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WHITE PAPER

Guidelines on genetic evaluation and management of Lynch syndrome: A consensus statement by the U.S. Multi-Society Task Force on Colorectal Cancer

The Multi-Society Task Force, in collaboration with invited experts, developed guidelines to assist health care providers with the appropriate provision of genetic testing and management of patients at risk for and affected with Lynch syndrome as follows: Figure 1 provides a colorectal cancer risk assessment tool to screen individuals in the office or endoscopy setting; Figure 2 illustrates a strategy for universal screening for Lynch syndrome by tumor testing of patients diagnosed with colorectal cancer; Figures 3-6 provide algorithms for genetic evaluation of affected and at-risk family members of pedigrees with Lynch syndrome; Table 10 provides guidelines for screening at-risk and affected persons with Lynch syndrome; and Table 12 lists the guidelines for the management of patients with Lynch syndrome. A detailed explanation of Lynch syndrome and the methodology utilized to derive these guidelines, as well as an explanation of, and supporting literature for, these guidelines are provided.

Colorectal cancer (CRC) is a major American health problem that ranks as the second leading cause of cancer death after lung cancer. In the United States, approximately 143,000 new cases are diagnosed each year, and 51,000 Americans die annually from this disorder.[1]

The cause of CRC is multifactorial, with environment and inheritance playing varying roles in different patients.[2] Approximately 70%−80% of patients with CRC seem to have sporadic disease with no evidence of an inherited disorder. In the remaining 20%−30%, a potentially definable inherited component might be causative.[3]

Lynch syndrome (LS), an autosomal dominant condition, is the most common cause of inherited CRC, accounting for about 3% of newly diagnosed cases of colorectal malignancy.[4-8] The eponym "Lynch syndrome" recognizes Dr Henry T. Lynch, the first author on the original 1966 publication that comprehensively described this condition.[9]

In the early 1990s, mutation of genes in the DNA mismatch repair (MMR) pathway were implicated as the cause of LS,[10-13] and the presence of the mutations now defines the syndrome. Since then, germline testing with increasing sensitivity has been available for patients, as additional genetic discoveries have occurred. When used appropriately, genetic testing for LS can confirm the diagnosis at the molecular level, justify surveillance of at-risk persons, decrease the cost of surveillance by risk stratification, aid in surgical and chemoprevention management, and help in decisions concerning family and career planning. However, when used inappropriately, genetic testing can misinform affected patients with false-negative results and waste patient and societal resources.

The goal of this consensus document is to critically analyze the current literature and provide "best practice" evidence-based recommendations for diagnosis and management strategies to health care providers caring for these patients.

METHODOLOGY

Literature review

A systematic computer-aided search of MEDLINE from 2005 to 2012 was performed focusing on LS, hereditary nonpolyposis colorectal cancer (HNPCC), and associated reports of genetic testing. The search identified all literature under the medical subject headings and text words, "hereditary nonpolyposis colorectal cancer," "HNPCC," "Lynch syndrome," "Muir Torre syndrome," "Turcot syndrome," and "gene/genetic testing." In addition, a search was conducted using references from all retrieved reports, review articles, and textbook chapters. Publications were retrieved, and the authors synthesized and assessed the quality of the available data with respect to topicality and timeliness. Differences among reviewers concerning inclusions were resolved by consensus. Editorials and letters to the editors were excluded from this review.

Levels of evidence

A variety of different types of publications were reviewed, including randomized controlled trials, retrospective and prospective observational cohorts, and population-based and case-control studies. The strength of the evidence from these sources was rated according to the National Cancer Institute levels of evidence for cancer genetic studies (Table 1).[14]

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TABLE 1. Levels of Evidence by National Cancer Institute Levels of Evidence for Cancer Genetic Studies

Level of evidence	Description
I	Evidence obtained from at least 1 well-designed and well-controlled randomized controlled trial that has either: a. Cancer end point with mortality or incidence, or b. Intermediate end point
II	Evidence obtained from well-designed and well-conducted nonrandomized controlled trials that have: a. Cancer end point b. Intermediate end point
III	Evidence obtained from well-designed and well-conducted cohort or case-control studies with: a. Cancer end point b. Intermediate end point
IV	Evidence from descriptive studies with: a. Cancer end point b. Intermediate end point
V	Conclusions from authorities based on clinical experience, descriptive studies and/or expert committees

TABLE 2. Rating of Evidence by Grades of Recommendation, Assessment, Development, and Evaluation Methodology

Rating of evidence	Impact of potential future research
A. High quality	Very unlikely to change confidence in the estimate of effect
B. Moderate quality	Likely to have an important impact on confidence and might change estimate of effect
C. Low quality	Very likely to have an important impact on confidence in the estimate of effect and is likely to change the estimate
D. Very low quality	Any estimate of effect is very uncertain

In addition, a well-accepted rating of evidence, Grades of Recommendation, Assessment, Development, and Evaluation (GRADE), which relies on expert consensus about whether new research is likely to change the confidence level (CL) of the recommendation was also utilized for evaluation of LS interventions (Table 2).[15]

TABLE 3. Gene-Specific Cumulative Risks of Colorectal Cancer by Age 70 Years in Lynch Syndrome

Gene mutation carriers	Risk, %	Mean age at diagnosis, y	References
Sporadic cancer	5.5	69	29
MLH1/MSH2	Male: 27–74 Female: 22–53	27–46	17–21, 23
MSH6	Male: 22 Female: 10 Male and female: 18	54–63	17, 22
PMS2	Male: 20 Female: 15	47–66	25

Process

The Multi-Society Task Force is composed of gastroenterology specialists with a special interest in CRC, representing the following major gastroenterology professional organizations: American College of Gastroenterology, American Gastroenterological Association Institute, and the American Society for Gastrointestinal Endoscopy. Also, experts on LS from academia and private practice were invited authors of this guideline. Representatives of the Collaborative Group of the Americas on Inherited Colorectal Cancer and the American Society of Colon and Rectal Surgeons also reviewed this manuscript. In addition to the Task Force and invited experts, the practice committees and Governing Boards of the American Gastroenterological Association Institute, American College of Gastroenterology, American Society for Gastrointestinal Endoscopy reviewed and approved this document.

LYNCH SYNDROME CHARACTERISTICS

Clinical manifestations

In 1966, Dr Henry T. Lynch and colleagues reported familial aggregation of CRC with stomach and endometrial tumors in 2 extended pedigrees and designated this condition *cancer family syndrome*.[9] Later, to differentiate this syndrome from the other well-known inherited form of CRC, familial adenomatous polyposis, the appellation *hereditary nonpolyposis colorectal cancer* was utilized. In 1984, the term *Lynch syndrome* was coined by Boland and Troncale to refer to this disorder.[16] Today this condition is called Lynch syndrome. This designation is correctly applied to families and patients with a germline mutation in an MMR gene or loss of expression of the *MSH2* gene due to deletion in the *EPCAM* gene. Also, this name is