

AGA SECTION

Guidelines on Genetic Evaluation and Management of Lynch Syndrome: A Consensus Statement by the US Multi-Society Task Force on Colorectal Cancer

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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.

Keywords: Lynch Syndrome; Colorectal Cancer; Genetic Testing.

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

Abbreviations used in this paper: CAPP2, Colorectal/Adenoma/Carcinoma Prevention Programme; CL, confidence level; CRC, colorectal cancer; EC, endometrial cancer; FCRCTX, familial colorectal cancer type X; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation; HNPCC, hereditary nonpolyposis colorectal cancer; IHC, immunohistochemistry; LS, Lynch syndrome; MMR, mismatch repair; MSI, microsatellite instability; NCCN, National Comprehensive Cancer Network.

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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

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

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.

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

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

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

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

EPCAM gene. Also, this name is more appropriate than HNPCC because most LS patients will develop one or several adenomatous polyps, which makes the term *nonpolyposis* misleading.

LS is an autosomal dominant disorder with colorectal malignancy as the major clinical consequence.^{4–8} The lifetime risk of CRC in LS has been variably estimated and appears dependent on sex and the MMR gene mutated.^{17–23} Most reports of lifetime risks of CRC for *MLH1* and *MSH2* gene mutation carriers range from 30% to 74% (Table 3). Lower cumulative lifetime risk for colorectal malignancy ranging from 10% to 22% has been found in patients with *MSH6* mutations²⁴ and 15%–20% in those with *PMS2* mutations.²⁵ Mean age at CRC diagnosis in LS patients is 44–61 years^{6,26–28} compared with 69 years in sporadic cases of CRC.²⁹ In LS, colorectal tumors arise primarily (60%–80%) on the right side of the colon (proximal to the splenic flexure) compared with 30% in sporadic CRC.³⁰ A high rate of metachronous CRC (16% at 10 years; 41% at 20 years) is noted in LS patients with segmental surgical resection of the initial CRC.^{31–33} The precursor lesion for LS

appears to be a discrete colonic adenoma, which can occasionally be flat rather than elevated/polypoid. Compared with patients with attenuated polyposis syndromes, LS patients develop fewer colorectal adenomas by age 50 years (usually <3 neoplasms).³⁴ LS colorectal adenomas typically demonstrate features of increased risk of cancer, including villous histology and high-grade dysplasia.³⁵ The adenoma–carcinoma sequence appears more rapid in LS with polyp to cancer dwell times estimated at 35 months compared with 10–15 years in sporadic cancer.³⁴ This phenomenon is likely related to dysfunction of the MMR genes, leaving frequent DNA mismatches in multiple genes leading to malfunction of these genes. The histopathology of LS CRC is more frequently poorly differentiated, can be signet cell histology, abundant in extracellular mucin, with tumor infiltrating lymphocytes, and distinguished by a lymphoid (Crohn's-like pattern and/or peritumoral lymphocytes) host response to tumor.^{36,37} LS patients have improved survival from CRC stage for stage compared with those with sporadic cancer.³⁸

In addition to CRC, LS patients have a significantly increased risk for a wide variety of extracolonic malignancies (Table 4). The highest risk is for endometrial cancer (EC), which occurs in up to 54% of women with *MLH1* and *MSH2* mutations, with lower risk in those with *PMS2* (15%) mutations²⁵ and much higher risk in persons with *MSH6* mutations (71%).²⁴ LS caused by *MSH6* mutation is also characterized by later onset of colorectal and endometrial cancers than with other MMR gene alternations. Increased lifetime risk of transitional cell carcinoma of the ureter, renal pelvis, and bladder; adenocarcinomas of the ovary, stomach, hepatobiliary tract, and small bowel; brain cancer (glioblastoma); and cutaneous sebaceous neoplasms also occur in LS families.^{17,28,39–53} An increased risk of pancreas cancer in LS has been described by some investigators^{50,54} but not others.⁴⁴ The relationship between LS and breast cancer is unclear. Although a small increase in absolute risk of breast cancer (18%) has been found,^{48,55} most registry

Table 4. Cumulative Risks of Extracolorectal Cancer by Age 70 Years in Lynch Syndrome

Cancer	Risk general population, %	Risk in LS, %	Mean age at diagnosis, y	References
Endometrium	2.7		65	17–19, 21, 22, 24, 25
MLH1/MSH2		14–54	48–62	
MSH6		17–71	54–57	
PMS2		15	49	
Stomach	<1	0.2–13	49–55	17, 40, 44–48
Ovary	1.6	4–20	43–45	17, 28, 39, 40, 44, 46, 48
Hepatobiliary tract	<1	0.02–4	54–57	17, 28, 39, 44
Urinary tract	<1	0.2–25	52–60	17, 39, 40, 44, 46, 48, 49
Small bowel	<1	0.4–12	46–49	17, 40, 44, 46, 48
Brain/central nervous system	<1	1–4	50	39, 40, 44, 46
Sebaceous neoplasm	<1	1–9	NA	41, 42
Pancreas	1.5	0.4–4.0	63–65	44, 50–52
Prostate	16.2	9–30	59–60	44, 48, 53, 59
Breast	12.4	5–18	52	44, 48, 56, 57

NA, Not available.

Table 5. Amsterdam I and II Criteria for Diagnosis of Hereditary Nonpolyposis Colorectal Cancer

Amsterdam I criteria

1. Three or more relatives with histologically verified colorectal cancer, 1 of which is a first-degree relative of the other two. Familial adenomatous polyposis should be excluded.
2. Two or more generations with colorectal cancer.
3. One or more colorectal cancer cases diagnosed before the age of 50 years.

Amsterdam II criteria

1. Three or more relatives with histologically verified HNPCC-associated cancer (colorectal cancer, cancer of the endometrium, small bowel, ureter, or renal pelvis), 1 of which is a first-degree relative of the other 2. Familial adenomatous polyposis should be excluded.
2. Cancer involving at least 2 generations.
3. One or more cancer cases diagnosed before the age of 50 years.

reports have not demonstrated this consistently.^{46,56} However, there are early-onset breast cancers in some LS kindreds in which tumors have the microsatellite instability (MSI) phenotype.^{57,58} In several studies, the relative risk of prostate cancer is 2.0- to 2.5-fold higher than the general population risk.^{48,59} Also, an excess of laryngeal and hematologic malignancies has been described, but a definite association to LS has not been established.^{30,60,61} An association between sarcoma and LS probably exists, but the magnitude of risk is unclear.⁶²

Phenotypic stigmata of LS are found rarely on physical examination, but can include café au lait spots, cutaneous sebaceous gland tumors, and keratoacanthomas.^{63,64} Café au lait spots are found in patients with biallelic mutations of the MMR genes. This variant of LS is referred to as constitutional MMR deficiency syndrome and will be described here.

Clinical Criteria

In 1990, the International Collaborative Group on Hereditary Nonpolyposis Colorectal Cancer established criteria (Amsterdam I Criteria) for HNPCC (Table 5).⁶⁵ All of the following are required to diagnose HNPCC: 3 or more relatives with histologically verified colorectal cancer, 1 of which is a first-degree relative of the other 2 (familial adenomatous polyposis should be excluded); CRC involving at least 2 generations; and 1 or more CRC cases diagnosed before the age of 50 years. In response to concern that these standards were too stringent for clinical and research application, more sensitive criteria (Amsterdam II criteria) were established in 1999 (Table 5).⁶⁶ Amsterdam II criteria include some extracolonic tumors commonly seen in LS as qualifying cancers—in particular, cancer of the

endometrium, small bowel, ureter, or renal pelvis. Most experts today expand the spectrum of LS-related tumors to also include cancer of the ovary, stomach, hepatobiliary tract, and brain.

The Revised Bethesda Guidelines are a third set of clinicopathologic criteria developed to identify individuals who deserve investigation for LS by evaluation of MSI and/or immunohistochemistry (IHC) testing of their tumors (Table 6).⁶⁷

Terminology/Differential Diagnosis

HNPCC designates patients and/or families who fulfill the Amsterdam I or II criteria. LS is applied to patients and families in which the genetic basis can be linked to a germline mutation in one of the DNA MMR genes or the *EPCAM* gene. Lynch-like syndrome describes patients and/or families in which molecular testing demonstrates the presence of MSI and/or abnormalities in the expression of MMR gene proteins on IHC testing of tumor tissue expression, but no pathogenic germline mutation can be found in the patient (eg, in the absence of a BRAF mutation and/or MLH1 promoter hypermethylation when there is loss of tumor expression of the MLH1 protein). In a recent publication, about half of LLS patients had biallelic somatic mutations of MLH1 or MSH2 to explain the MMR deficient tumors without having causal germline or promoter mutations.⁶⁸

Familial colorectal cancer type X (FCRCTX) refers to patients and/or families that meet Amsterdam I criteria, but, when tumors are tested, lack the MSI characteristic of LS.^{10,11,69–75} Studies suggest that the age at diagnosis of CRC in these pedigrees is slightly older than in families with LS. Also, the lifetime risk of CRC appears substantially lower in FCRCTX families than in LS^{69,70,72}; the standardized

Table 6. Revised Bethesda Guidelines

1. CRC diagnosed at younger than 50 years.
2. Presence of synchronous or metachronous CRC or other LS-associated tumors.^a
3. CRC with MSI-high pathologic-associated features (Crohn-like lymphocytic reaction, mucinous/signet cell differentiation, or medullary growth pattern) diagnosed in an individual younger than 60 years old.
4. Patient with CRC and CRC or LS-associated tumor^a diagnosed in at least 1 first-degree relative younger than 50 years old.
5. Patient with CRC and CRC or LS-associated tumor^a at any age in 2 first-degree or second-degree relatives.

^aLS-associated tumors include tumor of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and keratoacanthomas.

incidence ratio for CRC in FCRCTX pedigrees was 2.3 (95% CL: 1.7–3.0) compared with 6.1 (95% CL: 5.7–7.2) for individuals in pedigrees with LS.⁶⁹ In addition, in FCRCTX families, risk of extracolonic cancers found in LS is not significantly higher than the general population.⁷¹

Muir-Torre syndrome, a rare variant of LS, is diagnosed in patients and/or families with LS and skin sebaceous gland neoplasms (sebaceous adenomas and carcinomas) and/or neoplasms of the hair follicle (keratoacanthomas).⁷³ Mutations in any of the MMR genes can be found in these patients, but *MSH2* mutation appears most common.⁵⁰ MSI can be identified in the skin neoplasms and colorectal tumors of affected patients.⁷⁴

Turcot's syndrome is defined as patients and/or families with colorectal neoplasia and brain tumors. However, these families can be cases of LS (associated with glioblastomas) or familial adenomatous polyposis (associated with medulloblastomas), so Turcot's syndrome is not an independent entity.⁷⁵

Constitutional mismatch repair deficiency syndrome is the term applied to patients and/or families with biallelic mutations of the DNA MMR genes. These patients are characterized by café au lait spots, early (in childhood and teenage years) onset of colorectal neoplasia or other LS cancers, oligopolyposis in the small bowel and/or colon, brain tumors, and hematologic malignancies.^{63,64}

Genetic Alterations

Germline Mutations

LS is caused by inactivation of one of several DNA MMR genes. These genes function to maintain fidelity of the DNA during replication by correction of nucleotide base mis-pairs and small insertions or deletions generated by mis-incorporations or slippage of DNA polymerase during DNA replication. Germline mutation in the MMR genes *MLH1*, *MSH2*, *MSH6*, and *PMS2* cause LS.^{10,76–79} Also, deletions of the terminal codon of the *EPCAM* gene (previously called the TACSTD1 gene), located just upstream from the *MSH2* gene, result in silencing of the *MSH2* gene in tissues that express *EPCAM* and, consequently, produce a phenotype very similar to LS.⁸⁰ In an investigation of 2 families, when the deletion is isolated to the stop codon of *EPCAM*, a colon-only phenotype occurs.⁸¹ In another study, if the deletion also includes critical portions of the *MSH2* promoter, a full LS phenotype results.⁸² Mutations in *MLH1* and *MSH2* account for up to 90% and *MSH6* about 10% of mutations found in LS families. In the past, *PMS2* mutations have been identified rarely because of the presence of multiple *PMS2* pseudogenes, which confuse genetic diagnostics.^{83,84} A recent study found *PMS2* mutations in 6% of all LS families.⁸⁵

Germline Epimutations

Rare patients have been reported with germline *MLH1* hypermethylation. These patients do not have *MLH1* sequence variations or rearrangements. This epimutation appears to be mosaic, involving different tissues to varying extents and is typically reversible so that offspring are

usually unaffected, but inheritance has been demonstrated in a few families. Patients with this epimutation have early-onset LS and/or multiple LS cancers.⁸⁶

Tumor Alterations

LS is caused by a single dominant mutation inherited in the germline, which increases risk for cancer. The LS cancers form only after a second hit (by one of several genetic damage mechanisms) occurs within somatic tissue, which causes loss of function to the normal (wild-type) allele inherited from the unaffected parent; this results in total loss of DNA MMR activity in that cell and subsequent MSI. Therefore, the disease is inherited as a Mendelian dominant. However, the tumors occur after somatic biallelic gene inactivation, with one mutation inherited and the other acquired.

Microsatellite instability. MSI is a phenomenon manifested by ubiquitous mutations at simple repetitive sequences (microsatellites) found in the tumor DNA (but not in the DNA of the adjacent normal colorectal mucosa) of individuals with MMR gene mutations.⁸⁷ MSI is characterized by abnormal expansion or contraction of these microsatellite repeats. Microsatellite repeats are normally found through the genome primarily in intronic sequences. MSI in CRC indicates a defect in one of the MMR genes caused by either somatic changes of the gene (hypermethylation of the *MLH1* promoter) or a germline defect (LS). MSI is found in most (>90%) colon malignancies in patients with LS (due to germline MMR gene mutation) and in 12% of patients with sporadic CRC (due to somatic hypermethylation of the *MLH1* gene).⁸⁷ MSI is graded as MSI-high ($\geq 30\%$ of markers are unstable), MSI-low (<30% of markers are unstable), and MS-stable (no markers are unstable).⁸⁸ Most CRCs in LS are MSI-high. The significance of MSI-low tumors is controversial. Some evidence suggests that MSI-low is due to *MSH6* germline mutation in certain cases,⁸⁹ but this phenomenon is most often caused by somatic inactivation of the *MSH3* gene, which is common and not inherited.^{90,91} Somatic down-regulation of *MSH3* is accompanied by MSI-low, as well as mutations at trinucleotide and tetranucleotide repeats, but not mutations at mononucleotide and dinucleotide repeats, which are used for standard ascertainment of MSI.⁹⁰ In addition, germline mutations in *MLH3* have not been associated with an LS phenotype.^{92,93}

Loss of expression of DNA mismatch repair proteins. IHC of CRCs utilizing antibodies to the MMR gene proteins *MLH1*, *MSH2*, *MSH6*, and *PMS2* evaluates for the loss of MMR protein expression and assists in the identification of patients with LS.⁹⁴ Deleterious alterations (either germline or somatic) in specific DNA MMR are indicated by loss or partial production of the MMR protein produced by that gene. *MSH2* and *MSH6* proteins are often lost concurrently and indicate *MSH2* mutation. Isolated loss of *MSH2* or *MSH6* on IHC testing has high specificity for a germline mutation of the *MSH2* or *MSH6* gene, respectively, hence the diagnosis of LS. Also, loss of the *MSH2* protein can be caused by germline mutation in the *EPCAM* gene rather than *MSH2* gene. Similarly, *MLH1* and *PMS2* proteins are also often lost

together; this generally indicates loss of MLH1 function either due to germline mutation or somatic (not germline) silencing of the *MLH1* gene (see Somatic methylation of MLH1). Isolated loss of PMS2 protein generally indicates an underlying germline *PMS2* mutation.

Somatic methylation of *MLH1*. Aberrant *MLH1* gene promoter methylation is a somatic event that is confined to the CRC and is rarely inherited. Aberrant methylation of *MLH1* is responsible for causing loss of MLH1 protein expression and results in MSI found in approximately 12% of sporadic cancers.⁹⁵ The methylation of *MLH1* must be biallelic to abrogate MMR activity.

***BRAF* mutations.** The *BRAF* gene, a member of the *RAF-RAS* gene family, encodes a cytoplasmic serine/threonine kinase, an important component of the mitogen-activated protein kinase signaling pathway. Somatic mutations in the *BRAF* gene, largely at codon 600, are noted in 15% of sporadic CRCs. These are CRCs that develop through a methylation pathway called CpG island methylator phenotype. These cancers can also demonstrate MSI-high through somatic promoter methylation of *MLH1*.

Somatic *BRAF* V600 mutations have been detected predominantly in sporadic CRC^{96,97} of the type discussed here. Consequently, the presence of a *BRAF* mutation in an MSI-high CRC is usually, but not always, evidence against the presence of LS.⁹⁸

Identification of Lynch Syndrome

Several strategies have been developed to identify patients with LS. These include clinical criteria, prediction models, tumor testing, germline testing, and universal testing. The effectiveness of these strategies will be discussed here (Table 7).

Clinical Criteria

Amsterdam criteria. Utilizing Amsterdam II criteria (Table 5) involves the clinical evaluation of the patient and patient’s pedigree for colorectal and other LS cancers. Analysis from several sources reveals that patients and families meeting Amsterdam II criteria have a 22% sensitivity and 98% specificity for diagnosis of LS.^{5,6,8,99,100} However, when a large number of families were collected

and exhaustive searches performed for germline mutations in DNA MMR genes, fully 40% of families that meet the Amsterdam I criteria do not have LS.⁶⁹

Revised Bethesda guidelines. These guidelines specify circumstances in which a patient’s CRC should be tested for MSI (Table 6). The sensitivity and specificity for LS in those meeting any one of the guidelines is 82% and 77%, respectively.^{6,7}

Colorectal Cancer Risk Assessment Tool. Clinical criteria to identify patients at high risk for CRC are complex and difficult to apply in a busy office or endoscopy practice. Kastrinos and colleagues¹⁰¹ developed and validated a simple 3-question CRC risk assessment tool. When all 3 questions were answered “yes,” the tool correctly identified 95% of individuals with germline mutations causing LS. The cumulative sensitivity was 77% to identify patients with characteristics suggestive of hereditary CRC and who should undergo a more extensive risk assessment. This tool can be found in Figure 1.

Computational Models

Several clinical prediction models exist to determine an individual’s risk for LS, including the MMRpredict, MMRpro, and the PREMM_{1,2,6} models. All appear to outperform existing clinical criteria, including the revised Bethesda guidelines.^{99,100,102,103}

MMRpredict model. This model uses sex, age at diagnosis of CRC, location of tumor (proximal vs distal), multiple CRCs (synchronous or metachronous), occurrence of EC in any first-degree relative, and age at diagnosis of CRC in first-degree relatives to calculate risk of the patient having an LS gene mutation. Reported sensitivity and specificity for this model is 69% and 90%, respectively.^{5,100} This model appears to have the best specificity for LS of other calculators of gene mutation. This model can be accessed online at: hnpccpredict.hgu.mrc.ac.uk/.

MMRpro model. This model utilizes personal and family history of colorectal and endometrial cancer, age at diagnosis, and molecular testing results for MMR genes, when available, to determine the risk of a patient having a germline mutation of *MLH1*, *MSH2*, or *MSH6*.¹⁰⁴ This calculator also indicated the risk for future cancer in pre-symptomatic gene carriers and other unaffected individuals.

Table 7. Sensitivity and Specificity for Lynch Syndrome Utilizing Different Strategies

Criteria	Sensitivity (range)	Specificity (range)	References
Clinical			
Amsterdam II criteria	0.22 (0.13–0.67)	0.98 (0.97–1.0)	5, 6, 8, 99, 100
Revised Bethesda Guidelines	0.82 (0.78–0.91)	0.77 (0.75–0.79)	6, 7
Models			
MMRpredict	0.69 (0.68–0.75)	0.90 (0.86–0.94)	5, 100
MMRPro	0.89 (0.60–1.0)	0.85 (0.60–1.0)	100
PREMM _{1,2,6}	0.90 (0.60–1.0)	0.67 (0.60–1.0)	105
Tumor testing			
MSI	0.85 (0.75–0.93)	0.90 (0.87–0.93)	107
IHC	0.83 (0.75–0.89)	0.89 (0.68–0.95)	107

	YES	NO
1. Do you have a first-degree relative (mother, father, brother, sister, or child) with any of the following conditions diagnosed before age 50? <ul style="list-style-type: none"> • Colon or rectal cancer • Cancer of the uterus, ovary, stomach, small intestine, urinary tract (kidney, ureter, bladder), bile ducts, pancreas, or brain 	<input type="checkbox"/>	<input type="checkbox"/>
2. Have you had any of the following conditions diagnosed before age 50? <ul style="list-style-type: none"> • Colon or rectal cancer • Colon or rectal polyps 	<input type="checkbox"/>	<input type="checkbox"/>
3. Do you have three or more relatives with a history of colon or rectal cancer? (This includes parents, brothers, sisters, children, grandparents, aunts, uncles, and cousins.)	<input type="checkbox"/>	<input type="checkbox"/>

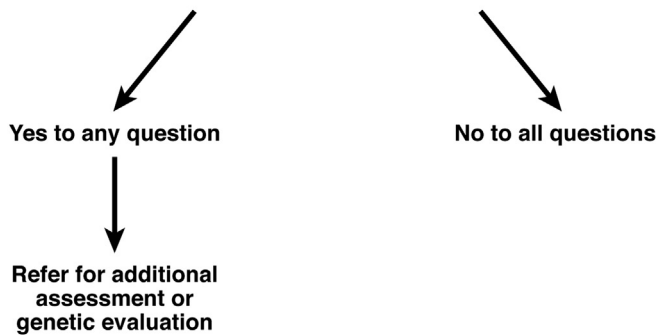


Figure 1. Colorectal cancer risk assessment tool. Adapted with permission from Kastrinos et al.¹⁰¹

The sensitivity and specificity of this model is 89% and 85%, respectively, and can be found at: www4.utsouthwestern.edu/breasthealth/cagene/.

PREMM_{1,2,6} model. Variables utilized in this model include proband, sex, personal, and/or family history of colorectal, endometrial, or other LS cancers.¹⁰⁵ This calculator gives a specific estimate of risk for a *MLH1*, *MSH2*, and *MSH6* mutation. Analysis of the accuracy of this model reveals a sensitivity of 90% and specificity of 67%. PREMM_{1,2,6} appears to have the best sensitivity but worse specificity compared with the others. The use of this model to determine risk of LS in the general population was a cost-effective approach when a 5% cutoff was used as a criterion for undergoing germline genetic testing.¹⁰⁶ This model can be found at: premm.dfc.harvard.edu.

Tumor Testing

Testing of tumor tissue can be done on archived formalin-fixed tissue from surgical resection specimens or biopsies from colorectal or endometrial cancer. Some experts would also recommend testing adenomas >1 cm in size in appropriate individuals. Laboratories in the United States are required to save specimens for at least 7 years.

Microsatellite instability testing. The sensitivity for diagnosing LS using molecular testing of CRC tissue for MSI is estimated at 85%, with a specificity of 90%.¹⁰⁷

Immunohistochemistry testing. IHC testing of tumor tissue for evidence of lack of expression of MMR gene

proteins has an overall reported sensitivity and specificity for LS of 83% and 89%, respectively. As discussed here, loss of *MLH1* protein is likely secondary to somatic events, and loss of *MSH2* protein is likely from a germline mutation.¹⁰⁷ Of note, the specificity of MSI and IHC testing decreases with increasing age due to increased prevalence of somatic *MLH1* hypermethylation. In persons older than age 70 years, the use of *BRAF* testing (as will be discussed) when loss of *MLH1* expression is seen, can help distinguish sporadic CRC tumors with somatic loss of *MLH1* from those individuals who do require testing for a germline mutation for LS.¹⁰⁸ An advantage of IHC testing is that lack of a specific mismatch gene protein can direct germline testing to that specific gene.

The accuracy of IHC is operator dependent and varies according to the experience and skill of the laboratory performing the testing. Consequently, prudence would suggest that this testing be performed in recognized reference laboratories with high-quality control measures.

Universal Testing

Utilization of clinical criteria and modeling to identify patients with LS has been criticized for less than optimal sensitivity and efficiency. Studies of molecular testing of all CRCs reveal that up to 28% of LS patients would be missed with the most liberal of clinical criteria—the revised Bethesda guidelines.^{25,109–112} Evaluation of Genomic Application in Practice and Prevention, a project sponsored by the Office of Public Health Genomics at the Center for

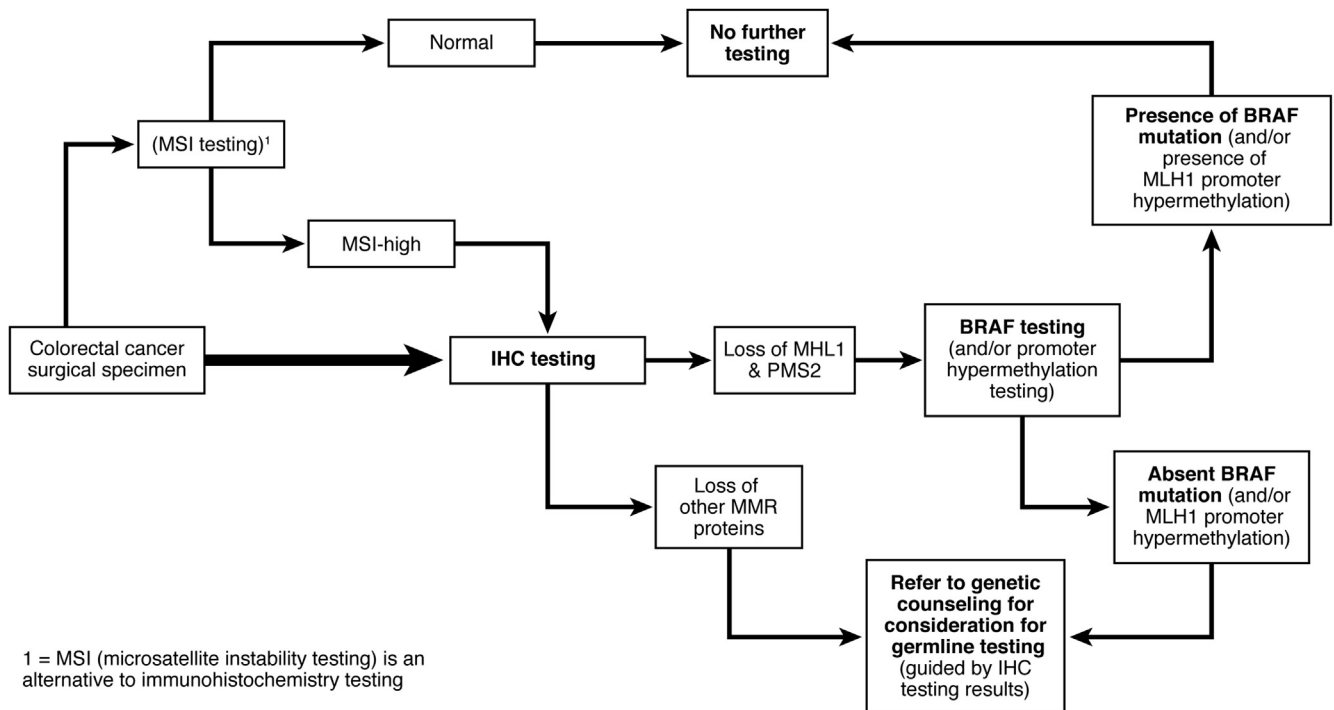


Figure 2. Universal screening by tumor testing.

Disease Control and Prevention, determined that sufficient evidence exists to offer genetic testing for LS to all individuals with newly diagnosed CRC.¹¹³ The rationale was to reduce morbidity and mortality of relatives of patients with LS. Evaluation of Genomic Application in Practice and Prevention concluded that there was insufficient evidence to recommend a specific genetic testing strategy.¹¹³ Universal testing for LS has also been endorsed by the Healthy People 2020 and the National Comprehensive Cancer Network (NCCN). Evaluation of a universal strategy by Ladabaum et al revealed that a systematic application of testing among patients with newly diagnosed CRC at ≤ 70 years of age could provide substantial clinical benefits at acceptable costs.¹¹⁴ Other studies have also reported the cost effectiveness of universal CRC testing.¹¹⁵ Ladabaum et al concluded that IHC testing of CRCs for MMR gene proteins followed by *BRAF* mutation testing of the tumors when MLH1 protein expression is absent, emerged as the most cost-effective approach. Patients with absence of *BRAF* mutation would then have germline testing for a mutation in the presumed altered MMR gene.

Additional reports suggest that universal tumor IHC testing among individuals with CRC had greater sensitivity for identification of LS compared with other strategies, including Bethesda guidelines, or a selective strategy (tumor testing of patients with CRC ≤ 70 years of age or older patients meeting Bethesda guidelines).^{112,116}

Although universal testing of CRC is recommended, development and implementation of such a screening system are complicated. These programs require cooperation and effective communication across multiple disciplines, ensuring that patients at risk for LS are identified, notified of

abnormal results, and referred for genetic counseling and genetic testing.¹¹⁷

Panel testing for germline mutations in >20 cancer-causing genes (which include the MMR and *EPCAM* genes) is now available commercially as a single test. Inevitably, advances in technology will decrease the cost of such analysis. In the future, germline testing, rather than tumor evaluation, might be the most cost-effective universal testing approach.

Genetic Testing

Germline testing of individuals for a deleterious mutation in *MLH1*, *MSH2*, *MSH6*, *PMS2*, or *EPCAM* genes has several benefits. First, it can confirm the diagnosis of LS in a patient and/or family. Second, it can determine the status of at-risk family members in pedigrees where the pathogenic mutation has been found. Third, it can direct the management of affected and unaffected individuals.

Indications for Testing

Universal testing (tumor testing). As per the recommendations of the Evaluation of Genomic Application in Practice and Prevention group from the Centers for Disease Control and Prevention, discussed here, testing all patients with CRC for LS is recommended. If utilizing this strategy, most experts would recommend routine tumor-based testing on all CRCs with IHC followed by *BRAF* testing, if there is a lack of expression of MLH1 (Figure 2). Alternatively, the CRC can be initially tested for MSI. Universal tumor testing is likely to become the future national standard of care and is already conducted in some US hospitals.

Indications:	Genetic counseling:
<ul style="list-style-type: none"> • Amsterdam I/II Criteria • Revised Bethesda Guidelines • Uterine cancer < 50 yr. • Known Lynch Syndrome mutation in family • $\geq 5\%$ chance of mutation by prediction models 	<ul style="list-style-type: none"> • Family history evaluation • Education • Risk assessment • Management recommendations • Informed consent for genetic testing • Genetic testing and interpretation of results

Figure 3. Traditional testing strategy indications and genetic counseling.

But this standard requires development of sufficient local and community infrastructure to appropriately handle genetic results before implementation as discussed. Consequently, the Multi-Society Task Force endorses testing all patients with CRC 70 years of age or younger as described here when appropriate infrastructure for testing exists. If tumor testing is done for those aged 70 years or younger only, a thorough family history is essential for those CRC patients older than 70 years; IHC and/or MSI testing should be performed for any individual whose personal and family history fulfill the Amsterdam or Bethesda guidelines or who have a $\geq 5\%$ risk prediction based on the prediction models.

Guideline: Testing for MMR deficiency of newly diagnosed CRC should be performed. This can be done for all CRCs, or CRC diagnosed at age 70 years or younger, and in individuals older than 70 years who have a family history concerning for LS. Analysis can be done by IHC testing for the MLH1/MSH2/MSH6/PMS2 proteins and/or testing for MSI. Tumors that demonstrate loss of MLH1 should undergo BRAF testing or analysis of MLH1 promoter hypermethylation (Figure 2). To facilitate surgical planning, tumor testing on suspected CRC should be performed on preoperative biopsy specimens, if possible. This guideline is a strong recommendation, with evidence level III, and GRADE moderate-quality evidence.

Traditional testing (selective tumor and/or germline testing). Traditional indications for LS genetic testing (tumor and/or germline testing) have been developed through expert consensus by several institutions and national organizations, including the NCCN.^{118–122} Genetic testing for LS is indicated for affected individuals in families meeting Amsterdam I or II criteria (Table 5) or revised Bethesda guidelines (Table 6), those with EC diagnosed at younger than 50 years old, first-degree relatives of those with known MMR/*EPCAM* gene mutation, and some experts would recommend individuals with $>5\%$ chance of gene mutation by computer modeling.¹⁰⁶

When considering genetic testing, efforts should be made to first perform tumor testing for MSI and/or IHC in an affected relative from the family. If a tumor sample is not available, then germline testing of the *MMR* genes of an unaffected individual is reasonable (focusing on family members most likely to carry a mutation). Genetic testing should be offered to all at-risk relatives in families with known MMR/*EPCAM* gene mutations. In these cases, germline testing can be specific for the known gene mutation that causes LS in the pedigree.

Guideline: Individuals who have a personal history of a tumor showing evidence of MMR deficiency (without evidence of *MLH1* promoter methylation); uterine cancer diagnosed at younger than age 50 years; a known family MMR gene mutation; fulfill Amsterdam criteria or revised Bethesda guidelines; and/or have a personal risk of $\geq 5\%$ chance of LS based on prediction models should undergo genetic evaluation for LS (Figure 3–6). This guideline is a strong recommendation, with evidence level III, and GRADE moderate-quality evidence.

Process of Genetic Testing

Genetic counseling. Recommendations for rational use of genetic testing for cancer predisposition have been published by several groups.^{123–126} They advocate pre- and post-test genetic counseling by trained health care professionals due to the clinical, psychosocial, financial, and ethical issues raised during the testing process. Of concern, a nationwide study of individuals undergoing genetic testing for hereditary CRC revealed major practitioner lapses, including failure to obtain informed consent, misinterpretation of test results (giving false-negative results), and pursuing expensive nonindicated testing.¹⁴ The Commission on Cancer has established standards for genetics professionals, including experience and education in cancer genetics and appropriate certification.¹²⁷

Components of the counseling session should include the collection of personal and family medical history; education about the disorder; exploration of psychosocial dimensions; informed consent, including cost and risk of genetic discrimination; disclosure of test results; and follow-up, including the ability of the patient to recontact the counselor for future discoveries pertinent to the patient's management. Details of this process can be found in Trimbath and Giardiello¹²⁸ and in the American Society of Clinical Oncology Policy Statement on Genetic Testing for Cancer Susceptibility.¹²⁷

In the past, several barriers to patient acceptance of germline testing existed, including cost of genetic tests (exceeding \$4800 in some cases) and patient concern about

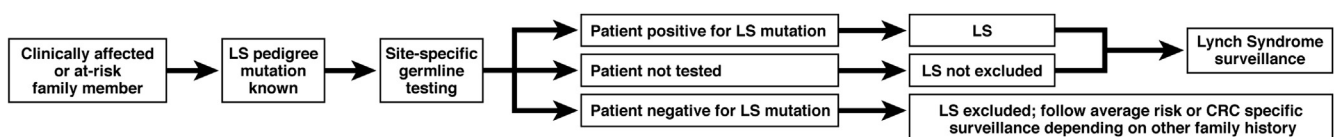


Figure 4. Traditional testing strategy when family mutation known.

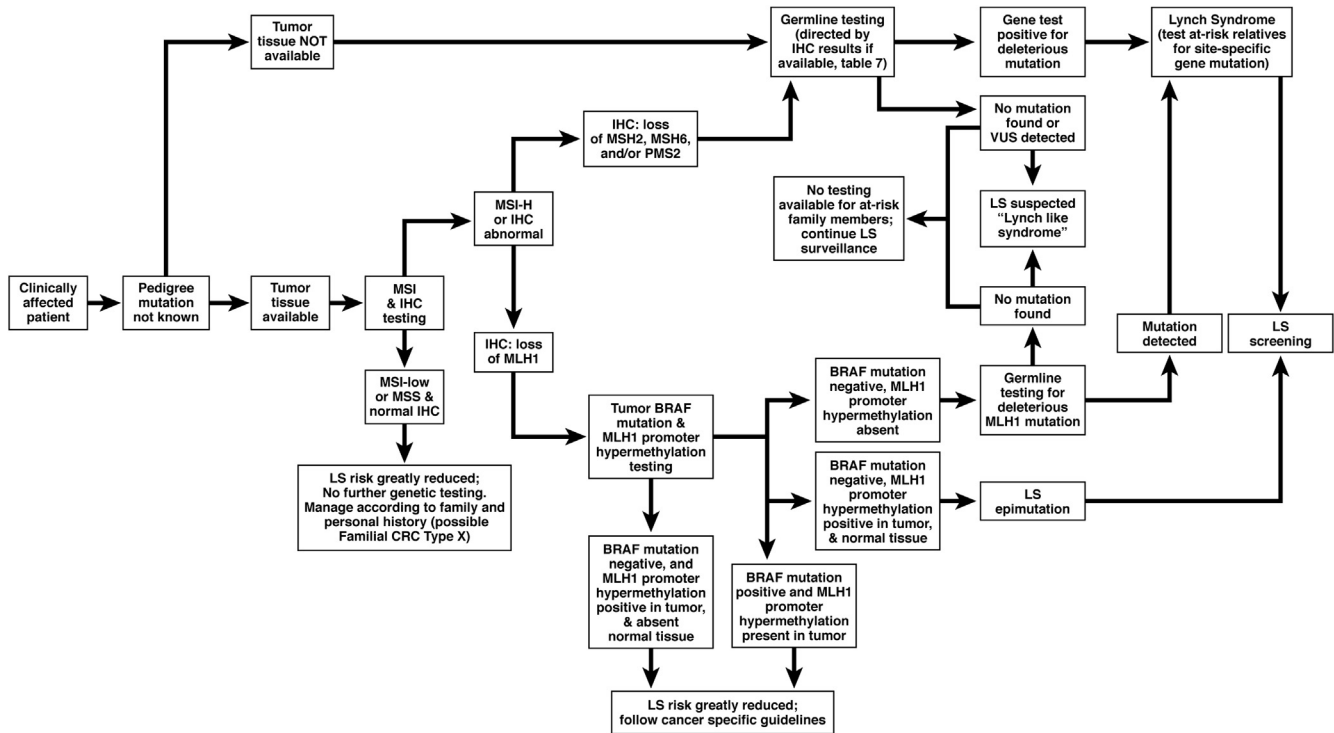


Figure 5. Traditional testing strategy when patient is clinically affected and the family mutation is unknown.

genetic discrimination. In recent years, improved insurance coverage and genetic laboratory preauthorization (checking insurance plan for out-of-pocket patient cost before testing) have eroded this barrier. Also, federal legislation, the Genetic Information Nondiscrimination Act of 2008, has eliminated a positive gene test as a health insurance pre-existing condition or factor for employment in most patients. However, currently, no legislation outlaws the use of this information in military personnel or in disability, long-term care, and life insurance procurement.

Universal testing strategy. Figure 2 outlines the pathway for universal testing.

Traditional testing strategy. Figure 3 reviews the indications for traditional genetic assessment and the components of genetic counseling. Figures 4–6 outline the pathways for traditional testing as described here.

Clinically affected members—family mutation known. When the gene mutation causing LS in the pedigree is known, clinically affected patients can have site-specific germline testing to confirm the diagnosis of LS in the patient. A negative test result for the pedigree mutation in a patient with CRC would indicate that the patient does not have LS, but coincidentally developed a sporadic CRC (phenocopy) (Figure 4).

Clinically affected member—family mutation not known. Most often patients are affected with CRC in families meeting Amsterdam criteria or Bethesda guidelines, or with other indications for genetic testing, but no LS gene mutation has been established in the pedigree. In this circumstance, if the patient’s CRC tissue is available (required by federal law to be kept for 7 years after procurement), MSI and/or IHC testing can be done on tumor

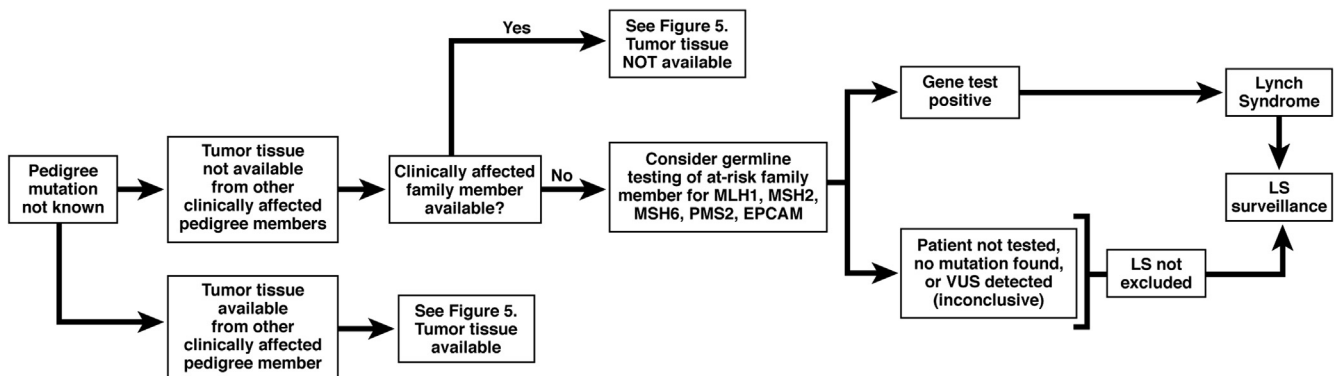


Figure 6. Traditional testing strategy of at-risk family member when family mutation is unknown.

tissue. If microsatellite testing is stable and IHC reveals the presence of all 4 MMR proteins, then LS is essentially excluded and no additional testing is suggested. The interpretation of these results is that the patient has sporadic (noninherited) CRC. But consideration for the diagnosis of FCRCTX should be given in a patient with a family history meeting Amsterdam I criteria (Figure 5).

Conversely, if MSI testing reveals high instability or IHC testing reveals absence of 1 or more MMR proteins, then, in most circumstances, germline testing of the MMR/*EPCAM* genes is warranted. Specific germline testing can be guided by IHC results (see Table 8). Additional tumor testing for *BRAF* mutation and/or hypermethylation of the *MLH1* promoter should precede genetic testing when concomitant loss of MLH1 and PMS2 proteins is noted (caused by somatic hypermethylation of the *MLH1* promoter). Germline testing can result in the following possibilities: a deleterious (pathogenic) mutation of an MMR/*EPCAM* gene that confirms the diagnosis of LS in the patient and family; no mutation found—an inconclusive finding unless a deleterious mutation is found in other family members; and a variant of unknown significance—an inconclusive finding unless future status of the alteration is determined by the testing laboratory (a variant of unknown significance is a variation in a genetic sequence whose association with disease risk is unknown). In the latter 2 circumstances, when IHC reveals loss of MSH2, MSH6, or PMS 2 protein alone, suspicion of LS should be maintained and the diagnosis of Lynch-like syndrome entertained. When no germline mutation is found in patients with MLH1 protein loss, *BRAF* and *MLH1* promoter testing for hypermethylation can help differentiate between patients with somatic and germline mutations. Epigenetic mutations causing LS are very rare but are characterized by *MLH1* promoter methylation in both the tumor and normal tissue.

When tumor tissue of the clinically affected patient is not available, germline testing can be done. If a deleterious mutation is found, then the diagnosis of LS can be confirmed in the patient. If not, then the patient and family members should be treated as per the patient's personal and family history.

Clinically unaffected (at-risk) member—family mutation known. Mutation-specific germline testing can be done in the at-risk member when the family mutation is known and render a dichotomous test result. If the gene mutation is found (positive), the individual has LS; if the gene mutation is not found (negative), the person does not have LS (Figure 4).

Clinically unaffected (at-risk) member—family mutation not known. In this circumstance, first seek a clinically affected family member to genetically test to attempt to identify the family deleterious gene mutation (Figure 6). An affected family member is the most informative individual to test to find the pedigree mutation. Initially, an evaluation of the tumor is preferred to germline genetic testing if tissue is available. Once the deleterious mutation has been determined, the at-risk person can be definitively tested. If no clinically affected family member is available, germline testing of the at-risk person can be done.

If a deleterious mutation is found in the unaffected member, then the diagnosis of LS is made. However, receiving results of “no mutation found” or “variant of unknown significance” are inconclusive results and no additional family genetic testing can be done.

Of note, new types of mutations or genetic alterations are continuously being reported, such as the effect of *EPCAM* deletions on *MSH2* expression, or the rare germline epimutations of *MLH1*. Also, commercial laboratories doing the germline testing might lack sensitive technology for determining genetic rearrangements (in which all of the genetic components are retained), or alterations in the promoters or introns of the DNA MMR genes. Consequently, families with suspicious clinical histories and concurrent evidence of MMR deficiency through tumor testing should be counseled to undergo periodic repeated assessments as new genetic data can emerge that ultimately elucidate the underlying cause of the cancer risk in their families. In addition, the use of genetic panels might uncover patients and families with forms of attenuated polyposis, such as MYH-associated polyposis, attenuated familial adenomatous polyposis, and polymerase proofreading polyposis; there is often blurring of the clinical presentations of these syndromes and LS.

Lynch Syndrome Management

Screening

Patients with LS are at increased risk for the development of colorectal and extracolonic cancers at early ages. Although there is insufficient evidence to assess the benefit of annual history, physical examination, and patient and family education, expert opinion would recommend this practice starting at 20–25 years old. The use of other screening tests is discussed here.

Colorectal cancer. CRC prevention in LS families is guided by the distinctive characteristics of these malignancies, including the younger age of presentation, right-sided colon predominance, and rapid polyp growth with shorter dwell time before malignant conversion. Evidence for the effectiveness of colorectal screening in decreasing CRC mortality has been documented in studies by Järvinen et al^{129–131} (Table 9). Persons at-risk for LS who took up colonoscopic surveillance had 65% ($P = .003$) fewer deaths from CRC compared with those who refused surveillance. Update of this Finnish study, which analyzed colonoscopic surveillance in LS mutation carriers, found no difference in CRC deaths between mutation carriers and mutation-negative relatives.¹³¹ Dove-Edwin et al reported the results of a prospective observational study of colonoscopy surveillance of members in HNPCC or LS families revealing a 72% decrease in mortality from CRC in those undergoing screening.¹³² In several studies,^{32,133–135} more frequent colonoscopy screening (≤ 2 years) was associated with earlier-stage CRC at diagnosis and less CRC than less frequent colonoscopy. At least every 2-year colonoscopic surveillance of LS patients is supported by the data presented here and the rapid adenoma–carcinoma sequence reported in these patients.

Table 8. Colorectal Cancer Testing Result and Additional Testing Strategies

MSI	Immunohistochemistry protein expression				Possible causes	Additional tests
	MLH1	MSH2	MSH6	PMS2		
MSS/MSI-L	+	+	+	+	Sporadic cancer	None
MSI-H	+	+	+	+	Germline mutation in MMR or EPCAM genes	Consider MLH1, MSH2, then MSH6, PMS2, EPCAM genetic testing
MSI-H	NA	NA	NA	NA	Sporadic or germline mutation in the MMR or EPCAM genes	Consider IHC to guide germline testing If IHC is not done germline testing of MLH1, MSH2, MSH6, PMS2, and EPCAM genes
MSI-H or NA	–	+	+	–	Sporadic cancer or germline mutation of MLH1	Consider BRAF/MLH1 promoter methylation testing MLH1 genetic testing if no BRAF mutation and absent hypermethylation or if testing not done
MSI-H or NA	–	+	+	+	Germline mutation MLH1	MLH1 genetic testing
MSI-H or NA	+	+	+	–	Germline mutation of PMS2, rarely MLH1	PMS2 genetic testing if negative MLH1 testing
MSI-H or NA	+	–	–	+	Germline mutation of MSH2 or EPCAM, rarely of MSH6	Consider MSH2 genetic testing, if negative EPCAM, if negative MSH6
MSI-H or NA	+	–	+	+	Germline mutation of MSH2	MSH2 genetic testing if negative EPCAM testing
MSI-H MSI-L or NA	+	+	–	+	Germline mutation of MSH6, less likely MSH2	MSH6 genetic testing if negative MSH2 testing

NOTE. Adapted from the National Comprehensive Cancer Network Clinical Practice Guidelines in Oncology: Colorectal Cancer Screening. Lynch syndrome. Version 2.2012. Available at: http://www.nccn.org/professionals/physiangls/PDF/colorectal_screening.pdf.¹²²
MSI-L, microsatellite low; MSI, microsatellite high; MMR, mismatch repair genes (ie, MLH1, MSH2, MSH6, PMS2); NA, not available; +, protein present in tissue; –, protein not present in tissue.

Table 9. Studies of Colorectal Screening in Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

First author, year	Reference	Subjects	Design	Findings
Järvinen, 1995	129	252 at-risk persons from 20 of 22 families with MMR mutations	Observational: all invited for colonoscopy screening; 133 had every 3 y colonoscopy, 118 declined colonoscopy	62% less CRC in screened ($P = .03$) Tumor stage more favorable in screened No deaths in screened vs 5 deaths in nonscreened
Järvinen, 2000	130	252 at-risk persons from 20 of 22 families with MMR mutations	Observational: follow-up of reference 129	62% reduction in CRC in screened ($P = .02$) No deaths from CRC in screened vs 9 deaths in nonscreened
de Vos tot Nederveen Cappel, 2002	32	857 members of 114 HNPCC or MMR-positive families	Observational: Tumor stage with more frequent (≤ 2 y) vs less frequent colonoscopy; 10-y risk of CRC with partial vs subtotal colectomy	Earlier stage CRC with more frequent colonoscopy 15.7% risk of CRC with partial vs 3.4% with subtotal colectomy at 10 y
Dove-Edwin, 2005	132	554 at-risk members of 290 families with HNPCC or MMR mutations	Prospective observational: evaluation of efficacy of colonoscopy	Estimated 72% decrease in CRC death in screened individuals
Järvinen, 2009	131	242 MMR mutation-positive and 367 mutation-negative subjects	Observational: Cancer incidence/survival at 11.5 y follow-up of colonoscopy surveillance	No increase in cancer mortality in mutation positive vs negative persons
Stuckless, 2012	135	322 MSH2 mutation carriers	Observational: Cancer incidence and survival in 152 screened vs 170 not screened by colonoscopy	Median age to CRC later in screened vs nonscreened Survival statistically improved in screened vs nonscreened

Guideline: Screening for CRC by colonoscopy is recommended in persons at risk (first-degree relatives of those affected) or affected with LS every 1 to 2 years, beginning between ages 20–25 years or 2–5 years before the youngest age of diagnosis of CRC in the family if diagnosed before age 25 years. In surveillance of MMR germline mutation-positive patients, consideration should be given to annual colonoscopy. The age of onset and frequency of colonoscopy in this guideline is in agreement with most organizations and authorities.^{122,131,136–138} This guideline is a strong recommendation, with evidence level III, and GRADE moderate-quality evidence (Table 10).

In carriers of deleterious *MSH6* and *PMS2* mutations, the risk of CRC is lower and age at diagnosis later^{22,25} than in patients with *MLH1* and *MSH2* mutations. In these affected individuals, consideration could be given to starting screening at age 30 years in *MSH6* and 35 years in *PMS2* carriers, unless an early-onset cancer exists in a given family.

Endometrial cancer. EC is the second most common cancer occurring in LS. Estimates of the cumulative lifetime risk of EC in LS patients range from 21% to 60%, with variability depending on specific gene mutation; reports of age at diagnosis of this malignancy are clearly a decade or more younger than sporadic EC, but range from 48 to 62 years old.

Due to the worrisome cumulative risk of EC, several annual screening modalities have been proposed, including pelvic examinations, transvaginal ultrasound, endometrial sampling, and CA-125 testing. Few studies of these interventions have been conducted. At present, the literature

reports reveal no evidence of survival benefit from endometrial surveillance (Table 11). Decrease in death from EC can be difficult to prove because 75% of LS patients with EC present with stage I disease and have an 88% 5-year survival rate. Investigation of transvaginal ultrasound reveals poor sensitivity and specificity for the diagnosis of EC in this population.^{139–141} However, endometrial sampling appears useful in identifying some asymptomatic patients with EC and those with premalignant endometrial lesions^{142–144} (Table 11).

Guideline: Screening for EC should be offered to women at risk for or affected with LS by pelvic examination and endometrial sampling annually starting at age 30–35 years (Table 10). The strength of evidence for this guideline is expert consensus—level V, GRADE low-quality evidence, and is in concert with other expert opinion.^{122,137,138}

Ovarian cancer. Estimates of the cumulative lifetime risk of ovarian cancer in LS patients ranges from 0.3% to 20%. Currently, no studies on the effectiveness of ovarian screening are available for women in LS families. In patients with hereditary breast cancer from mutation of *BRCA1* or *BRCA2* at increased risk for ovarian cancer, 1 investigator found transvaginal ultrasound and CA-125 screening not useful.¹⁴⁵

Guideline: Screening for ovarian cancer should be offered to women at risk for or affected with LS by transvaginal ultrasound annually starting at age 30–35 years (Table 10). The strength of evidence for this guideline is expert consensus—level V and GRADE low-quality evidence. In the absence of data on this issue, several consensus panels have suggested that transvaginal

Table 10. Guidelines for Screening At-Risk or Affected Persons With Lynch Syndrome

Intervention	Recommendation	Strength of recommendation
Colonoscopy	Every 1–2 y beginning at age 20–25 y or 2–5 y younger than youngest age at diagnosis of CRC in family if diagnosis before age 25 y Considerations: Start at age 30 y in <i>MSH6</i> and 35 in <i>PMS2</i> families Annual colonoscopy in MMR mutation carriers	Strong recommendation: Level of evidence (III): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer GRADE rating: moderate
Pelvic examination with endometrial sampling	Annually beginning at age 30–35 y	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
Transvaginal ultrasound	Annually beginning at age 30–35 y	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
EGD with biopsy of the gastric antrum	Beginning at age 30–35 y and subsequent surveillance every 2–3 y can be considered based on patient risk factors	Offer to patient: Level of evidence (V): expert consensus GRADE rating: low
Urinalysis	Annually beginning at age 30–35 y	Consideration: Level of evidence (V): expert consensus GRADE rating: low

EGD, esophagogastroduodenoscopy; GRADE, Grades of Recommendation, Assessment, Development, and Evaluation.

Table 11. Studies of Endometrial and Ovarian Cancer Screening and Prophylactic Surgery in Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

First author, year	Reference	Subjects	Design	Findings
Dove-Edwin, 2002	139	292 women from HNPCC or HNPCC-like families	Observational: all offered transvaginal ultrasound	2 cases of EC presented with symptoms, neither detected by ultrasound
Rijcken, 2003	140	41 women with MMR mutations or fulfilled Amsterdam I criteria followed for median of 5 y	Observational: all offered annual pelvic examination, transvaginal ultrasound, CA-125	17 of 179 ultrasounds gave reason for endometrial sampling with 3 premalignant lesions noted; 1 interval EC presented symptomatically
Renkonen-Sinisalo, 2007	141	175 women with MMR mutations	Observational: all offered transvaginal ultrasound and endometrial biopsy	14 cases of EC; 11 diagnosed by surveillance Biopsy diagnosed 8 of 11 ECs and 14 cases of premalignant hyperplasia Ultrasound indicated 4 EC cases but missed 6 others 4 cases of ovarian cancer, none found by ultrasound
Lécuru, 2008	142	62 women (13 with MMR mutation, 49 met Amsterdam II criteria)	Observational: annual hysteroscopy and endometrial biopsy	3 malignancies in 3 patient with abnormal bleeding; 3 cases of hyperplasia in asymptomatic patients; hysteroscopy 100% sensitive for cancer or hyperplasia
Gerritzen, 2009	143	100 women from families with MMR mutation	Observational: annual transvaginal ultrasound, CA-125, endometrial sampling	3 atypical hyperplasias and 1 endometrial cancer diagnosed 1 stage III ovarian cancer developed despite ultrasound
Stuckless, 2013	144	174 women with MSH2 gene mutation	Case-control: Cases: 54 patients with at least 1 screening examination (transvaginal, endometrial biopsy or CA-125 test) Controls: matched women without screening	Stage I/II cancer diagnosed in 92% of screened patients compared with 71% in control group ($P = .17$) 2 of 3 deaths in the screened group from ovarian cancer
Schmeler, 2006	146	315 women with MMR mutation with and without gynecologic surgery	Retrospective: risk of uterine and ovarian cancer in patients with and without prophylactic/clinically indicated gynecologic surgery	No uterine or ovarian cancer in surgery group vs 33% and 5% cancer, respectively, in nonsurgery group

ultrasound for ovarian cancer is a screening consideration in LS.^{122,137,138}

Prophylactic hysterectomy and oophorectomy. As discussed here, patients with LS have substantial risk for uterine and ovarian cancer. One US study showed benefit for prophylactic gynecologic surgery to reduce or eliminate gynecologic cancer¹⁴⁶ (Table 11). Retrospective analysis of 315 women with MMR mutations who did and did not have gynecologic surgery revealed no cancers in the surgical group compared with a 33% and 5.5% rate of uterine and ovarian cancer, respectively, in the nonsurgical group.¹⁴⁶ Cost-effectiveness analysis modeling of gynecologic screening vs prophylactic gynecologic surgery (hysterectomy

and bilateral salpingo-oophorectomy) in a theoretical population of 30-year-old women with LS revealed that prophylactic surgery had lower cost and higher quality-adjusted life-years.¹⁴⁷ An additional modeling study evaluated multiple screening and surgical strategies. This investigation concluded that annual screening starting at age 30 years followed by prophylactic surgery at age 40 years was the most effective gynecologic cancer prevention strategy, but incremental benefit over prophylactic surgery at age 40 years alone was attained at substantial cost.¹⁴⁸

Guideline: Hysterectomy and bilateral salpingo-oophorectomy should be recommended to women with LS who have finished childbearing or at age 40

years (Table 12). Patient considerations in this decision could include differences in uterine cancer risk, depending on MMR gene mutation; morbidity of surgery; and the risk of menopausal symptoms, osteoporosis, and cardiac disease if hormone replacement therapy is not given. The strength of evidence for this guideline is observational study—level IV and GRADE moderate-quality evidence. This recommendation is in agreement with the Mallorca Group.¹³⁸ The NCCN recommends considering prophylactic surgery after child bearing is completed.¹²²

Gastric cancer. Some studies have estimated the lifetime risk of gastric cancer in LS as high as 13%, but currently this appears to be much lower in North America and Western Europe. A carefully conducted time trend study of gastric cancer found an 8.0% and 5.3% lifetime risk of this malignancy in males and females with MMR gene mutation, respectively, and lack of familial clustering.⁴⁷ The majority of gastric cancers in LS patients appear to be histologically classified as intestinal type^{45,47} and, consequently, potentially amenable to endoscopic surveillance.

Data on screening for gastric cancer are lacking. However, Renkonen-Sinisalo et al¹⁴⁹ reported that precursor lesions for gastrointestinal cancer, including *Helicobacter pylori* infection, and intestinal metaplasia were seen in 26% and 14%, respectively, of patients with MMR mutations (Table 13).

Guideline: Screening for gastric cancer should be considered in persons at risk for or affected with LS by esophagogastroduodenoscopy (EGD) with gastric biopsy of the antrum at age 30–35 years with treatment of *H pylori* infection when found. Subsequent, surveillance every 2–3 years can be considered based on individual patient risk factors (Table 10). The strength of evidence for this guideline is expert consensus—level V and GRADE low-quality evidence.

This guideline is in concert with that of the NCCN.¹²² The Mallorca group recommends initial screening EGD with biopsy without a recommendation for ongoing surveillance.¹³⁸

Small intestinal cancer. The lifetime risk for this cancer ranges from 0.4% to 12.0%.^{17,28,39,40,44,48} Two large

studies of extracolonic cancer in patients with MMR mutations came to opposite conclusions, with lifetime risks of 0.6% and 12%, respectively.^{17,48} Another investigation revealed that the majority of small bowel cancers in an LS cohort were located in the duodenum or ileum¹⁵⁰ and within the reach of EGD and colonoscopy with dedicated ileal intubation. There appears to be no evidence of familial clustering of this extracolonic malignancy.⁴⁶

Studies of small bowel screening in LS patients are lacking. However, one screening investigation of 35 gene mutation carriers found that 2 had jejunal adenomas and 1 had a jejunal cancer¹⁵¹ (Table 13). Six additional patients had capsule endoscopy images of uncertain clinic relevance, prompting additional invasive investigation in 5 patients. A recent publication suggested that routine surveillance of the small bowel in LS was not cost efficient.⁴⁶ However this calculation could change with additional literature evidence.

Guideline: Routine screening of the small intestine is not recommended. This guideline is in concert with the Mallorca group,¹³⁸ which does not recommend routine screening of the small intestine, but suggests attention to investigation of the distal duodenum and ileum during endoscopic studies. The NCCN suggests capsule endoscopy screening can be considered¹²² at 2–3 year intervals beginning at age 30–35 years.

Urinary cancer. Estimates of the lifetime risk of urinary tract cancer in LS ranges from 0.2% to 25% in men with MSH2 mutations. This includes elevated risk for transitional cell carcinoma of the ureter, renal pelvis, and bladder.^{17,28,39,40,44,48,49,152,153} Currently, a dearth of literature on screening for urinary cancer in LS patients exists. One retrospective study evaluating screening for urinary cancer by urine cytology in individuals in HNPCC or LS families found poor sensitivity (29%) in diagnosing cancer in asymptomatic patients and production of many false-positive results requiring invasive investigation¹⁵² (Table 13). Screening studies have not been effective with urine cytology and urinalysis for microscopic hematuria for urinary cancer in the general population and in groups at higher risk for bladder cancer from environmental

Table 12. Guidelines for Management of Affected Persons with Lynch Syndrome

Intervention	Recommendation	Strength of recommendation
Colectomy with ileorectal anastomosis	Patients with colon cancer or colorectal neoplasia not removable by endoscopy Consideration for less extensive surgery in patients older than age 60–65 y	Strong recommendation: Level of evidence (III): well-designed and conducted cohort or case-controlled studies from more than 1 group with cancer GRADE rating: moderate
Hysterectomy and bilateral salpingo-oophorectomy	After childbearing or age 40 y	Recommendation: Level of evidence (IV): observation study GRADE rating: moderate
Daily aspirin	Treatment of an individual patient with aspirin is a consideration after discussion of patient-specific risks, benefits, and uncertainties of treatment is conducted	Consideration: Level of evidence (I): randomized controlled study GRADE rating: moderate

Table 13. Studies of Screening for Extracolorectal/Gynecological Cancers in Hereditary Nonpolyposis Colorectal Cancer/Lynch Syndrome

First author, year	References	Subjects	Design	Findings
Renkonen-Sinisalo, 2002 (gastric)	149	73 patients with MMR mutation; 32 MMR mutation–negative family members	Observational: upper endoscopy with gastric biopsies	In MMR gene–positive patients: <i>H pylori</i> in 26%, atrophy 14%, intestinal metaplasia 14% No statistical difference between gene-positive and gene-negative groups
Saurin, 2010 (small bowel)	151	35 patients with MMR mutations	Observational: capsule endoscopy and CT enteroclysis screening of small bowel	Small bowel neoplasms 8.6% (1 patient with jejunal carcinoma and 2 with jejunal adenoma) Capsule endoscopy found all lesions; CT enteroscopy found cancer but missed adenomas
Myrhøj, 2008 (urinary)	152	977 at-risk persons in families suspected to have HNPCC/LS	Observational: retrospective review of screening urine cytology and diagnosis of urinary cancer	0.1% of urine cytology examinations lead to diagnosis of urothelial tumor 10 times more urine cytology examinations lead to false-positive diagnosis Sensitivity of urine cytology was 29%

factors.^{154,155} The benefit of ultrasound screening is unknown. In summary, limited data exist to advocate urinary screening. Expert consensus concludes that urinalysis is inexpensive, noninvasive, usually part of a routine physical examination, easily done, and should be considered in LS patients. Future studies could change this consideration.

Guideline: Screening for cancer of the urinary tract should be considered for persons at risk for or affected with LS, with urinalysis annually starting at age 30–35 years (Table 10). The strength of evidence for this guideline is expert consensus—level V and GRADE low-quality evidence. The guideline is in concert with the NCCN.¹²² The Mallorca group¹³⁸ does not recommend routine screening for urinary cancers.

Pancreatic cancer. Risk of pancreatic cancer in LS patients was noted to be elevated in 2 cohort studies. In 1 study, the standardized incident ratio for pancreatic cancer was 10.7 (95% confidence interval: 2.7–47.7), with a 10-year cumulative risk of 0.95%,⁵¹ and the other reported a 8.6-fold increase (95% confidence interval: 4.7–15.7), with cumulative risk of 3.7% by age 70 years.⁵⁰ In 1 investigation, the risk of pancreatic cancer was not elevated in a cohort in which the pancreatic cancers were validated by dedicated histologic review.⁵²

Guideline: Routine screening of the pancreas is not recommended. The benefit of screening for pancreatic cancer with this magnitude of risk is not established. This recommendation is in concert with other societies.^{122,138}

However, an international pancreas consensus panel recommends that MMR gene mutation carriers with 1 affected first degree relative with pancreatic cancer should be considered for screening.¹⁵⁶

Other cancers. There are conflicting data about the risk of several extracolonic cancers in patients with LS patients. With regard to prostate cancer, several studies have revealed no significantly increased risk of this malignancy.^{42,51} Other investigations draw opposite conclusions, with relative risk ranging from 2.5- to 10-fold and lifetime risk ranging from 9% to 30% by age 70 years.^{48,53,59,157} In breast cancer, inconsistent data exist. One large study revealed no increased risk in LS patients.⁴⁶ In contrast, a British study of 121 MMR mutation families found an increased risk of breast cancer for positive and obligate *MLH1* mutation carriers with a cumulative risk of 18.2% to age 70 years (95% CI: 11.9–24.5), but not for *MSH2* carriers.⁴⁴ A German and Dutch study found a mild increase in cumulative risk of breast cancer of 14% by age 70 years.⁴⁸ In a recent prospective study of patients with MMR mutations an increased cumulative risk of breast cancer of 4.5% during 10 years of observation was noted (standardized incident ratio = 3.95; 95% CI: 1.59–8.13).⁵¹

Guideline: Routine screening of the prostate and breast cancer is not recommended beyond what is advised for the general population. This recommendation is in concert with other societies.^{122,138}

Treatment

Colectomy. The treatment for patients with colon cancer or premalignant polyps that cannot be removed by colonoscopy is colectomy. The risk of metachronous CRC after partial colectomy is summarized in [Table 14](#). With partial colectomy, a high 10-year cumulative risk of CRC (16%–19%) is reported in several studies, even in those patients undergoing vigilant colonoscopic surveillance^{32–34} and is ingravescens with longer observation. This risk is substantially reduced if a subtotal (anastomosis of the small bowel to sigmoid) or total (ileorectal anastomosis) colectomy is performed (0–3.4%).^{32–34} In a Dutch study, no difference in global quality of life was noted between 51 LS patients who underwent partial colectomy, and 53 who underwent subtotal colectomy, although functional outcomes (eg, stool frequency, stool-related aspects, and social impact) were worse after subtotal colectomy than after partial colectomy.¹⁵⁸ Comparison of life expectancy gained performing total colectomy vs hemicolectomy in LS patients at ages 27, 47, and 67 years by Markov modeling was 2.3, 1, and 0.3 years, respectively.¹⁵⁹ These investigators concluded that total colectomy is the preferred treatment in LS, but hemicolectomy might be an option in older patients.

Although most LS CRCs are right sided, up to 20% can occur in the rectum. When this happens surgical decision making needs to include the use of neoadjuvant chemotherapy and consideration of total proctocolectomy and

ileal pouch-anal anastomosis. This surgical option is commonly performed in familial adenomatous polyposis patients with severe rectal polyposis or cancer. However, familial adenomatous polyposis patients are usually younger than those with LS, in whom this operation would pose a significant challenge to surgical recovery and post-operative quality of life. However, Kalady et al found a risk of metachronous advanced neoplasia (cancer and severe dysplasia) of 51% in HNPCC patients who had an anterior resection for rectal cancer.¹⁶⁰ Win et al found the overall risk of cancer to be 24.5% and a cumulative risk to 30 years of 69%.³³ Therefore, total proctocolectomy with ileal pouch-anal anastomosis is an important option to discuss with patients with rectal cancer and LS.

Guideline: Colectomy with ileorectal anastomosis is the primary treatment of patients affected with LS with colon cancer or colon neoplasia not removable by endoscopy (Table 12). Consideration for less extensive surgery should be given in patients older than 60–65 years of age and those with underlying sphincter dysfunction. This guideline is a strong recommendation with level III evidence and GRADE moderate-quality evidence. The NCCN¹²² and Mallorca group¹³⁸ both recommend colectomy with ileorectal anastomosis with no deference to patient age.

Chemoprevention. Resistant starch and aspirin have been assessed as chemopreventive agents in patients with LS ([Table 15](#)). The Colorectal/Adenoma/Carcinoma

Table 14. Risk of Metachronous Colorectal Cancer in Lynch Syndrome Patients With Colectomy

First author, year	Reference	Subjects	Design	Findings
de Vos tot Nederveen Cappel, 2002	31	110 patients with MMR gene mutation or meet HNPCC criteria with CRC and partial colectomy; 29 MMR gene mutation patients with colorectal cancer and total colectomy	Observational: risk of colorectal cancer in patients with partial vs subtotal colectomy	10-y cumulative risk of colorectal cancer 15.7% with partial colectomy and 3.4% after subtotal colectomy
Win, 2013	33	79 patients with MMR gene mutation and proctectomy for rectal cancer undergoing post surgical surveillance by colonoscopy on average every 1.6 y	Observational: retrospective cohort study of risk of metachronous colon cancer after surgery	Cumulative risk of colon cancer was 19%, 47%, 69% at 10, 20, and 30 y, respectively
Parry, 2001	32	332 MMR gene mutation carriers with CRC and partial colectomy; 50 patients with CRC and extensive colectomy	Observational: retrospective cohort study of risk of colorectal cancer in patients with partial vs subtotal colectomy	Cumulative risk of colon cancer was 16%, 41%, 62% at 10, 20, and 30 y respectively None of patients with extensive surgery diagnosed with CRC
Kalady, 2012	160	55 HNPCC patients with proctectomy for rectal cancer undergoing postsurgical surveillance by colonoscopy	Observational: retrospective cohort study of risk of advanced neoplasia (cancer and severe dysplasia) in patients with proctectomy	55% advanced neoplasia (15.2% developed colon cancer at median of 6 y)

Prevention Programme 2 (CAPP2) was a randomized placebo-controlled trial with a 2×2 design investigating the effect of resistant starch (Novelose) 30 g/d and aspirin 600 mg/d taken up to 4 years on development of colorectal adenoma and cancer.¹⁶¹ This study randomized 727 participants to starch or placebo and 693 between aspirin and placebo. The use of resistant starch, aspirin, or both had no effect on the incidence of colorectal neoplasia in LS carriers during a mean period of follow-up of 29 months. CAPP2 follow-up analysis of the long-term effect (median follow-up of 52.7 months) of resistant starch again revealed no effect on CRC development.¹⁶²

The CAPP2 investigators also evaluated the long-term effect of 600 mg of aspirin on CRC development.¹⁶³ At a mean follow-up of 55.7 months, intention-to-treat analysis of time to first CRC showed a hazard ratio of 0.63 (95% CI: 0.35–1.13; $P = .12$). For participants completing 2 years of intervention (258 on aspirin and 250 on placebo) per-protocol analysis yielded a hazard ratio of 0.41 (95% CI: 0.19–0.86; $P = .02$). An intention-to-treat analysis of all LS cancers (ie, colorectal, endometrial, ovarian, pancreatic, small bowel, gallbladder, ureter, stomach, kidney, and brain) revealed a protective effect of aspirin vs placebo (hazard ratio = 0.65; 95% CI: 0.42–1.00; $P = .05$). During the intervention, adverse events did not differ between aspirin and placebo groups.

The chemoprotective effect of aspirin on colorectal and extracolonic cancer noted in the CAPP2 study of LS patients is supported by a recent meta-analysis of randomized trials of daily aspirin use vs no aspirin (primarily in patients with

cardiovascular disease) with a mean duration of treatment of 4 years or longer.¹⁶⁴ This study found decreased risk of death from colorectal and extracolonic cancer after 10 to 20 years of follow-up. Of note, the benefit was unrelated to aspirin doses >75 mg/d.

The CAPP2 trial has several limitations. First, ascertainment of the end point, CRC, was not standardized, and more intensive colonoscopic evaluation could have occurred in the aspirin group than in the nonaspirin group because of more frequent adverse effects after intervention. Second, the extracolonic cancers did not undergo molecular evaluation to assess whether they were related to the germline MMR mutation. Also, the dose of daily aspirin utilized in the CAPP2 trial is significantly higher than that noted to be effective (75 mg/d) in CRC chemoprevention in sporadic CRC.

The CAPP3 is underway to establish the optimum dose and duration of aspirin treatment. Although data exist to suggest that aspirin can decrease the risk of colorectal and extracolonic cancer in LS, currently the evidence is not sufficiently robust or mature to make a recommendation for its standard use.¹⁶⁴

Guideline: Growing but not conclusive evidence exists that use of aspirin is beneficial in preventing cancer in LS patients. Treatment of an individual patient with aspirin is a consideration after discussion of patient-specific risks, benefits, and uncertainties of treatment is conducted (Table 12). The strength of evidence for this guideline is evidence obtained from at least 1 randomized controlled trial—level I and GRADE moderate-quality

Table 15. Chemopreventive Trials in Lynch Syndrome

First author, year	Reference	Subjects	Design	Findings
Burn, 2008 (CAPP2 study)	161	1071 LS patients from 43 centers	Randomized, placebo-controlled, 2×2 design 727 randomized to resistant starch (30 g/d) or placebo; 693 randomized to aspirin (600 mg/d) or no aspirin	No effect on incidence of colorectal adenoma/cancer by starch or aspirin or both at mean follow-up of 29 months
Mathers, 2012 (CAPP2 study)	162	918 LS patients from 43 centers	Long-term follow-up report on randomized, placebo-controlled, 2×2 design 463 randomized to resistant-starch; 455 randomized to placebo	No effect on incidence of CRC by starch at median follow-up of 52.7 months
Burn, 2011 (CAPP2 study)	163	861 LS patients from 43 centers	Long-term follow-up report on randomized, placebo-controlled, 2×2 design 427 randomized to aspirin (600 mg/d); 434 randomized to placebo	600 mg aspirin/d for mean of 25 months reduced cancer incidence after 55.7 months Time to first CRC hazard ratio (HR) by per protocol analysis, 0.41 (95% CI: 0.19–0.86; $P = .02$); intention-to treat analysis of all LS cancers, HR = 0.65; 95% CI: 0.42–1.00; $P = .05$)

evidence. This approach is endorsed by the Mallorca group¹³⁸ and the NCCN.¹²²

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Reprint requests

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Conflicts of interest

These authors disclose the following: C. Richard Boland and Randall W. Burt are consultants for Myriad Genetic. Jason A. Dominitz received resources in support of this work from the VA Puget Sound Health Care System, Seattle, Washington. The views expressed in this article are those of the authors and do not necessarily represent the views of the Department of Veterans Affairs. David A. Johnson is a clinical investigator for EXACT Sciences, a consultant for Epigenomics, and on the advisory board for Given Imaging. Tonya Kaltenbach is a research grant recipient and consultant for Olympus American Inc. David A. Lieberman is on the advisory board for Given Imaging and Exact Sciences. Douglas J. Robertson is on the advisory board of Given Imaging. Sapna Syngal is an unpaid advisor/collaborator with Myriad genetics and a consultant for Archimedes, Inc. Douglas K. Rex is a consultant for Olympus America, Braintree Laboratories, Ferring Pharmaceuticals, Epigenomics, EXACT Sciences, Given Imaging, received research support from Olympus America; and is on the speaker's bureau for Olympus America and Boston Scientific. The remaining authors disclose no conflicts.

This guideline was reviewed and approved by governing boards of the American College of Gastroenterology, the American Gastroenterological Association, the American Society for Gastrointestinal Endoscopy, and the American Society of Colon and Rectal Surgeons.