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

Francis M. Giardiello, MD,[1] John I. Allen,[2] Jennifer E. Axilbund,[1] C. Richard Boland,[3] Carol A. Burke,[4] Randall W. Burt,[5] James M. Church,[4] Jason A. Dominitz,[6,7] David A. Johnson,[8] Tonya Kaltenbach,[9] Theodore R. Levin,[10] David A. Lieberman,[11] Douglas J. Robertson,[12,13] Sapna Syngal,[14-16] and Douglas K. Rex,[17]

[1]Johns Hopkins University School of Medicine, Baltimore, Maryland, USA; [2]Yale University School of Medicine, New Haven, Connecticut, USA; [3]Baylor University Medical Center, Dallas, Texas, USA; [4]Cleveland Clinic, Cleveland, Ohio, USA; [5]University of Utah, Salt Lake City, Utah, USA; [6]VA Puget Sound Health Care System, Seattle, Washington, USA; [7]University of Washington, Seattle, Washington, USA; [8]Eastern Virginia Medical School, Norfolk, Virginia, USA; [9]Stanford University, Palo Alto, California, USA; [10]Kaiser Permanente Medical Center, Walnut Creek, California, USA; [11]Oregon Health and Science University, Portland, Oregon, USA; [12]White River Junction VA Medical Center, White River Junction, Vermont, USA; [13]Geisel School of Medicine at Dartmouth, White River Junction, Vermont, USA; [14]Brigham and Women's Hospital, Boston, Massachusetts, USA; [15]Dana Farber Cancer Institute, Boston, Massachusetts, USA; [16]Harvard Medical School, Boston, Massachusetts, USA; [17]Indiana University School of Medicine, Indianapolis, Indiana, USA.

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Abstract

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.

Introduction

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.

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 (e.g., 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 promotor mutations (68).

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	
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

LYNCH SYNDROME CHARACTERISTICS

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)

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.

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.
[a]LS-associated tumors include tumor of the colorectum, endometrium, stomach, ovary, pancreas, ureter, renal pelvis, biliary tract, brain, small bowel, sebaceous glands, and kerotoacanthomas.

GENETIC ALTERATIONS

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)

IDENTIFICATION OF LYNCH SYNDROME

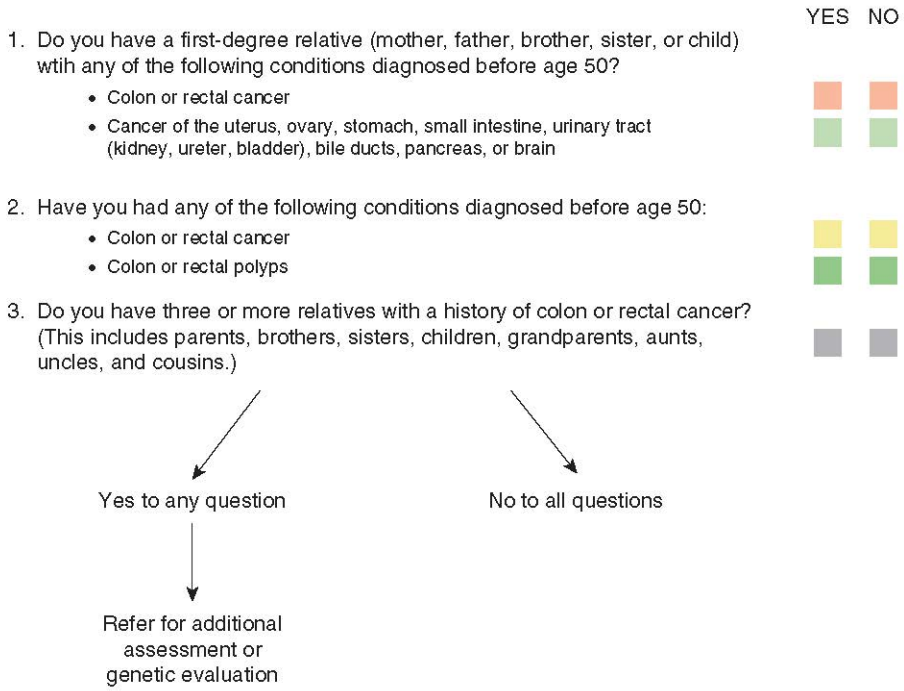

Figure 1. Colorectal cancer risk assessment tool. Adapted with permission from Kastrinos *et al.* (101).

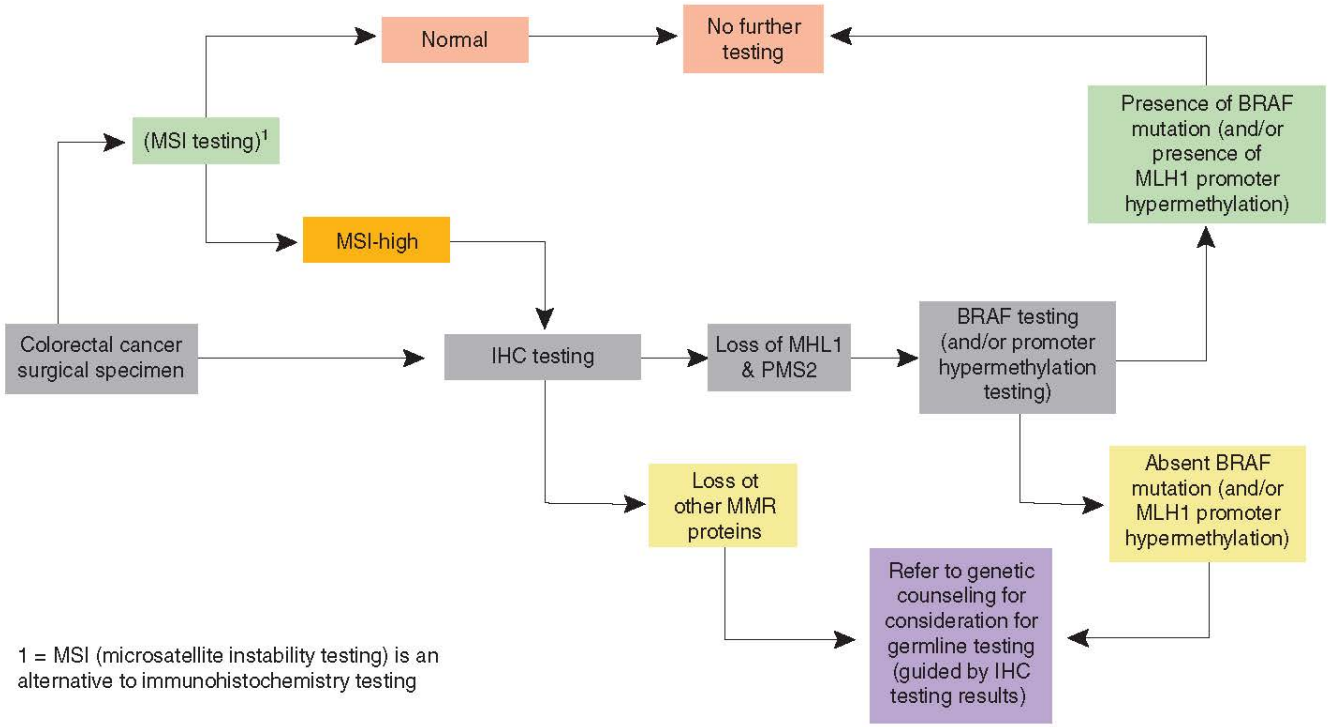

Figure 2. Universal screening by tumor testing.

GENETIC TESTING

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 immunohistochemistry (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 pre-operative biopsy specimens, if possible. This guideline is a strong recommendation, with evidence level III, and GRADE moderate-quality evidence.

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 ≥ 5 % chance of LS based on prediction models should undergo genetic evaluation for LS (**Figures 3 – 6**). This guideline is a strong recommendation, with evidence level III, and GRADE moderate-quality evidence.

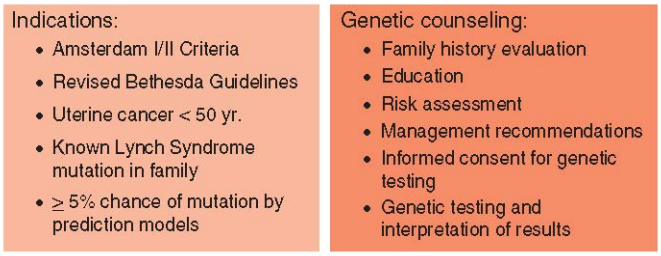

Figure 3. Traditional testing strategy indications and genetic counseling.

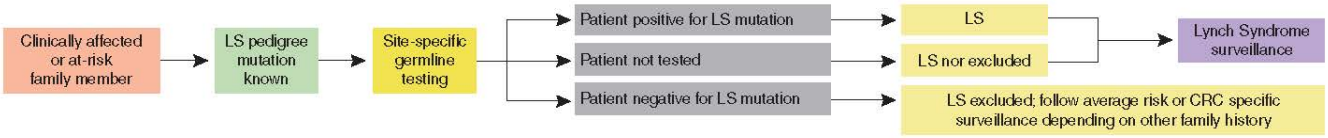

Figure 4. Traditional testing strategy when family mutation known.

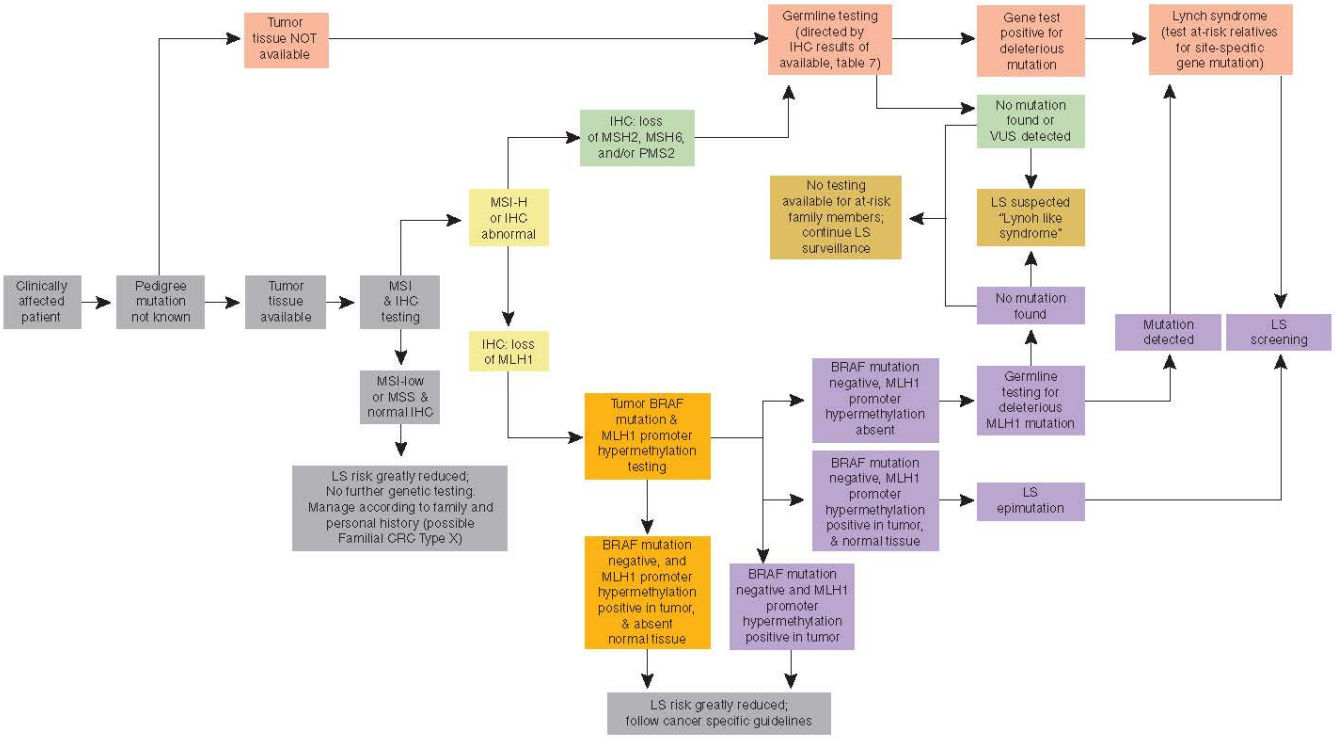

Figure 5. Traditional testing strategy when patient is clinically affected and the family mutation is unknown.

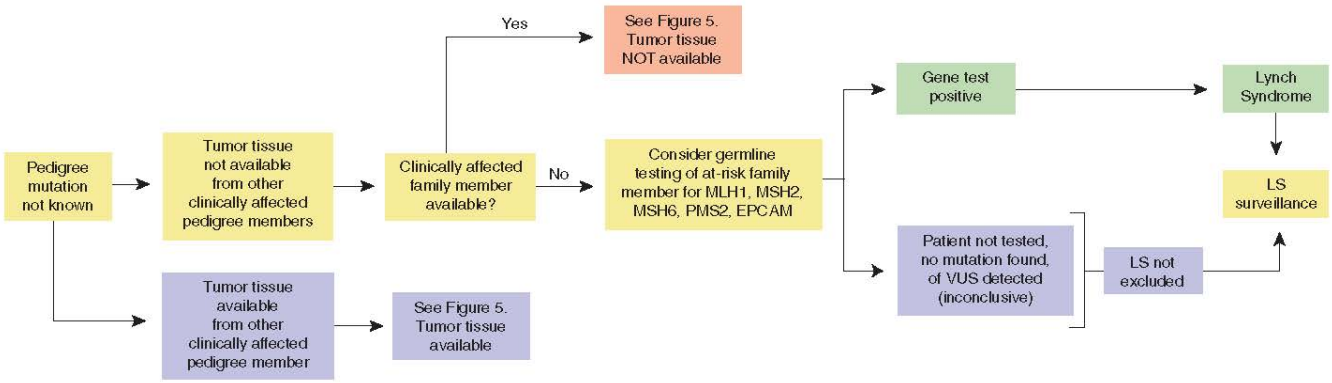

Figure 6. Traditional testing strategy of at-risk family member when family mutation is unknown.

LYNCH SYNDROME MANAGEMENT

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.

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).

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 ultrasound for ovarian cancer is a screening consideration in LS (122,137,138).

Table 8. Colorectal cancer testing result and additional testing strategies

	Immunohistochemistry protein expression					
MSI	**MLH1**	**MSH2**	**MSH6**	**PMS2**	**Possible causes**	**Additional tests**
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 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/physiciangls/PDF/colorectal_screening.pdf (122).
MSI-L, microsatellite low; MSI, microsatellite high; MMR, mismatch repair genes (i.e., MLH1, MSH2, MSH6, PMS2); NA, not available; +, protein present in tissue; −, protein not present in tissue.

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 MSH6 and 35 in PMS2 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.		

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).

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).

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

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 considered (122) at 2–3 year intervals beginning at age 30–35 years.

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 group (138) does not recommend routine screening for urinary cancers.

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).

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).

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 NCCN (122) and Mallorca group (138) both recommend colectomy with ileorectal anastomosis with no deference to patient age.

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 uncertain- ties 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 evidence. This approach is endorsed by the Mallorca group (138) and the NCCN (122).