NCCN National Comprehensive Cancer Network®

NCCN

Genetic/Familial High-Risk Assessment: Colorectal Version 1.2016

Clinical Practice Guidelines in Oncology

Dawn Provenzale, MD, MS; Samir Gupta, MD; Dennis J. Ahnen, MD; Travis Bray, PhD; Jamie A. Cannon, MD; Gregory Cooper, MD; Donald S. David, MD; Dayna S. Early, MD; Deborah Erwin, PhD; James M. Ford, MD; Francis M. Giardiello, MD, MBA; William Grady, MD; Amy L. Halverson, MD; Stanley R. Hamilton, MD; Heather Hampel, MS, CGC; Mohammad K. Ismail, MD; Jason B. Klapman, MD; David W. Larson, MD, MBA; Audrey J. Lazenby, MD; Patrick M. Lynch, MD, JD; Robert J. Mayer, MD; Reid M. Ness, MD, MPH; Scott E. Regenbogen, MD; Niloy Jewel Samadder, MD; Moshe Shike, MD; Gideon Steinbach, MD, PhD; David Weinberg, MD, MSc; Mary Dwyer, MS; and Susan Darlow, PhD

Abstract

This is a focused update highlighting the most current NCCN Guidelines for diagnosis and management of Lynch syndrome. Lynch syndrome is the most common cause of hereditary colorectal cancer, usually resulting from a germline mutation in 1 of 4 DNA mismatch repair genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), or deletions in the *EPCAM* promoter. Patients with Lynch syndrome are at an increased lifetime risk, compared with the general population, for colorectal cancer, endometrial cancer, and other cancers, including of the stomach and ovary. As of 2016, the panel recommends screening all patients with colorectal cancer for Lynch syndrome and provides recommendations for surveillance for early detection and prevention of Lynch syndrome-associated cancers.

J Natl Compr Canc Netw 2016;14(8):1010–1030

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.

Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.

Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States. In 2015, an estimated 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer will have occurred in the United States. During the same year, experts estimate that 49,700 peo-

Please Note

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of consensus of the authors regarding their views of currently accepted approaches to treatment. Any clinician seeking to apply or consult the NCCN Guidelines® is expected to use independent medical judgment in the context of individual clinical circumstances to determine any patient's care or treatment. The National Comprehensive Cancer Network® (NCCN®) makes no representation or warranties of any kind regarding their content, use, or application and disclaims any responsibility for their applications or use in any way. **The full NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal are not printed in this issue of *JNCCN* but can be accessed online at NCCN.org.**

Disclosures for the Genetic/Familial High-Risk Assessment: Colorectal Panel

At the beginning of each NCCN Guidelines panel meeting, panel members review all potential conflicts of interest. NCCN, in keeping with its commitment to public transparency, publishes these disclosures for panel members, staff, and NCCN itself.

Individual disclosures for the NCCN Genetic/Familial High-Risk Assessment: Colorectal Panel members can be found on page 1030. (The most recent version of these guidelines and accompanying disclosures are available on the NCCN Web site at NCCN.org.)

These guidelines are also available on the Internet. For the latest update, visit NCCN.org.

ple will die of colon and rectal cancer.[1] CRC often occurs sporadically, but familial cancer syndromes are common in this disease. Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer), familial adenomatous polyposis (FAP), and MutY human homolog (MUTYH)-associated polyposis (MAP). Other entities include Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, juvenile polyposis, and serrated polyposis syndromes (SPS).[2-4]

Criteria for Further Risk Evaluation for High-Risk Syndromes

NCCN criteria for further risk evaluation for hereditary syndromes associated with CRC include a known mutation in the family, personal history of CRC and more than 10 adenomas, personal history of CRC or endometrial cancer and additional risk factors, including:

- CRC diagnosis at younger than 50 years;
- High microsatellite instability (MSI) or abnormal immunohistochemistry (IHC)-based staining of one or more DNA mismatch repair proteins (*MLH1*, *MSH2*, *MSH6*, *PMS2*) within the tumor;
- Synchronous or metachronous Lynch syndrome-associated cancers;
- High PREMM[1,2,6] Lynch syndrome prediction model score 5% or higher; or
- Family history of Lynch syndrome-associated cancers.

NCCN criteria for further risk evaluation among individuals unaffected by cancer include a

Text cont. on page 1022.

National Comprehensive Cancer Network®

HRCCS*

Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2016

*HIGH-RISK COLORECTAL CANCER SYNDROMES

CRITERIA FOR FURTHER RISK EVALUATION FOR HIGH-RISK SYNDROMES

- Known mutation in the family
  or
- An individual with colorectal cancer (CRC) and >10 adenomas (See APC/MUTYH-1*)
  or
- An individual affected with colorectal or endometrial cancer with one or more of the following:
  - Diagnosed <50 y
  - MSI-high or immunohistochemical staining showing the absence of one or more mismatch repair proteins
  - Synchronous or metachronous Lynch syndrome (LS)-related cancers[a]
  - ≥1 first-degree relative with any LS-related cancer[a] diagnosed <50 y
  - ≥2 first-degree or second-degree relatives with LS-related cancers,[a] regardless of age
  - PREMM[1,2,6] score ≥5%
    or
- An individual unaffected with colorectal or endometrial cancer with ≥5% risk of having an MMR gene mutation based on PREMM[1,2,6] or a family history of one or more of the following:
  - First-degree relative with colorectal or endometrial cancer diagnosed <50 y
  - First-degree relative with colorectal or endometrial cancer and another synchronous or metachronous LS-related cancera
  - ≥2 first-degree or second-degree relatives with LS-related cancers;[a] ≥1 diagnosed <50 y
  - ≥3 first-degree or second-degree relatives with LS-related cancers;a regardless of age
  - Individuals with a first-degree relative with polyposis (See APC/MUTYH-1*)
  - Individual with a desmoid tumor, multifocal or bilateral CHRPE, cribriform-morular variant of papillary thyroid cancer, or hepatoblastoma
  - Individual with multiple GI hamartomatous polyps See PJS-1* and JPS-1* and NCCN Guidelines for Cowden Syndrome (available at NCCN.org) or serrated polyposis syndrome (See SPS-1*)

RISK ASSESSMENT/ GENETIC COUNSELING[b,c]

- Detailed family history
- Detailed medical and surgical history
- Directed examination for related manifestations
- Psychosocial assessment and support
- Risk counseling
- Education support
- Discussion of genetic testing[b]
- Informed consent

HIGH-RISK SYNDROME

- LS (See LS-1)
- Classical familial adenomatous polyposis (FAP)
- Attenuated FAP (AFAP)
- *MUTYH*-associated polyposis (MAP)

  → See *APC* and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1*)
- Peutz-Jeghers syndrome (PJS) (See PJS-1*)
- Juvenile polyposis syndrome (JPS) (See JPS-1*)
- Serrated polyposis syndrome (SPS) (See SPS-1*)
- No syndromes, but familial risk present → See NCCN Guidelines for Colorectal Cancer Screening for Positive Family History (available at NCCN.org) or See Colonic Adenomatous Polyposis of Unknown Etiology (CPUE-1*)

*Available online, in these guidelines, at NCCN.org

[a]LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.

[b]See Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer (HRS-A).

[c]Genetic counseling/patient education is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, gastroenterologist, surgeon, oncology nurse, or other health professional with expertise and experience in cancer genetics should be involved early in counseling patients who potentially meet criteria for an inherited syndrome.

Genetic/Familial High-Risk Assessment: Colorectal, Version 1.2016

*LYNCH SYNDROME

CLINICAL TESTING CRITERIA FOR LYNCH SYNDROME
(based on personal and family history)

Meeting one or more of these criteria warrants further personalized risk assessment, genetic counseling, and often genetic testing and management.

- Meets revised Bethesda Guidelines[a]
  - CRC diagnosed in a patient who is younger than 50 years of age.
  - Presence of synchronous, or metachronous, colorectal, or other LS-related tumors,[b] regardless of age.
  - CRC with the MSI-H histology[c] diagnosed in a patient who is younger than 60 years of age.
  - CRC diagnosed in a patient with one or more first-degree relatives with an LS-related cancer,[b] with one of the cancers being diagnosed before age 50 years.
  - CRC diagnosed in a patient with two or more first- or second-degree relatives with LS-related cancers[b] regardless of age.
- Meets Amsterdam II criteria[d,e]
  - At least three relatives must have a cancer associated with LS (colorectal, cancer of endometrium, small bowel, ureter, or renal-pelvis); all of the following criteria should be present:
  - One must be a first-degree relative of the other two;
  - At least two successive generations must be affected;
  - At least one relative with cancer associated with LS should be diagnosed before age 50 years;
  - FAP should be excluded in the CRC case(s) (if any);
  - Tumors should be verified whenever possible.
- Endometrial cancer at age <50 y
- Known LS in family
- Consider testing individuals with ≥5% risk of LS on one of the following mutation prediction models: MMRpro, PREMM[1,2,6], or MMRpredict. Testing affected individuals in the family with an LS-related cancer[b] is preferred.

→ See Risk Status (LS-2)

[a]Adapted with permission from Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda Guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261-268.

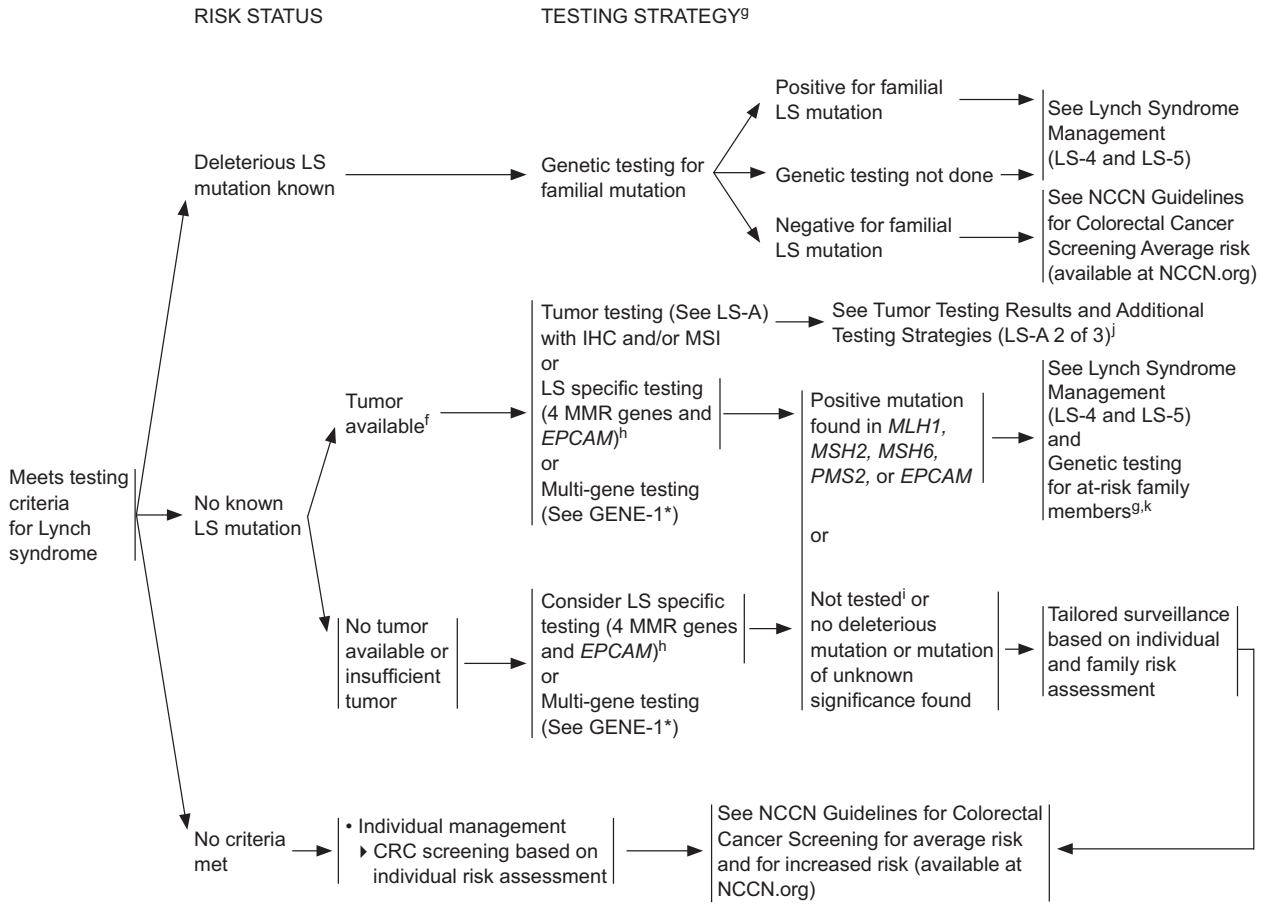
[b]LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, biliary tract, brain (usually glioblastoma as seen in Turcot syndrome), and small intestinal cancers, as well as sebaceous gland adenomas and keratoacanthomas as seen in Muir-Torre syndrome.

[c]Presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

[d]From Vasen HFA. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol 2000;18(suppl 1):81s-92s.

[e]Approximately 50% of patients with LS will be missed by these criteria, and approximately 50% of patients will meet the criteria and not have LS but a high familial risk of uncertain etiology.

*LYNCH SYNDROME



*Available online, in these guidelines, at NCCN.org

[f]If there is more than one affected family member, first consider: youngest age at diagnosis, multiple primaries, and colorectal or endometrial cancers. Limitations of interpreting test results should be discussed if testing tumors other than colorectal or endometrial cancers. If IHC/MSI previously done, see LS-A 2 of 3.

[g]Proper pretest counseling should be done by an individual with expertise in genetics.

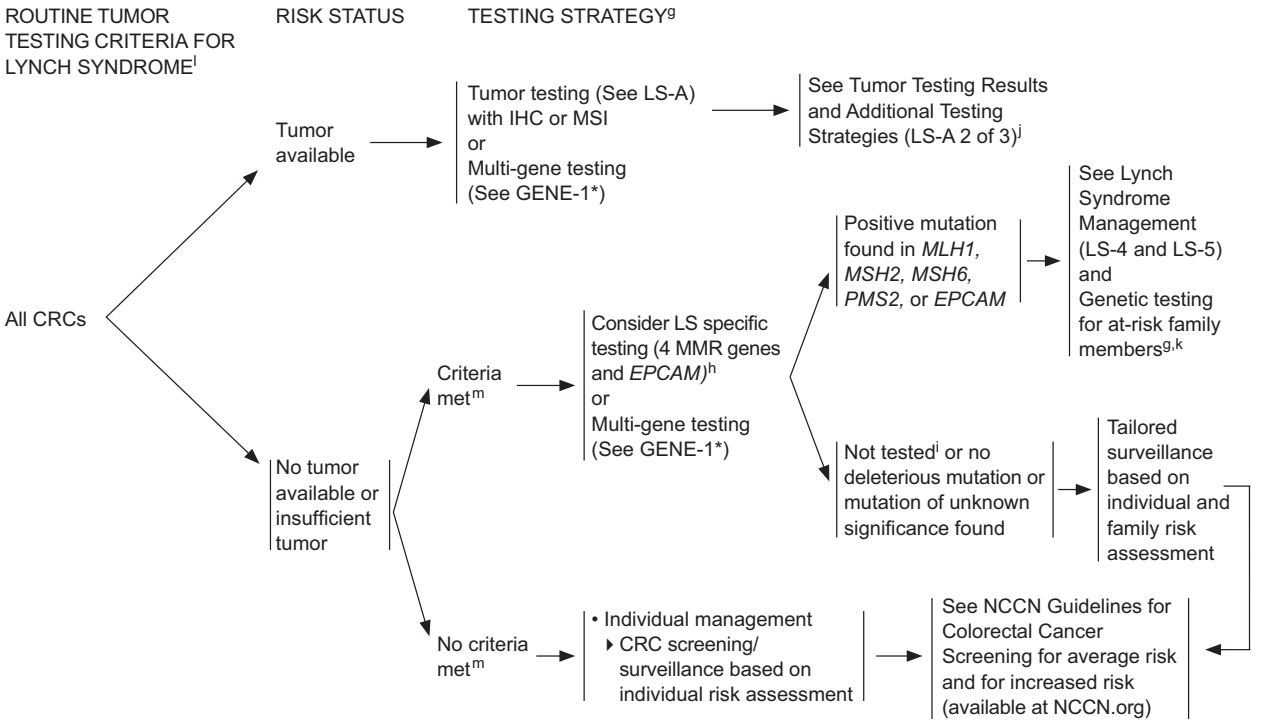
[h]The decision to test all 4 MMR genes and *EPCAM* concurrently versus sequentially (stepwise) is left to the discretion of the clinician.

[i]Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

[j]For individuals found to have a deleterious LS mutation, see LS management recommendations (LS-4 and LS-5).

[k]An at-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

*LYNCH SYNDROME



*Available online, in these guidelines, at NCCN.org

[g]Proper pretest counseling should be done by an individual with expertise in genetics.

[h]The decision to test all 4 MMR genes and *EPCAM* concurrently versus sequentially (stepwise) is left to the discretion of the clinician.

[i]Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

[j]For individuals found to have a deleterious LS mutation, see LS management recommendations (LS-4 and LS-5).

[k]An at-risk family member can be defined as a first-degree relative of an affected individual and/or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known mutation in the family.

[l]The panel recommends universal screening of all CRCs to maximize sensitivity for identifying individuals with Lynch syndrome and to simplify care processes. However, evidence suggests an alternate option would be to limit screening to individuals with CRC diagnosed <70 y plus those >70 meeting Bethesda guidelines. Counseling by an individual with expertise in genetics is not required prior to *routine* tumor testing. An infrastructure needs to be in place to handle the screening results.

[m]See Clinical Testing Criteria for Lynch Syndrome (LS-1).

*LYNCH SYNDROME

LYNCH SYNDROME MANAGEMENT

Surveillance for *MLH1, MSH2, MSH6, PMS2,* and *EPCAM* Mutation Carriers[n,o]

- Colon cancer:
  - Colonoscopy at age 20–25 y or 2–5 y prior to the earliest colon cancer if it is diagnosed before age 25 y and repeat every 1–2 y.
  - There are data to suggest that aspirin may decrease the risk of colon cancer in LS but optimal dose and duration of aspirin therapy are uncertain
- Endometrial and ovarian cancer:
  - Prophylactic hysterectomy and bilateral salpingo-oophorectomy (BSO) is a risk-reducing option that should be considered by women who have completed childbearing.
  - Patients must be aware that dysfunctional uterine bleeding warrants evaluation.
  - There is no clear evidence to support screening for endometrial cancer for LS. However, annual office endometrial sampling is an option.
  - While there may be circumstances where clinicians find screening helpful, data do not support routine ovarian screening for LS. Transvaginal ultrasound for ovarian and endometrial cancer has not been shown to be sufficiently sensitive or specific as to support a positive recommendation, but may be considered at the clinician's discretion. Serum CA-125 is an additional ovarian screening test with caveats similar to transvaginal ultrasound.

→ See Follow-up of Surveillance Findings (LS-6)

Other Extracolonic Cancers[p]

- Gastric and small bowel cancer: There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer for LS. Selected individuals or families or those of Asian descent[q] may consider EGD with extended duodenoscopy (to distal duodenum or into the jejunum) every 3–5 y beginning at age 30–35 y. Consider testing and treating H.pylori.
- Urothelial cancer: Consider annual urinalysis starting at 30–35 y.
- Central nervous system (CNS) cancer: Consider annual physical/neurologic examination starting at 25–30 y; no additional screening recommendations have been made.
- Pancreatic cancer: Despite data indicating an increased risk for pancreatic cancer, no effective screening techniques have been identified; therefore, no screening recommendation is possible at this time.
- Breast cancer: There have been suggestions that there is an increased risk for breast cancer in LS patients; however, there is not enough evidence to support increased screening above average-risk breast cancer screening recommendations.

Lynch Syndrome Management Continued (LS-5)

[n]See Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared to the General Population (LS-B; available online, in these guidelines, at NCCN.org).

[o]Other than colon and endometrial cancer, screening recommendations are expert opinion rather than evidence-based.

[p]For MSH-6 and PMS-2, the risk of other LS-related cancers is reportedly low; however, due to limited data no gene specific screening recommendations are possible at this time.

[q]Vasen HF, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): Recommendations by a group of European experts. Gut 2013;62:812-823.

*LYNCH SYNDROME

LYNCH SYNDROME MANAGEMENT

Risk to Relatives
- Advise patients to tell their relatives about possible inherited cancer risk, options for risk assessment, and management.
- Recommend genetic counseling and consideration of genetic testing for at-risk relatives.

Reproductive Options
- For patients of reproductive age, advise about options for prenatal diagnosis and assisted reproduction including pre-implantation genetic diagnosis. Discussion should include known risks, limitations, and benefits of these technologies.
- For patients of reproductive age, advise about the risk of a rare recessive syndrome (constitutional MMR deficiency [CMMRD syndrome][r]) if both partners are a carrier of a mutation/s in the same MMR gene or *EPCAM* (for example, if both partners carry a mutation in the *PMS2* gene, then their future offspring have a risk for CMMRD syndrome).

[r]Wimmer K, Kratz CP, Vasen HF, et al. EU-Consortium Care for CMMRD (C4CMMRD). Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 2014;51:355-365.

*LYNCH SYNDROME

SURVEILLANCE FINDINGS	FOLLOW-UP
No pathologic findings	• Continued surveillance[s] • Consider prophylactic hysterectomy/BSO if postmenopausal or childbearing completed
Adenocarcinomas	See appropriate NCCN Guidelines for Treatment of Cancer by Site (available at NCCN.org)
Adenomas	• Endoscopic polypectomy with follow-up colonoscopy every 1–2 y depending on: ‣ location, character ‣ surgical risk ‣ patient preference
Adenomas not amenable to endoscopic resection or high-grade dysplasia	• Segmental or extended colectomy depending upon clinical scenario[t] → Lower endoscopic exam every 1–2 y • Consider prophylactic hysterectomy/BSO at time of colon surgery if postmenopausal or family completed

[s]May consider subtotal colectomy if patient is not a candidate for optimal surveillance.

[t]The type of surgical procedure chosen should be based on individual considerations and discussion of risk. Surgical management is evolving. See Definitions of Common Colorectal Resections (CSCR-B) in the NCCN Guidelines for Colorectal Cancer Screening.

*LYNCH SYNDROME

PRINCIPLES OF IHC AND MSI TESTING FOR LYNCH SYNDROME

General

- IHC and MSI analyses are screening tests (either by themselves or in conjunction) that are typically done on colon and endometrial cancer tissue to identify individuals at risk for LS. Greater than 90% of LS tumors are MSI-H (microsatellite instability-high) and/or lack expression of at least one of the mismatch repair (MMR) proteins by IHC. Ten percent to 15% of sporadic colon cancers exhibit abnormal IHC and are MSI-H most often due to abnormal methylation of the MLH1 gene promoter, rather than due to LS (an inherited mutation of one of the MMR genes or *EPCAM*). Mutant BRAF V600E is found in the majority of sporadic MSI CRCs and is rarely found in LS-related CRCs. Thus, the presence of an abnormal MLH1 IHC test increases the possibility of LS but does not make a definitive diagnosis. Those with a germline mutation are then identified as LS patients. Also, sporadic endometrial cancers may exhibit abnormal MSI/IHC due to abnormal methylation of the MLH1 promoter. Somatic MMR genetic testing of the corresponding gene(s) (see "Plausible Etiologies" for possibilities on LS-A 2 of 3) could be performed on tumor DNA to asses for somatic mutations that might explain the abnormal IHC and/or MSI results.
- The Bethesda criteria (See LS-1) are intended to help identify CRC patients whose tumors should be tested for MMR defects, by MSI and/or IHC analysis, thereby identifying patients with a greater chance of having LS. Although more sensitive than the Amsterdam criteria (See LS-1), up to 50% of patients with LS fail to meet even the revised Bethesda Guidelines.

IHC

- IHC refers to staining tumor tissue for protein expression of the 4 MMR genes known to be mutated in LS: *MLH1, MSH2, MSH6*, and *PMS2*. A normal IHC test implies all 4 MMR proteins are normally expressed, and thus it is unlikely that an underlying MMR gene mutation is present. An abnormal test means that at least one of the proteins is not expressed and an inherited mutation may be present in the related gene. Loss of protein expression by IHC in any one of the MMR genes guides genetic testing (mutation detection) to the gene(s) where protein expression is not observed or to the corresponding protein dimer. Absent expression of one or more of the 4 DNA MMR proteins is often reported as abnormal or "positive" IHC. When "positive" IHC is reported, caution should be taken in making sure that positive refers to absence of MMR protein expression, and not presence of expression.
- Abnormal MLH1 IHC should be followed by tumor testing for presence of *BRAF* V600E mutation (or with IHC for *BRAF*) or hypermethylation of the MLH1 promoter, which are associated with sporadic colorectal tumors (or for sporadic endometrial tumors hypermethylation of MLH1 promoter only), and subsequently by genetic testing if the latter are negative (See LS-A 2 of 3). Those with a germline mutation are then identified as LS patients. *BRAF* V600E mutation tumor testing does not apply to endometrial cancer.
- There is a 5%–10% false-negative rate with IHC testing.

MSI

- MSI-H in tumors refers to the tumor having a proportion of alterations in a predetermined panel of microsatellite repeat markers that indicates the loss of MMR activity. Its significance, use, and implications are similar to that of IHC, although the tests are slightly complementary.
- Laboratories vary in their approach in testing MSI. Dinucleotide markers may be less specific than mononucleotide markers of MSI (Xicola RM, Llor X, Pons E. Performance of different microsatellite marker panels for detection of mismatch repair-deficient colorectal tumors. J Natl Cancer Inst. 2007;99:244-52.)
- There is a 5%–10% false-negative rate with MSI testing.

*LYNCH SYNDROME

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

Tumor Testing[a]							Plausible Etiologies	Additional Testing[d,e]
IHC				MSI	*BRAF* V600E[b]	MLH1 Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
+	+	+	+	MSS/MSI-Low	N/A	N/A	1) Sporadic cancer 2) Other (not Lynch syndrome) hereditary CRC syndrome	1) None[c]
+	+	+	+	MSI- High	N/A	N/A	1) Germline mutation in any LS gene 2) Sporadic cancer	1) Germline LS genetic testing[f] 2) If germline testing negative, consider somatic MMR genetic testing[h]
N/A	N/A	N/A	N/A	MSI- High	N/A	N/A	1) Sporadic cancer 2) Germline mutation in any of the LS genes	1) Consider IHC analysis and additional testing depending on IHC results 2) If IHC not performed, consider germline LS genetic testing[f]
--	+	+	--	N/A	N/A	N/A	1) Sporadic cancer 2) Germline mutation *MLH1* or rarely *PMS2*	1) Consider *BRAF*[b]/methylation studies 2) Germline LS genetic testing[f]
--	+	+	--	N/A	Positive	N/A	1) Sporadic cancer 2) Rarely germline *MLH1* mutation or constitutional *MLH1* epimutation	1) None, unless young age of onset or significant family history; then consider constitutional *MLH1* epimutation testingg and/or germline LS genetic testing[f]
--	+	+	--	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline *MLH1* mutation or constitutional *MLH1* epimutation	
--	+	+	--	N/A	Negative	Negative	1) Germline mutation *MLH1* or rarely *PMS2* *2)* Sporadic cancer	1) Germline LS genetic testing[f] 2) If germline testing negative, consider somatic MMR genetic testing[h]
+	--	--	+	N/A	N/A	N/A	1) Germline mutation *MSH2*/*EPCAM*; rarely germline mutation in *MSH6* *2)* Sporadic cancer	
+	+	+	--	N/A	N/A	N/A	1) Germline mutation *PMS2* 2) Germline mutation *MLH1*	
+	--	+	+	N/A	N/A	N/A	1) Germline mutation *MSH2*/*EPCAM* 2) Sporadic cancer	
+	+	--	+	N/A	N/A	N/A	1) Germline mutation *MSH6* 2) Germline mutation *MSH2* 3) Sporadic cancer/Treatment effect[i]	1) Germline LS genetic testing[f] 2) If applicable, consider MSI analysis or repeat IHC testing on nontreated tumor[i] 3) If germline testing negative, consider somatic MMR genetic testing[h]
–	+	+	+	N/A	N/A	N/A	1) Germline mutation *MLH1*; possibly sporadic cancer or *PMS2* mutation	1) Germline LS genetic testing[f] 2) If germline testing of *MLH1* negative, consider *BRAF*[b]/methylation studies 3) If germline testing negative, consider somatic MMR genetic testing[h]
–	–	–	–	N/A	N/A	N/A	1) Germline mutation in *any* LS gene 2) Sporadic cancer	

N/A= Either testing was not done or results may not influence testing strategy. + normal staining of protein -- absent staining of protein

See Footnotes on LS-A 3 of 3

*LYNCH SYNDROME

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES

Footnotes from LS-A 2 of 3

[a]Tumor testing strategies apply to colorectal and endometrial cancers. Limited data exist regarding the efficacy of tumor testing in other LS tumors.

[b]Testing is not appropriate for tumors other than colorectal cancer.

[c]If strong family history (ie, Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) are present, additional testing may be warranted in the proband, or consider tumor testing in another affected family member due to the possibility of a phenocopy.

[d]Individuals with abnormal MSI and/or IHC tumor results and no germline mutation detected in the corresponding gene(s) may still have undetected Lynch syndrome. At this time, no consensus has been reached as to whether these patients should be managed as LS (LS-4 and LS-5) or managed based on personal/family history (See NCCN Guidelines for Colorectal Cancer Screening* - for average risk and for increased risk). Growing evidence suggests that the majority of these individuals with abnormal tumor results and no germline mutation found have double somatic mutations/changes in the MMR genes. Although the efficacy has not yet been proven, genetic testing of the corresponding gene(s) could be performed on tumor DNA to assess for somatic mutations. Individuals found to have double somatic mutations/changes in the MMR genes likely do not have LS and management should be based on personal/family history.

[e]Prior to germline genetic testing, proper pre-test counseling should be done by an individual with expertise in genetics.

[f]Germline LS genetic testing may include testing of the gene/s that are indicated (see “Plausible Etiologies” for possibilities on LS-A 2 of 3) by the abnormal tumor test results, or instead, multi-gene testing that includes *MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM* concurrently may be performed.

[g]Evaluation for constitutional *MLH1* epimutation involves *MLH1* promoter hypermethylation studies on blood or other sources of normal tissue.

[h]Somatic MMR genetic testing of the corresponding gene(s) (see “Plausible Etiologies” for possibilities on LS-A 2 of 3) could be performed on tumor DNA to asses for somatic mutations that might explain the abnormal IHC and/or MSI results.

[i]Absent *MSH6* in rectal tumor tissue may be due to treatment effect (neoadjuvant chemoradiotherapy).

*To view the most recent version of these guidelines, visit NCCN.org

Text cont. from page 1011.

PREMM[1,2,6] score 5% or higher or a family history including the criteria above, polyposis, or manifestations associated with FAP, attenuated FAP, MAP, Peutz-Jeghers syndrome, juvenile polyposis syndrome, serrated polyposis syndrome, or Cowden syndrome (ie, desmoid tumor, multifocal or bilateral congenital hypertrophy of the retinal pigment epithelium, cribriform-morular variant of papillary thyroid cancer, hepatoblastoma, or multiple gastrointestinal hamartomatous polyps). Detailed strategies for screening for Lynch syndrome are provided below; see the NCCN guidelines for detail on follow-up patients meeting risk criteria for other syndromes.

Lynch Syndrome

This update focuses on Lynch syndrome because it is the most common hereditary cause of colorectal cancer, accounting for 2% to 4% of all CRC cases,[5-8] and because a consensus is emerging across medical speciality societies and expert groups regarding the best strategies for identifying patients with this condition. Lynch syndrome results from a germline mutation in 1 of 4 DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).[9] Additionally, deletions in the *EPCAM* gene, which lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing, cause Lynch syndrome.[10,11] Identification of Lynch syndrome is important for both individuals with cancer, because of high personal risk for metachronous Lynch syndrome cancers (ie, endometrial cancer after colorectal cancer or vice versa, or second colorectal cancer), and for their families because of autosomal dominant inheritance and potentially high penetrance. After identification of Lynch syndrome, surveillance (particularly for first or metachronous CRC) offers an opportunity for early detection and perhaps even prevention of cancer among mutation carriers. Further, cancer site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency in affected persons, including gastric, ovarian, pancreatic, urethral, brain (glioblastoma), and small intestinal cancers, as well as sebaceous gland adenomatous polyps and keratoacanthomas.

Definitive Testing in the Setting of Known Lynch Syndrome Mutation

When a known MMR or *EPCAM* mutation exists in the family, the individual should be tested for the familial mutation. If the test is positive or if testing is not performed for any reason, the individual should follow surveillance for Lynch syndrome outlined subsequently. Individuals who test negative for the familial mutation are considered to be at average risk, not zero risk, for CRC and should follow guidelines for average risk screening.

Strategies for Screening for Lynch Syndrome in Absence of Known Mutation: The traditional approach to identifying individuals at risk for Lynch syndrome has generally employed a 2-step screening process. First, patients meeting clinical criteria based on family history, personal history of cancer, and/or pathologic characteristics are identified, followed by additional application of screening with a molecular test. Commonly employed clinical criteria include Amsterdam II criteria, Bethesda Guidelines, and risk prediction models.

Amsterdam II criteria outline increased risk for Lynch syndrome in a family with a proband affected by CRC or any other Lynch syndrome–associated cancer (ie, endometrial, small bowel, ureter, or renal-pelvic cancers), and 3 relatives with a Lynch syndrome–associated cancer provided the following family criteria are met:

- One relative is a first-degree relative of the other 2;
- At least 2 successive generations are affected;
- At least 1 Lynch syndrome associated cancer was diagnosed before age 50 years.

Additionally, Amsterdam II criteria stipulate that FAP should be excluded and tumors should be verified through pathologic examination.[12] Approximately 50% of families meeting the Amsterdam II criteria have a mutation in an MMR gene.[13] These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.[14]

Bethesda guidelines were later developed and updated to provide broader clinical criteria for Lynch syndrome screening.[15] Updated Bethesda criteria[16] are:

- CRC diagnosed in a patient younger than 50 years;
- Synchronous, metachronous, colorectal, or other tumor associated with Lynch syndrome;
- CRC tumor has MSI-H histology (ie, presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) in a patient younger than 60 years; and
- CRC in a patient with a family history of cancer diagnosed earlier than age 50 and associated with Lynch syndrome. If more than one relative was diagnosed with a Lynch syndrome-associated cancer, then the age criterion is not needed.

One study reported that *MLH1* and *MSH2* mutations were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria.[17] Another study reported on the accuracy of the revised Bethesda criteria, concluding that the guidelines were useful for identifying patients who should undergo further testing.[18] Patients fulfilling the revised Bethesda criteria had an odds ratio for carrying a germline mutation in *MLH1* or *MSH2* of 33.3 (95% CI, 4.3–250; *P*=.001). Still, a considerable number of patients with Lynch syndrome do not meet even the revised Bethesda guidelines.[7]

Statistical models that predict risk for carrying a mutation in a DNA MMR gene are an additional commonly applied clinical approach to identifying individuals at risk for Lynch syndrome.[14,19–21] These models give probabilities of mutations or of the development of future cancers based on family and personal history. The PREMM[1,2,6] model can be used online (http://premm.dfci.harvard.edu/) and the MMR predict model is also available for online use (http://hnpccpredict.hgu.mrc.ac.uk/). MMRpro is also available for free download (http://www4.utsouthwestern.edu/breasthealth/cagene/).

Overall, based on clinical criteria, the panel recommends additional evaluation for Lynch syndrome for individuals who 1) meet the revised Bethesda guidelines or Amsterdam II criteria; 2) are diagnosed with endometrial cancer before age 50 years (given the heightened risk of endometrial cancer in women with Lynch syndrome)[22,23]; or 3) have known Lynch syndrome in the family. For individuals meeting one or more of the first 2 criteria, the panel recommends genetic testing or additional screening of tumor tissue (if available) for MSI or for absent expression of one or more of the 4 DNA MMR proteins via IHC (described in detail in subsequent sections).

A problem with nearly all clinically based criteria for identifying individuals with Lynch syndrome is suboptimal sensitivity. This has led several groups to study an alternative strategy, referred to as "universal screening," in which all individuals newly diagnosed with CRC undergo either MSI or IHC testing for absence of one of the 4 DNA MMR proteins. This approach provides a sensitivity of 100% (95% CI, 99.3%–100%) and a specificity of 93.0% (95% CI, 92.0%–93.7%) for identifying individuals with Lynch syndrome.[24] An alternative approach is to test all patients with CRC diagnosed before age 70 years and patients diagnosed at older ages who meet the Bethesda guidelines.[24] This approach gave a sensitivity of 95.1% (95% CI, 89.8%–99.0%) and a specificity of 95.5% (95% CI, 94.7%–96.1%). This alternative approach had improved sensitivity compared with the revised Bethesda criteria, and improved specificity compared with universal screening regardless of age.

The cost-effectiveness of universal screening has been established and has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention (EGAPP) working group at the CDC, the US Multi-Society Task Force on Colorectal Cancer, and the European Society for Medical Oncology.[25–29]

Routine Tumor Testing Criteria for Lynch Syndrome: As of 2016, the panel recommends universal screening of all patients with CRCs, to maximize sensitivity for Lynch syndrome detection and simplify care processes. Additionally, because research has shown high sensitivity of a universal testing approach for identifying women with endometrial cancer due to Lynch syndrome, in 2016 the panel also endorses universal screening of all endometrial tumors.[30] The panel emphasizes that great care must be taken in implementing system-level universal testing to avoid loss to follow-up of patients with abnormal tests and to avoid misinterpretation of the molecular screening tests. The panel accordingly recommends that an infrastructure needs to be in place to handle the screening results.[31] The panel concluded that counseling by an individual with expertise in genetics is not required prior to routine tumor testing, but strongly recommends follow-up with a provider with expertise in genetics after a positive screen (see subsequent sections).

Initial Tumor Testing Methodologies: Screening for Lynch syndrome currently requires performance of 1 of 2 molecular tests, either after the aforementioned clinical criteria are met or as part of universal screening strategies with either 1) IHC analysis for MMR protein expression; or 2) analysis for MSI, which results from MMR deficiency.[32] Greater than 90% of Lynch syndrome tumors are MSI-H and/or lack expression of at least one of the MMR proteins by IHC.

IHC analysis has the advantage of predicting which gene is most likely to be mutated (the gene for the affected protein or its corresponding dimer partner) and thus the first candidate(s) for germline sequencing.[32] Interpretation of IHC test reports can

sometimes be confusing; when "positive" IHC is reported, care should be taken to ensure that "positive" means abnormal absence of MMR protein expression, as opposed to normal presence of expression.

MSI testing panels may consist of mononucleotide and dinucleotide markers.[33] In a study including 1,058 patients with CRC, detection of MMR deficiency using a panel that included both mononucleotide and dinucleotide markers (BAT26, BAT25, D5S346, D2S123, and D17S250) was compared with that of a panel including only mononucleotide markers (BAT26, BAT25, NR21, NR22, and NR24).[34] Sensitivity and positive predictive value of the panel including only mononucleotide markers (95.8% and 88.5%, respectively) were better, compared with the panel including both mononucleotide and dinucleotide markers (76.5% and 65.0%, respectively).

Some studies have shown that both IHC and MSI are cost-effective and useful for determining high-risk patients who may have *MLH1*, *MSH2*, and *MSH6* germline mutations.[27,35,36] However, conclusive data are not yet available that establish which strategy is optimal.[9,18,37–40] A review showed that the sensitivities of MSI and IHC testing are 77% to 89% and 83%, respectively; specificities are 90% and 89%, respectively.[27] An analysis of 5,591 unrelated CRC probands undergoing both MSI and IHC testing showed a concordance rate of 97.5%.[24] Some experts advocate for using both methods when possible.[41] However, the panel recommends using only one test initially. If normal results are found and Lynch syndrome is strongly suspected, then the other test may be performed.

Follow-up Testing of Individuals with Increased Risk Based on Screening: If abnormal MSI or IHC for one of the DNA MMR proteins is identified within a colorectal or endometrial cancer, then a differential diagnosis must be considered (see LS-A 2 of 3, page 1020). For example, 10% to 15% of colorectal cancers have MSI or abnormal IHC (particularly in the case of absent *MLH1* expression) due to sporadic development of cancer, rather than an underlying inherited (germline) genetic mutation. The table on LS-A 2 of 3 (see page 1020) in the NCCN Guidelines identifies a range of test result scenarios, the differential diagnosis, and recommended follow-up. In some scenarios, such as with absent *MSH2* expression by IHC, follow up germline testing for indicated genes is directly recommended. In other scenarios, additional testing of tumor tissue is recommended. For example, for the common scenario of absent *MLH1* expression by IHC, the panel recommends additional tumor testing for presence of *MLH1* hypermethylation and/or *BRAF* V600E mutation, either of which would be consistent with sporadic, rather than Lynch syndrome associated, cancer.[29,32,42,43]

Where genetic testing is recommended (see LS-A 2 of 3, page 1020), the panel recommends consultation with an individual with expertise in genetics, and germline testing to exclude presence of Lynch-associated mutations. The approach to mutation testing is evolving. Previously, a sequential approach in which 1 or 2 genes were sequenced guided by either disease prevalence or IHC results, followed by additional testing of other genes, was used. Recognition of scenarios in which IHC results were not available also allowed for syndrome-specific testing of the panel of genes that cause Lynch syndrome (*MLH1*, *MSH2*, *MSH6*, *PMS2*, and *EPCAM*) simultaneously. Reductions in cost of sequencing and recognition that some patients meeting Lynch syndrome testing criteria may have germline mutations not associated with Lynch syndrome have led to growing use of so called "multigene" panels in clinical practice. These test not only for Lynch syndrome–associated genes, but also additional mutations. As of 2016, the panel recommends that any of these 3 approaches may be employed as follow-up and has provided new guidance on the potential role, strengths, and limitations of multigene panels in the evaluation of Lynch syndrome, as well as other hereditary cancer syndromes.

Follow-up of Genetic Test Results: If a deleterious mutation is found, the panel recommends that Lynch syndrome management guidelines be followed (see LS-4, page 1016).

If no deleterious mutation is found, clinicians are advised to confirm that testing for large rearrangements and deletions of MMR genes were performed by the lab test provider. If still no deleterious mutation is found or a variant of uncertain significance is identified, the panel recommends tailored surveillance based on individual and family risk assessment. Notably, some individuals with abnormal MSI and/or IHC tumor results and no germline mutation detected in the corresponding gene(s) may still have undetected Lynch syndrome. At this time, no con-

sensus has been reached as to whether these patients (sometimes referred to as having "Lynch-like syndrome") should be managed as having Lynch syndrome or managed based on personal/family history. Growing evidence suggests a subset of these individuals may have double somatic mutations/changes in the MMR genes.[44] Although the efficacy of the approach has not yet been proven, genetic testing of the corresponding gene(s) could be performed on tumor DNA to assess for somatic mutations. Individuals found to have double somatic mutations/changes in the MMR genes may not have Lynch syndrome, but double somatic mutations might also be due to non-Lynch germline mutations. Thus, management should be based on personal/family history until further research on Lynch-like syndrome emerges. Additionally, germline testing may be normal despite a strong family history (ie, Amsterdam criteria) or additional features of hereditary cancer syndromes (multiple colon polyps) being present. In these cases, additional testing may be warranted in the proband (such as expanded multigene testing), or tumor testing in an affected family member could be considered due to the possibility of a phenocopy.

Newly Identified Lynch Syndrome

When a mutation is found in the family, it offers an opportunity to provide predictive testing for at-risk family members. An at-risk family member can be defined as a first-degree relative of an affected individual or proband. If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known family mutation.

There are many other issues involved in the process of genetic counseling for individuals for presymptomatic testing for cancer susceptibility. Some individuals elect not to undergo testing, and it is important to counsel these individuals so they continue with increased surveillance.

Surveillance for Patients with Lynch Syndrome

The NCCN Panel carefully considered surveillance schemes for individuals with Lynch syndrome. Compared with the general population, these patients are at increased lifetime risk for CRC (52%–82% vs 5.5%), endometrial cancer (16%–60% vs 2.7%), and other cancers, including of the stomach and ovary.[22,23,45–48] Within the population of Lynch syndrome carriers, risk may vary by specific type of DNA MMR gene mutation. For example, individuals with *MSH6* and *PMS2* mutations have a 10% to 22% risk for colon cancer up to age 70, while those with *MLH1* and *MSH2* mutations have a 40% to 80% risk. As of 2016, the panel recognizes that controversy continues regarding whether mutation-specific risks should guide differential management.[49] The panel's current approach is to offer uniform recommendations for cancer surveillance and prevention, recognizing that, in some clinical scenarios, delaying initiation of surveillance (eg, later starting age for colonoscopy surveillance among *PMS2* carriers) may be appropriate, pending availability of large cohort studies of risk among specific mutation carriers.

Existing data on screening refer primarily to colon and endometrial cancers. More data are needed to evaluate the risk and benefits of extracolonic and extraendometrial cancer screening, and recommendations are based mainly on expert opinion.

Colon Cancer Surveillance: If Lynch syndrome is confirmed, colonoscopy is advised to start between the ages of 20 to 25 or 2 to 5 years younger than the youngest diagnosis age in the family, whichever comes first, and should be repeated every 1 to 2 years. This recommendation is based on a systematic review of data between 1996 and 2006 on the reduction in cancer incidence and mortality by colonoscopy[50] and is consistent with recommendations made by the US Multi-Society Task Force on Colorectal Cancer, the European Society for Medical Oncology, ASCO, the American Gastroenterological Association, and the American College of Gastroenterology.[28,29,42,43,51]

However, as mentioned previously, there is still some uncertainty regarding the best age to initiate colonoscopic surveillance. For example, the results of a meta-analysis in which CRC risk in 1,114 Lynch syndrome families (*MLH1* and *MSH2* mutation carriers) was examined showed that 5-year CRC risk for those ages 20 to 29 is about 1%, with the risk for those ages 30 to 39 being 3% to 5%, with greater risk in men.[52] The investigators argued that annual colonoscopy in patients ages 25 to 29 may be an overly aggressive recommendation that is not cost effective (ie, 155 men and 217 women in this age group would need to be screened to prevent one CRC death). However, the panel concluded that more evidence was needed to understand the best age to start screening.

Chromoendoscopy is a relatively new technique in which dye spray is used to enhance visualization

and that may be used during colonoscopy. A systematic review of 4 studies indicated that chromoendoscopy is a promising technique for improving detection of lesions and flat adenomas in patients with Lynch syndrome.[53] Only one of these studies was a prospective randomized trial, however, and this trial was limited by a small sample of patients who had already undergone colonoscopy and inadequate statistical power to detect clinically meaningful effects.[54] Chromoendoscopy may be considered for patients with Lynch syndrome, but larger prospective randomized trials are needed to better understand its role.

Endometrial and Ovarian Cancer Surveillance: Women with Lynch syndrome are at heightened risk for endometrial and ovarian cancers (up to 60% and 24%, respectively).[22,23,47,50] Education that enhances recognition of relevant symptoms (ie, dysfunctional uterine bleeding) is advised. Total abdominal hysterectomy and bilateral salpingo-oophorectomy (TAH/BSO) is an option that may be considered for risk reduction in women who have completed child-bearing and carry a *MLH1*, *MSH2*, *EPCAM*, *PMS2*, or *MSH6* mutation.[42,51,55–58] There is no clear evidence to support routine screening for gynecologic cancers. Annual endometrial sampling may be considered, but the benefit is uncertain.[55,58–62] Routine transvaginal ultrasound and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific,[55,59–63] but the panel recognized that there may be circumstances in which the clinician may find these tests helpful. An observational study showed that hormonal contraceptive use is associated with lower risk of endometrial cancer in carriers of MMR mutations (hazard ratio [HR], 0.39; 95% CI, 0.23—0.64, $P<.001$).[64] However, prospective data are needed before hormonal contraceptives are recommended for prevention of gynecologic cancers in patients with Lynch syndrome.

Surveillance for Other Cancers: The lifetime risk for gastric cancer varies widely between individuals with Lynch syndrome in different populations, from 2% to 4% in the Netherlands to 30% in Korea.[50,65] Most cases occur after age 40, and males have a stronger predisposition. Lynch syndrome is also associated with a 3% to 6% risk for small bowel cancer.[22,46,66–69] There is no clear evidence to support screening for gastric, duodenal, and small bowel cancer in patients with Lynch syndrome.[70] For selected individuals or families or those of Asian descent with *MLH1*, *MSH2*, or *EPCAM* mutations, physicians may consider upper esophagogastroduodenoscopy (EGD) extended to the distal duodenum or into the jejunum every 3 to 5 years starting at age 30 to 35.[71] Infection with Helicobacter pylori (*H. pylori*) is thought to be a cause of gastric cancer.[72,73] Given the increased risk of gastric cancer in patients with Lynch syndrome, testing and treating for *H. pylori* should be considered. This is consistent with recommendations by ASCO and the European Society for Medical Oncology.[28,42]

Risk of urinary tract cancer to age 70 in patients with Lynch syndrome is 1% to 6.7%,[23,74] with greater risk among carriers of *MSH2* mutations (6.9%), relative to *MLH1* (2.9%) and *MSH6* (1.7%) mutation carriers.[74] Because of this risk, annual urinalysis starting at age 30 to 35 years may also be considered to screen for urothelial cancers in carriers of *MLH1*, *MSH2*, or *EPCAM* mutations, given the relative ease and low cost compared with other tests.[75] Risk for pancreatic and brain cancer is also elevated in patients with Lynch syndrome.[23,46–48] However, no effective screening techniques have been identified for pancreatic cancer; therefore, no screening recommendation is possible at this time. Annual physical and neurologic examination starting at age 25 to 30 years may be considered for central nervous system cancer, but data to support this practice are lacking.

In addition, there have been suggestions of an increased risk for breast cancer in the Lynch syndrome population[76,77]; however, there is insufficient evidence to support increased screening above average-risk breast cancer screening recommendations.[42,51] A study of 188 men with Lynch syndrome also showed a 5-fold increase in risk of prostate cancer.[78] However, there is insufficient evidence to support prostate cancer screening among males with Lynch syndrome.[42,51]

Lynch Syndrome Surveillance Findings and Follow-up: If pathologic findings are noted, continued surveillance is recommended. If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered, although in general, extended surgery is limited to patients after CRC diagnosis. After subtotal colectomy, endoscopic surveillance of the rectum is required, at similar intervals as described previously.

Patients with confirmed adenocarcinoma should be treated following the appropriate NCCN Treatment Guidelines (available at www.NCCN.org).

For patients with adenomatous polyps, recommendations include endoscopic polypectomy with a follow-up colonoscopy every 1 to 2 years. This option depends on the location and characteristics of the polyp, the surgical risk, and patient preference. If an adenomatous polyp cannot be completely resected endoscopically, then segmental or extended colectomy may be performed. Postcolectomy patients should be followed up with lower endoscopic exams every 1 to 2 years.

Because surgical management is evolving, the option of segmental or extended segmental colectomy for patients with confirmed adenocarcinoma or adenomatous polyps is based on individual considerations and discussion of risks. For example, the US Multi-Society Task Force on Colorectal Cancer recommends that surgery in those older than 60 to 65 years and those with underlying sphincter dysfunction should potentially be less extensive.[29] Practically, a patient who is unable or unlikely to comply with frequent colonoscopy should be considered for more extensive colectomy, especially if young. Surgical principles for polyps are similarly controversial.

Reproductive Options: Patients of reproductive age should be advised regarding their options for prenatal diagnosis and assisted reproduction, including preimplantation genetic diagnosis. This discussion should include known risks, limitations, and benefits of these technologies. If both partners are a carrier of mutation(s) in the same MMR gene or *EPCAM* (eg, if both partners carry a mutation in the *PMS2* gene), then they should also be advised about the risk of constitutional MMR deficiency syndrome (CMMRD syndrome), a rare recessive syndrome.[79]

Chemoprevention in Lynch Syndrome: In the randomized CAPP2 trial, 861 participants with Lynch syndrome took either daily aspirin (600 mg) or placebo for up to 4 years; the primary endpoint was the development of CRC.[80] After a mean follow-up of 55.7 months, participants taking daily aspirin for at least 2 years had a 63% reduction in the incidence of CRC (incidence rate ratio [IRR], 0.37; 95% CI, 0.18–0.78; *P*=.008). These participants also saw protection from all Lynch syndrome cancers (IRR, 0.42; 95% CI, 0.25–0.72; *P*=.001). No protection was seen for participants who completed less than 2 years of the intervention. Subgroup analyses from this trial showed that the association between obesity and CRC in patients with Lynch syndrome may be attenuated by taking daily aspirin.[81] However, limitations of the CAPP2 trial highlight the need for larger and long-term randomized trials in this area.[82,83] In an observational study including 1,858 patients from the Colon Cancer Family Registry who have Lynch syndrome, aspirin use was associated with reduced risk of CRC, for both patients who took aspirin for 5 or more years (HR, 0.25; 95% CI, 0.10–0.62; *P*=.003) and those who took it for between 1 month and 4.9 years (HR, 0.49; 95% CI, 0.27–0.90; *P*=.02), compared with those who took aspirin for less than 1 month.[84]

At this time, the panel suggests that aspirin may be used to prevent cancer in patients with Lynch syndrome, but it is emphasized that the optimal dose and duration of therapy are currently unknown. The CAPP2 trial used a dose of 600 mg per day,[80] although many clinicians who prescribe daily aspirin as chemoprevention in patients with Lynch syndrome use a lower dose. The CAPP3 randomized double-blind trial is currently examining the effects of low, moderate, and high doses of daily aspirin on Lynch syndrome–associated cancer incidence (NCT02497820), but results are not yet available. The panel's recommendation to consider aspirin for chemoprevention is consistent with the stance of the American Gastroenterological Association.[43] The American College of Gastroenterology does not recommend standard use of aspirin for chemoprevention given the lack of evidence regarding its impact on CRC risk.[51]

Conclusions

Progress has been made in the evidence base surrounding risk for cancer, screening, and surveillance for Lynch syndrome. In particular, the panel strongly recommends screening for Lynch syndrome in all patients with primary colon and rectal cancers, to identify cancer survivors and families who may benefit from personalized cancer surveillance. Lynch syndrome may serve as a paradigm for the potential opportunities and challenges of implementing personalized cancer prevention, screening, and surveillance in usual practice.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
2. Burt R, Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128:1696–1716.
3. Giardiello FM, Offerhaus JG. Phenotype and cancer risk of various polyposis syndromes. Eur J Cancer 1995;31A:1085–1087.
4. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839–847.
5. Aaltonen LA, Salovaara R, Kristo P, et al. Incidence of hereditary nonpolyposis colorectal cancer and the feasibility of molecular screening for the disease. N Engl J Med 1998;338:1481–1487.
6. Hampel H, Frankel WL, Martin E, et al. Screening for the Lynch syndrome (hereditary nonpolyposis colorectal cancer). N Engl J Med 2005;352:1851–1860.
7. Hampel H, Frankel WL, Martin E, et al. Feasibility of screening for Lynch syndrome among patients with colorectal cancer. J Clin Oncol 2008;26:5783–5788.
8. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919–932.
9. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073–2087 e2073.
10. Kempers MJ, Kuiper RP, Ockeloen CW, et al. Risk of colorectal and endometrial cancers in EPCAM deletion-positive Lynch syndrome: a cohort study. Lancet Oncol 2011;12:49–55.
11. Rumilla K, Schowalter KV, Lindor NM, et al. Frequency of deletions of EPCAM (TACSTD1) in MSH2-associated Lynch syndrome cases. J Mol Diagn 2011;13:93–99.
12. Vasen HF, Watson P, Mecklin JP, Lynch HT. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative group on HNPCC. Gastroenterology 1999;116:1453–1456.
13. Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol 2000;18:81S–92S.
14. Barnetson RA, Tenesa A, Farrington SM, et al. Identification and survival of carriers of mutations in DNA mismatch-repair genes in colon cancer. N Engl J Med 2006;354:2751–2763.
15. Rodriguez-Bigas MA, Boland CR, Hamilton SR, et al. A National Cancer Institute Workshop on Hereditary Nonpolyposis Colorectal Cancer Syndrome: meeting highlights and Bethesda guidelines. J Natl Cancer Inst 1997;89:1758–1762.
16. Umar A, Boland CR, Terdiman JP, et al. Revised Bethesda guidelines for hereditary nonpolyposis colorectal cancer (Lynch syndrome) and microsatellite instability. J Natl Cancer Inst 2004;96:261–268.
17. Raedle J, Trojan J, Brieger A, et al. Bethesda guidelines: relation to microsatellite instability and MLH1 promoter methylation in patients with colorectal cancer. Ann Intern Med 2001;135:566–576.
18. Pinol V, Castells A, Andreu M, et al. Accuracy of revised Bethesda guidelines, microsatellite instability, and immunohistochemistry for the identification of patients with hereditary nonpolyposis colorectal cancer. JAMA 2005;293:1986–1994.
19. Balmana J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA 2006;296:1469–1478.
20. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 2006;296:1479–1487.
21. Kastrinos F, Steyerberg EW, Mercado R, et al. The PREMM(1,2,6) model predicts risk of MLH1, MSH2, and MSH6 germline mutations based on cancer history. Gastroenterology 2011;140:73–81.
22. Bonadona V, Bonaiti B, Olschwang S, et al. Cancer risks associated with germline mutations in MLH1, MSH2, and MSH6 genes in Lynch syndrome. JAMA 2011;305:2304–2310.
23. Kohlmann W, Gruber S. Lynch Syndrome. GeneReviews at GeneTests: Medical Genetics Information Resource 2014.
24. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555–1565.
25. Recommendations from the EGAPP Working Group: genetic testing strategies in newly diagnosed individuals with colorectal cancer aimed at reducing morbidity and mortality from Lynch syndrome in relatives. Genet Med 2009;11:35–41.
26. Ladabaum U, Wang G, Terdiman J, et al. Strategies to identify the Lynch syndrome among patients with colorectal cancer: a cost-effectiveness analysis. Ann Intern Med 2011;155:69–79.
27. Palomaki GE, McClain MR, Melillo S, et al. EGAPP supplementary evidence review: DNA testing strategies aimed at reducing morbidity and mortality from Lynch syndrome. Genet Med 2009;11:42–65.
28. Balmana J, Balaguer F, Cervantes A, Arnold D. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2013;24 Suppl 6:vi73–80.
29. Giardiello FM, Allen JI, Axilbund JE, et al. Guidelines on genetic evaluation and management of Lynch syndrome: a consensus statement by the US Multi-Society Task Force on colorectal cancer. Gastroenterology 2014;147:502–526.
30. Goodfellow PJ, Billingsley CC, Lankes HA, et al. Combined microsatellite instability, MLH1 methylation analysis, and immunohistochemistry for Lynch syndrome screening in endometrial cancers from GOG210: an NRG Oncology and Gynecologic Oncology Group study. J Clin Oncol 2015;33:4301–4308.
31. Marquez E, Geng Z, Pass S, et al. Implementation of routine screening for Lynch syndrome in university and safety-net health system settings: successes and challenges. Genet Med 2013;15:925–932.
32. Hendriks YM, de Jong AE, Morreau H, et al. Diagnostic approach and management of Lynch syndrome (hereditary nonpolyposis colorectal carcinoma): a guide for clinicians. CA Cancer J Clin 2006;56:213–225.
33. Boland CR, Thibodeau SN, Hamilton SR, et al. A National Cancer Institute Workshop on Microsatellite Instability for cancer detection and familial predisposition: development of international criteria for the determination of microsatellite instability in colorectal cancer. Cancer Res 1998;58:5248–5257.
34. Xicola RM, Llor X, Pons E, et al. Performance of different microsatellite marker panels for detection of mismatch repair-deficient colorectal tumors. J Natl Cancer Inst 2007;99:244–252.
35. Caldes T, Godino J, Sanchez A, et al. Immunohistochemistry and microsatellite instability testing for selecting MLH1, MSH2 and MSH6 mutation carriers in hereditary non-polyposis colorectal cancer. Oncol Rep 2004;12:621–629.
36. Vasen HF, Hendriks Y, de Jong AE, et al. Identification of HNPCC by molecular analysis of colorectal and endometrial tumors. Dis Markers 2004;20:207–213.
37. Hampel H, Frankel W, Panescu J, et al. Screening for Lynch syndrome (hereditary nonpolyposis colorectal cancer) among endometrial cancer patients. Cancer Res 2006;66:7810–7817.
38. Lindor NM, Burgart LJ, Leontovich O, et al. Immunohistochemistry versus microsatellite instability testing in phenotyping colorectal tumors. J Clin Oncol 2002;20:1043–1048.
39. Reyes CM, Allen BA, Terdiman JP, Wilson LS. Comparison of selection strategies for genetic testing of patients with hereditary nonpolyposis colorectal carcinoma: effectiveness and cost-effectiveness. Cancer 2002;95:1848–1856.
40. Shia J, Klimstra DS, Nafa K, et al. Value of immunohistochemical detection of DNA mismatch repair proteins in predicting germline mutation in hereditary colorectal neoplasms. Am J Surg Pathol 2005;29:96–104.
41. Pino MS, Chung DC. Application of molecular diagnostics for the detection of Lynch syndrome. Expert Rev Mol Diagn 2010;10:651–665.
42. Stoffel EM, Mangu PB, Gruber SB, et al. Hereditary colorectal cancer syndromes: American Society of Clinical Oncology Clinical Practice Guideline endorsement of the familial risk-colorectal cancer: European Society for Medical Oncology Clinical Practice Guidelines. J Clin Oncol 2015;33:209–217.
43. Rubenstein JH, Enns R, Heidelbaugh J, Barkun A. American Gastroenterological Association Institute Guideline on the Diagnosis and Management of Lynch Syndrome. Gastroenterology 2015;149:777–782.
44. Haraldsdottir S, Hampel H, Tomsic J, et al. Colon and endometrial cancers with mismatch repair deficiency can arise from somatic, rather than germline, mutations. Gastroenterology 2014;147:1308–1316.e1301.
45. Engel C, Loeffler M, Steinke V, et al. Risks of less common cancers in proven mutation carriers with lynch syndrome. J Clin Oncol 2012;30:4409–4415.
46. Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. JAMA 2009;302:1790–1795.
47. Watson P, Vasen HF, Mecklin JP, et al. The risk of extra-colonic, extra-endometrial cancer in the Lynch syndrome. Int J Cancer 2008;123:444–449.
48. Win AK, Young JP, Lindor NM, et al. Colorectal and other cancer risks for carriers and noncarriers from families with a DNA mismatch repair gene mutation: a prospective cohort study. J Clin Oncol 2012;30:958–964.

49. Win AK, Lindor NM, Young JP, et al. Risks of primary extracolonic cancers following colorectal cancer in lynch syndrome. J Natl Cancer Inst 2012;104:1363–1372.

50. Lindor NM, Petersen GM, Hadley DW, et al. Recommendations for the care of individuals with an inherited predisposition to Lynch syndrome: a systematic review. JAMA 2006;296:1507–1517.

51. Syngal S, Brand RE, Church JM, et al. ACG clinical guideline: Genetic testing and management of hereditary gastrointestinal cancer syndromes. Am J Gastroenterol 2015;110:223–262; quiz 263.

52. Jenkins MA, Dowty JG, Ait Ouakrim D, et al. Short-term risk of colorectal cancer in individuals with lynch syndrome: a meta-analysis. J Clin Oncol 2015;33:326–331.

53. Haanstra JF, Kleibeuker JH, Koornstra JJ. Role of new endoscopic techniques in Lynch syndrome. Fam Cancer 2013;12:267–272.

54. Stoffel EM, Turgeon DK, Stockwell DH, et al. Missed adenomas during colonoscopic surveillance in individuals with Lynch Syndrome (hereditary nonpolyposis colorectal cancer). Cancer Prev Res (Phila) 2008;1:470–475.

55. Chen LM, Yang KY, Little SE, et al. Gynecologic cancer prevention in Lynch syndrome/hereditary nonpolyposis colorectal cancer families. Obstet Gynecol 2007;110:18–25.

56. Schmeler KM, Lynch HT, Chen LM, et al. Prophylactic surgery to reduce the risk of gynecologic cancers in the Lynch syndrome. N Engl J Med 2006;354:261–269.

57. Stuckless S, Green J, Dawson L, et al. Impact of gynecological screening in Lynch syndrome carriers with an MSH2 mutation. Clin Genet 2013;83:359–364.

58. ACOG Practice Bulletin No. 147: Lynch syndrome. Obstet Gynecol 2014;124:1042–1054.

59. Auranen A, Joutsiniemi T. A systematic review of gynecological cancer surveillance in women belonging to hereditary nonpolyposis colorectal cancer (Lynch syndrome) families. Acta Obstet Gynecol Scand 2011;90:437–444.

60. Jarvinen HJ, Renkonen-Sinisalo L, Aktan-Collan K, et al. Ten years after mutation testing for Lynch syndrome: cancer incidence and outcome in mutation-positive and mutation-negative family members. J Clin Oncol 2009;27:4793–4797.

61. Renkonen-Sinisalo L, Butzow R, Leminen A, et al. Surveillance for endometrial cancer in hereditary nonpolyposis colorectal cancer syndrome. Int J Cancer 2007;120:821–824.

62. Rijcken FE, Mourits MJ, Kleibeuker JH, et al. Gynecologic screening in hereditary nonpolyposis colorectal cancer. Gynecol Oncol 2003;91:74–80.

63. Dove-Edwin I, Boks D, Goff S, et al. The outcome of endometrial carcinoma surveillance by ultrasound scan in women at risk of hereditary nonpolyposis colorectal carcinoma and familial colorectal carcinoma. Cancer 2002;94:1708–1712.

64. Dashti SG, Chau R, Ouakrim DA, et al. Female hormonal factors and the risk of endometrial cancer in Lynch syndrome. JAMA 2015;314:61–71.

65. Capelle LG, Van Grieken NC, Lingsma HF, et al. Risk and epidemiological time trends of gastric cancer in Lynch syndrome carriers in the Netherlands. Gastroenterology 2010;138:487–492.

66. Schulmann K, Engel C, Propping P, Schmiegel W. Small bowel cancer risk in Lynch syndrome. Gut 2008;57:1629–1630.

67. ten Kate GL, Kleibeuker JH, Nagengast FM, et al. Is surveillance of the small bowel indicated for Lynch syndrome families? Gut 2007;56:1198–1201.

68. Koornstra JJ, Kleibeuker JH, Vasen HF. Small-bowel cancer in Lynch syndrome: is it time for surveillance? Lancet Oncol 2008;9:901–905.

69. Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line PMS2 mutations. Gastroenterology 2008;135:419–428.

70. Renkonen-Sinisalo L, Sipponen P, Aarnio M, et al. No support for endoscopic surveillance for gastric cancer in hereditary non-polyposis colorectal cancer. Scand J Gastroenterol 2002;37:574–577.

71. Vasen HF, Blanco I, Aktan-Collan K, et al. Revised guidelines for the clinical management of Lynch syndrome (HNPCC): recommendations by a group of European experts. Gut 2013;62:812–823.

72. Correa P, Haenszel W, Cuello C, et al. A model for gastric cancer epidemiology. Lancet 1975;2:58–60.

73. Blaser MJ. Hypothesis: the changing relationships of Helicobacter pylori and humans: implications for health and disease. J Infect Dis 1999;179:1523–1530.

74. Joost P, Therkildsen C, Dominguez-Valentin M, et al. Urinary tract cancer in Lynch syndrome: increased risk in carriers of MSH2 mutations. Urology 2015;86:1212–1217.

75. Mork M, Hubosky SG, Roupret M, et al. Lynch syndrome: a primer for urologists and panel recommendations. J Urol 2015;194:21–29.

76. Skeldon SC, Semotiuk K, Aronson M, et al. Patients with Lynch syndrome mismatch repair gene mutations are at higher risk for not only upper tract urothelial cancer but also bladder cancer. Eur Urol 2013;63:379–385.

77. Win AK, Lindor NM, Jenkins MA. Risk of breast cancer in Lynch syndrome: a systematic review. Breast Cancer Res 2013;15:R27.

78. Haraldsdottir S, Hampel H, Wei L, et al. Prostate cancer incidence in males with Lynch syndrome. Genet Med 2014;16:553–557.

79. Wimmer K, Kratz CP, Vasen HF, et al. Diagnostic criteria for constitutional mismatch repair deficiency syndrome: suggestions of the European consortium 'care for CMMRD' (C4CMMRD). J Med Genet 2014;51:355–365.

80. Burn J, Gerdes AM, Macrae F, et al. Long-term effect of aspirin on cancer risk in carriers of hereditary colorectal cancer: an analysis from the CAPP2 randomised controlled trial. Lancet 2011;378:2081–2087.

81. Movahedi M, Bishop DT, Macrae F, et al. Obesity, aspirin, and risk of colorectal cancer in carriers of hereditary colorectal cancer: a prospective investigation in the CAPP2 study. J Clin Oncol 2015.

82. Cleland JG. Does aspirin really reduce the risk of colon cancer? Lancet 2012;379:1586; author reply 1587.

83. Jankowski J, Barr H, Moayyedi P. Does aspirin really reduce the risk of colon cancer? Lancet 2012;379:1586–1587; author reply 1587.

84. Ait Ouakrim D, Dashti SG, Chau R, et al. Aspirin, ibuprofen, and the risk of colorectal cancer in Lynch syndrome. J Natl Cancer Inst 2015;107.

Indivdual Disclosures of the NCCN Genetic/Familial High-Risk Assessment: Colorectal Panel				
Panel Member	**Clinical Research Support/Data Safety Monitoring Board**	**Scientific Advisory Boards, Consultant, or Expert Witness**	**Promotional Advisory Boards, Consultant, or Speakers Bureau**	**Date Completed**
Dennis J. Ahnen, MD	Cancer Prevention Pharmaceuticals	Cancer Prevention Pharmaceuticals; and EXACT Sciences Inc.	Ambry Genetics	1/19/16
Travis Bray, PhD	None	None	None	5/30/16
Jamie A. Cannon, MD	None	None	Intuitive Surgical, Inc.	3/18/16
Gregory Cooper, MD	None	None	None	5/5/16
Donald S. David, MD	Chimerix	None	None	4/1/16
Dayna S. Early, MD	None	None	None	3/20/16
Deborah Erwin, PhD	None	NYS Breast, Cervical and Ovarian Cancer Detection and Education Program Advice Council	None	1/12/16
James M. Ford, MD	None	None	None	11/20/15
Francis M. Giardiello, MD, MBA	None	None	None	6/2/16
William Grady, MD	None	None	None	4/15/16
Samir Gupta, MD[a]	None	Ambry Genetics; Clinical Genomics; Exact Sciences; and Guidepoint Global Consulting	None	10/19/15
Amy L. Halverson, MD	None	None	None	3/18/16
Stanley R. Hamilton, MD	None	Intervention Insights LLC	None	3/17/16
Heather Hampel, MS, CGC	Myriad Genetic Laboratories, Inc.	None	Beacon LBS; and GeneDx	4/6/16
Mohammad K. Ismail, MD	None	None	None	4/27/16
Jason B. Klapman, MD	None	None	None	5/31/16
David W. Larson, MD, MBA	None	None	None	3/09/16
Audrey J. Lazenby, MD	None	None	None	4/8/16
Patrick M. Lynch, MD, JD	Cancer Prevention Pharmaceuticals	Exact Sciences; and Myriad Genetic Laboratories, Inc.	Thetis Pharma	3/15/16
Robert J. Mayer, MD	Taiho Parmaceuticals Co., Ltd.	Casi Pharmaceuticals; and Taiho Parmaceuticals Co., Ltd.	None	4/13/16
Reid M. Ness, MD, MPH	None	None	None	1/29/16
Dawn Provenzale, MD, MS	None	None	None	4/26/16
Scott E. Regenbogen, MD	None	None	None	3/7/16
Niloy Jewel Samadder, MD	None	None	Cook Medical Inc.	7/14/15
Moshe Shike, MD	aspire corp	None	None	11/13/15
Gideon Steinbach, MD, PhD	None	None	None	2/8/16
David Weinberg, MD, MSc	None	None	None	7/12/16

[a]The following individuals have disclosed that they have an employment/governing board, patent, equity, or royalty conflict:
Samir Gupta, MD: Ambry Genetics and Exact Sciences
The NCCN Guidelines staff have no conflicts to disclose.