunohistochemistry; MAP, MUTYH-associated polyposis; MMR, mismatch repair; MSI, microsatellite instability; MSI-H, high microsatellite instability; PICO, population, intervention, comparator, and outcome; QALY, quality-adjusted life year.**

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generations affected.[21] Because these criteria are relatively specific but insensitive, the revised Bethesda guidelines were proposed as a more sensitive means to identify patients with CRC who should undergo microsatellite instability (MSI) testing.[22] These include patients with CRC diagnosed before 50 years of age, synchronous or metachronous CRC or other HNPCC-associated tumors, CRC with specific histological features diagnosed before 60 years of age, CRC in one or more first-degree relatives with an HNPCC-related tumor with one of the cancers diagnosed before 50 years of age, or CRC diagnosed in 2 or more first- or second-degree relatives with HNPCC-related tumors regardless of age.

The molecular diagnosis of Lynch syndrome now requires identification of a deleterious mutation in one of the Lynch syndrome–associated genes. Prediction models ($PREMM_{1,2,6}$[23] [an extension of $PREMM_{1,2}$[24]], MMRpro,[11] and MMRpredict[25]) have been developed to identify patients in whom genetic testing is likely to have reasonable yield. More recently, reflex IHC and/or MSI testing of all newly diagnosed CRCs (or a subset based on age or other clinical criteria) has gained acceptance as a strategy to identify patients with Lynch syndrome.[26–28] Because most CRCs that are MSI-H are sporadic, with loss of *MLH1* function due to acquired *MLH1* promoter methylation, second-step tumor testing strategies (*MLH1* promoter methylation or *BRAF* mutation testing) have been developed to select out patients whose MSI-H CRCs are likely sporadic and therefore do not require germline testing.[29,30]

The 5 questions selected for this technical review focus on 3 patient populations: adults unaffected by CRC or another cancer but with a family history of CRC or other Lynch syndrome–associated cancers, adults with CRC, and adults with Lynch syndrome. The questions address the clinical challenges of selection of people for Lynch syndrome germline testing and of risk mitigation strategies in patients with Lynch syndrome, focusing on CRC. Consideration of other Lynch syndrome–associated cancers, including management of the risk of gynecologic cancers or identification of possible Lynch syndrome in women with endometrial or ovarian cancer, is beyond the scope of this technical review. Other clinically relevant questions, including the role of subtotal colectomy in patients with established Lynch syndrome who develop CRC, are also beyond the scope of this review. Because of the limitations of the Amsterdam II criteria and revised Bethesda guidelines for identifying patients with mutations in Lynch syndrome–associated genes,[31,32] we chose to focus on the prediction models and tumor testing for selection of patients for germline testing.

AGA SECTION

Methods

Formulation of Clinical Questions

The participants (including UL, JMF, and ANB) were selected by the AGA Clinical Guidelines Committee based on clinical content and guidelines methodological expertise. Focused questions were generated, and a statement was framed for each question in terms of population, intervention, comparator, and outcome (PICO).[33] In accordance with a modified Delphi method, the questions and PICO statements were developed by multiple structured iterations until a consensus among experts was reached.[34,35] The final proposed clinically pertinent, focused questions and PICO statements related to 3 different populations: adults without a personal history of CRC or another cancer but with a family history of cancer that could be suggestive of Lynch syndrome, adults with CRC, and adults with Lynch syndrome. The final set of questions and statements was approved by the AGA Governing Board. The final PICO questions are shown in Appendix Table 1.

Search Strategy

An experienced librarian conducted 3 distinct computerized medical literature searches (according to grouping of PICO questions using a similar search strategy) using the following databases until November 2013: MEDLINE, EMBASE, Cochrane, and Health Technology Assessment.

All searches included a highly sensitive search strategy to identify reports of randomized trials, cohort studies, or case-control studies using a combination of controlled vocabulary and text words. The first search related to PICO questions 1, 2, 4, and 5 included the following terms: (1) hereditary nonpolyposis colorectal cancer or Lynch and (2) colonoscopy or immunohistochemistry or genetic testing or microsatellite instability or acetylsalicylic acid (complete search strings are shown in Appendix 2). The search related to PICO question 3 Q4 addressed the following: (1) colorectal neoplasms and (2) *BRAF* mutation or *MLH1* DNA methylation (Appendix 3). In addition, recursive searches and cross-referencing was performed; hand searches of articles identified after the initial search were also completed.

Trial Selection and Patient Population

All fully randomized controlled trials or observational studies published in English were included. Studies comprising pediatric populations as well as letters, notes, case reports, or comments were excluded.

Choice of Outcomes

Most questions assessed the following hierarchal outcomes: test performance characteristics of the different diagnostic tests focusing on sensitivity and specificity as well as psychological distress, quality of life, and costs. Questions 4 and 5 primarily assessed incidence and prevalence rates of CRC; incidence and prevalence rates of adenoma; and staging, mortality, procedural complications, quality of life, and costs of CRC. Question 4 also addressed serrated lesions, and question 5 addressed dyspeptic symptoms (Appendix Table 1).

Validity Assessment

Study eligibility was assessed independently by 3 investigators (UL, JMF, and ANB), with discrepancies resolved after discussion and reaching a consensus. Data extraction was thoroughly performed by content experts (UL, JMF, and ANB). Risk of bias for individual studies was assessed using the QUADAS-2 tool for observational diagnostic studies,[36] a modified Jadad score (one point added if allocation was concealed) for randomized trials,[37] and the Newcastle–Ottawa Scale for observational studies.[38] The quality of the evidence for each

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