NCCN: Continuing Education

Target Audience: This activity is designed to meet the educational needs of physicians, nurses, pharmacists, and other healthcare professionals who manage patients with cancer.

Accreditation Statements

In support of improving patient care, National Comprehensive Cancer Network (NCCN) is jointly accredited by the Accreditation Council for Continuing Medical Education (ACCME), the Accreditation Council for Pharmacy Education (ACPE), and the American Nurses Credentialing Center (ANCC), to provide continuing education for the healthcare team.

Medicine (ACCME): NCCN designates this journal-based CME activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Nursing (ANCC): NCCN designates this educational activity for a maximum of 1.0 contact hour.

Pharmacy (ACPE): NCCN designates this knowledge-based continuing education activity for 1.0 contact hour (0.1 CEUs) of continuing education credit. UAN: JA4008196-0000-19-011-H01-P

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: (1) review the educational content; (2) take the posttest with a 66% minimum passing score and complete the evaluation at **https://education.nccn.org/node/86075**; and (3) view/print certificate.

Pharmacists: You must complete the posttest and evaluation within 30 days of the activity. Continuing pharmacy education credit is reported to the CPE Monitor once you have completed the posttest and evaluation and claimed your credits. Before completing these requirements, be sure your NCCN profile has been updated with your NAPB e-profile ID and date of birth. Your credit cannot be reported without this information. If you have any questions, please e-mail education@nccn.org.

Release date: September 10, 2019; Expiration date: September 10, 2020

Learning Objectives:

Upon completion of this activity, participants will be able to:

- Integrate into professional practice the updates to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

Disclosure of Relevant Financial Relationships

The NCCN staff listed below discloses no relevant financial relationships:

Kerrin M. Rosenthal, MA; Kimberly Callan, MS; Genevieve Emberger Hartzman, MA; Erin Hesler; Kristina M. Gregory, RN, MSN, OCN; Rashmi Kumar, PhD; Karen Kanefield; and Kathy Smith.

Individuals Who Provided Content Development and/or Authorship Assistance:

Samir Gupta, MD, Panel Vice Chair, has disclosed that he has no relevant financial relationships.

Dawn Provenzale, MD, MS, Panel Chair, has disclosed that she has no relevant financial relationships.

Xavier Llor, MD, PhD, Panel Member, has disclosed that he is a scientific advisor for Exact Sciences.

Amy L. Halverson, MD, Panel Member, has disclosed that she has no relevant financial relationships.

William Grady, MD, Panel Member, had disclosed that he receives grant/research support from Janssen Pharmaceuticals and Tempus; receives consulting fees/honoraria from Boehringer-Ingelheim; and is a scientific advisor for Guardant Health, Freenome, and SEngine.

Daniel C. Chung, MD, Panel Member, has disclosed that he has no relevant financial relationships.

Sigurdis Haraldsdottir, MD, PhD, Panel Member, has disclosed that she has no relevant financial relationships.

Arnold J. Markowitz, MD, Panel Member, has disclosed that he has no relevant financial relationships.

Thomas P. Slavin Jr, MD, Panel Member, has disclosed that he has no relevant financial relationships.

Heather Hampel, MS, CGC, Panel Member, has disclosed that she is a scientific advisor for and receives consulting fees/honoraria from InVitae Genetics.

Reid M. Ness, MD, MPH, Panel Member, has disclosed that he has no relevant financial relationships.

Jennifer M. Weiss, MD, MS, Panel Member, has disclosed that he has no relevant financial relationships.

Mary A. Dwyer, MS, Senior Manager, Guidelines, NCCN, has disclosed that she has no relevant financial relationships.

Ndiya Ogba, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

To view all of the conflicts of interest for the NCCN Guidelines panel, go to NCCN.org/disclosures/guidelinepanellisting.aspx.

This activity is supported by educational grants from AstraZeneca, Celgene Corporation, Clovis Oncology, Eisai, Genentech, Genomic Health, Inc., Novartis, Taiho Oncology, Inc., and TESARO. This activity is supported by an independent educational grant from AbbVie. This activity is supported by educational funding provided by Amgen. This activity is supported by an unrestricted educational grant from Gilead Sciences, Medical Affairs.

Genetic/Familial High-Risk Assessment: Colorectal, Version 2.2019

Featured Updates to the NCCN Guidelines

Samir Gupta, MD[1,*]; Dawn Provenzale, MD, MS[2,*]; Xavier Llor, MD, PhD[3,*]; Amy L. Halverson, MD[4,*]; William Grady, MD[5,*]; Daniel C. Chung, MD[6,*]; Sigurdis Haraldsdottir, MD, PhD[7,*]; Arnold J. Markowitz, MD[8,*]; Thomas P. Slavin Jr, MD[9,*]; Heather Hampel, MS, CGC[10,*]; Reid M. Ness, MD, MPH[11,*]; Jennifer M. Weiss, MD, MS[12,*]; Dennis J. Ahnen, MD[13]; Lee-may Chen, MD[14]; Gregory Cooper, MD[15]; Dayna S. Early, MD[16]; Francis M. Giardiello, MD, MBA[17]; Michael J. Hall, MD, MS[18]; Stanley R. Hamilton, MD[19]; Priyanka Kanth, MD, MS[20]; Jason B. Klapman, MD[21]; Audrey J. Lazenby, MD[22]; Patrick M. Lynch, MD, JD[19]; Robert J. Mayer, MD[23]; June Mikkelson, MS, CGC[24]; Shajan Peter, MD[25]; Scott E. Regenbogen, MD[26]; Mary A. Dwyer, MS, CGC[27,*]; and Ndiya Ogba, PhD[27,*]

ABSTRACT

Identifying individuals with hereditary syndromes allows for improved cancer surveillance, risk reduction, and optimized management. Establishing criteria for assessment allows for the identification of individuals who are carriers of pathogenic genetic variants. The NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal provide recommendations for the assessment and management of patients with high-risk colorectal cancer syndromes. These NCCN Guidelines Insights focus on criteria for the evaluation of Lynch syndrome and considerations for use of multigene testing in the assessment of hereditary colorectal cancer syndromes.

J Natl Compr Canc Netw 2019;17(9):1032–1041
doi: 10.6004/jnccn.2019.0044

[1]UC San Diego Moores Cancer Center; [2]Duke Cancer Institute; [3]Yale Cancer Center/Smilow Cancer Hospital; [4]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [5]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [6]Massachusetts General Hospital Cancer Center; [7]Stanford Cancer Institute; [8]Memorial Sloan Kettering Cancer Center; [9]City of Hope National Medical Center; [10]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [11]Vanderbilt-Ingram Cancer Center; [12]University of Wisconsin Carbone Cancer Center; [13]University of Colorado Cancer Center; [14]UCSF Helen Diller Family Comprehensive Cancer Center; [15]Case Comprehensive Cancer Center/University Hospitals Seidman Cancer Center and Cleveland Clinic Taussig Cancer Institute; [16]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [17]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [18]Fox Chase Cancer Center; [19]The University of Texas MD Anderson Cancer Center; [20]Huntsman Cancer Institute at the University of Utah; [21]Moffitt Cancer Center; [22]Fred & Pamela Buffett Cancer Center; [23]Dana-Farber/Brigham and Women's Cancer Center; [24]Roswell Park Comprehensive Cancer Center; [25]O'Neal Comprehensive Cancer Center at UAB; [26]University of Michigan Rogel Cancer Center; and [27]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

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 of any patient with cancer is in a clinical trial. Participation in clinical trials is especially encouraged.

PLEASE NOTE

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®) are a statement of evidence and consensus of the authors regarding their views of currently accepted approaches to treatment. **The NCCN Guidelines Insights highlight important changes in the NCCN Guidelines recommendations from previous versions. Colored markings in the algorithm show changes and the discussion aims to further the understanding of these changes by summarizing salient portions of the panel's discussion, including the literature reviewed.**

The NCCN Guidelines Insights do not represent the full NCCN Guidelines; further, the National Comprehensive Cancer Network® (NCCN®) makes no representations or warranties of any kind regarding their content, use, or application of the NCCN Guidelines and NCCN Guidelines Insights and disclaims any responsibility for their application or use in any way.

The complete and most recent version of these NCCN Guidelines is available free of charge at NCCN.org.

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and the second leading cause of cancer death in the United States; in 2019, an estimated 101,420 new cases of colon cancer and 44,180 new cases of rectal cancer will be diagnosed.[1] Approximately 20% to 30% of CRCs are potentially linked to genetic factors, and hereditary CRC syndromes constitute 3% to 5% of all CRCs.[2–5] Hereditary CRC syndromes are associated with early onset of CRC and some with risk for extracolonic cancers.[6,7] Genetic susceptibility to CRC includes well-defined inherited syndromes, such as Lynch syndrome, familial adenomatous polyposis (FAP), and *MUTYH*–associated polyposis (MAP),[2,8] and rare inherited syndromes, including juvenile polyposis syndrome (JPS), Cowden syndrome/PTEN hamartoma tumor syndrome (PHTS), and Peutz-Jeghers syndrome (PJS).[9,10] Some syndromes are still being further characterized, such as the I1307K polymorphism in *APC*[11,12] and polymerase proofreading–associated polyposis secondary to germline mutations in *POLE* and *POLD1*.[13,14] In addition, there are other syndromes that do not yet have a clearly identified pathogenic variant, such as serrated polyposis syndrome.[15]

Hereditary cancer risk assessment is essential to identifying individuals and families at risk for developing certain types of cancers and provides targeted surveillance and management for affected individuals.[6] High-risk individuals may be identified based on phenotypic criteria, including family history and patient-specific factors, such as age at diagnosis and tumor phenotype. The presence of a genetic mutation may then be confirmed with single or multigene testing.[7] With the capacity to analyze several genes at the same time, multigene testing allows for the inclusion of multiple susceptibility genes simultaneously.[7] This is important to note because emerging evidence suggests a role for newly identified genes included on multigene panels that may be associated with increased risk of CRC or adenomatous polyposis.[16,17] However, an underrecognition of clinical criteria used to identify individuals with hereditary CRC syndromes may lead to incomplete risk assessments and subsequent inappropriate or insufficient surveillance recommendations. The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetic/Familial High-Risk Assessment: Colorectal provide recommendations for the assessment and management of patients with high-risk syndromes. These NCCN Guidelines Insights highlight important updates and summarize criteria for the evaluation of hereditary CRC syndromes, including colorectal polyposis syndromes and Lynch syndrome, and considerations for the use of multigene testing in the assessment of hereditary CRC syndromes.

Assessment of Risk for Hereditary CRC Syndromes

The NCCN Genetic/Familial High-Risk Assessment: Colorectal Panel recommends a stepwise approach to risk assessment for hereditary CRC syndromes (see HRS-1, facing page), which should include genetic counseling and patient education by a professional who has expertise and experience in cancer genetics if the assessment identifies factors associated with increased risk. The 2019 update included a section on principles of cancer risk assessment and counseling for individuals with potentially increased risk, which can guide shared decision-making regarding the need for genetic testing (see the complete version of these guidelines at NCCN.org).

Criteria for Evaluation of Polyposis Syndromes

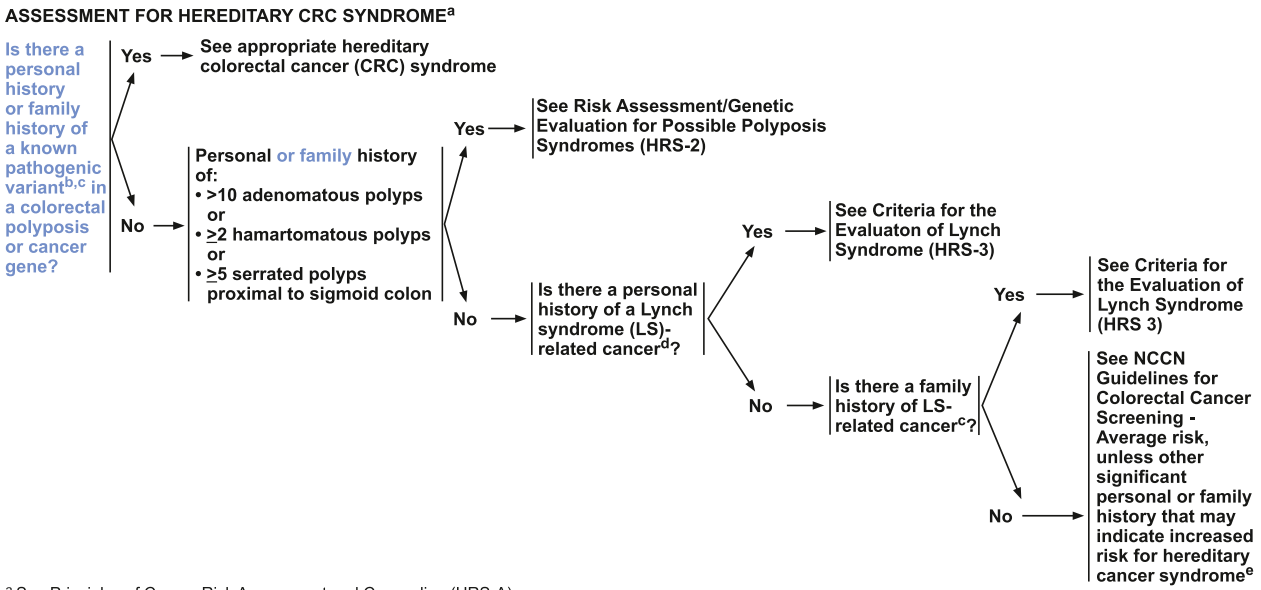
Previously identified polyposis syndromes include FAP, attenuated FAP (AFAP), MAP, and other rare genetic causes of multiple adenomatous polyps. Emerging data suggest that alterations in several other genes, including *AXIN2*, *GREM1*, *NTHL1*, *POLE*, *POLD1*, and *MSH3*, may contribute to some cases of adenomatous polyposis and increase CRC risk.[16] If there is no personal or family history of a known pathogenic variant in a colorectal polyposis or cancer gene, the patient's personal or family history of any of the following should trigger evaluation for a possible polyposis syndrome:

- >10 adenomatous polyps in a lifetime
- ≥2 hamartomatous polyps
- ≥5 serrated polyps proximal to the sigmoid colon

The panel recommends that individuals meeting any of the above criteria undergo detailed risk assessment and genetic evaluation for potential polyposis syndromes (see HRS-2, page 1036). The presence of >10 adenomas may be linked to FAP, AFAP, MAP, and rare genetic causes of multiple adenomatous polyps; the presence of ≥2 hamartomatous polyps may be associated with PJS, JPS, or Cowden syndrome/PHTS; and the presence of ≥5 serrated polyps proximal to the sigmoid colon may be associated with serrated polyposis syndrome.

Criteria for Evaluation of Lynch Syndrome

Lynch syndrome is one of the most common genetically determined predisposition syndromes, accounting for 2% to 4% of all CRC cases[8,18–20] and 2% to 3% of endometrial cancer cases.[21,22] Lynch syndrome results from a germline mutation in 1 of 4 DNA mismatch repair (MMR) genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*).[23] Deletions in the *EPCAM* gene, which lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing, also cause Lynch syndrome.[24,25] Individuals with Lynch syndrome are at increased risk for metachronous colon



[a] See Principles of Cancer Risk Assessment and Counseling (HRS-A).
[b] Pathogenic variant includes likely pathogenic variant. Slavin TP, Van Tongeren LR, Behrendt CE, et al. Prospective study of cancer genetic variants: Variation in rate of reclassification by ancestry. J Natl Cancer Inst 2018;110:1059-1066.
[c] Irrespective of degree of relatedness.
[d] LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, small intestinal cancers, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.
[e] Increased risk warranting genetic evaluation may be indicated by, but not restricted to personal or family history of congenital hypertrophy of the retinal pigment epithelium, osteomas, supernumerary teeth, desmoid tumor, cribriform variant of papillary thyroid cancer, brain cancer (usually medulloblastoma), and hepatoblastoma.

HRS-1

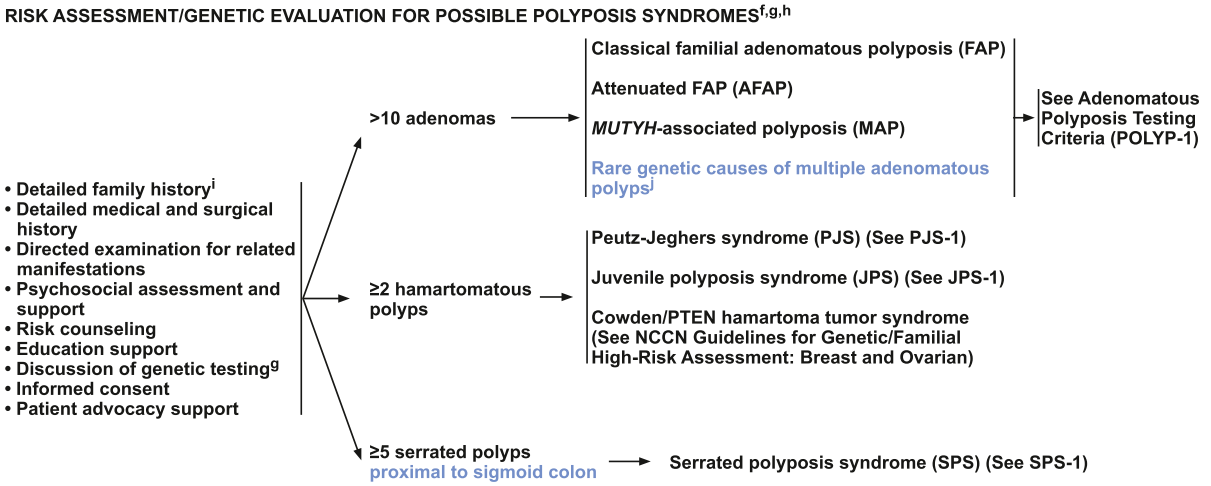
cancer and metachronous or synchronous extracolonic Lynch syndrome–related cancers. In addition to colon cancer, endometrial and ovarian cancers are the most common Lynch syndrome–associated cancers; less common associated cancers include gastric, pancreatic, biliary tract, ureter and renal pelvis, small intestine, and brain (usually glioblastoma), as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas, as seen in the Muir-Torre syndrome variant. Data are still emerging on whether Lynch syndrome consistently increases risk for breast and prostate cancer.[26–29] Identification of Lynch syndrome offers an opportunity for optimizing therapy and managing future risk for individuals with CRC or endometrial cancer, and for early detection and prevention of cancer for asymptomatic carriers of Lynch syndrome–associated mutations.

Available strategies for identification of Lynch syndrome have evolved over time. Historically, the Amsterdam criteria (I and II) were used to identify individuals who warrant further genetic testing (Table 1). These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.[32] Subsequently, the Bethesda Guidelines were developed to provide a broader clinical criteria for screening[33] (see Table 1). One study

Table 1. Revised Clinical/Pathologic Criteria to Identify Lynch Syndrome

Amsterdam II criteria[30]	Increased risk for Lynch syndrome in family with a proband unaffected by CRC or any other Lynch syndrome–associated cancer (eg, 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 affected • At least 1 Lynch syndrome–associated cancer diagnosed before age 50 years • Familial adenomatous polyposis excluded • Tumors verified through pathologic examination
Revised Bethesda criteria[31]	• CRC diagnosed before age 50 years • Synchronous or metachronous colorectal or other Lynch syndrome–associated tumor • CRC with microsatellite instability–high histology (ie, presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern) diagnosed before age 60 years • CRC in a patient with a family history of Lynch syndrome–associated cancer diagnosed before age 50 years • CRC diagnosed in >1 relative with Lynch syndrome–associated cancer, regardless of age

Abbreviation: CRC, colorectal cancer.

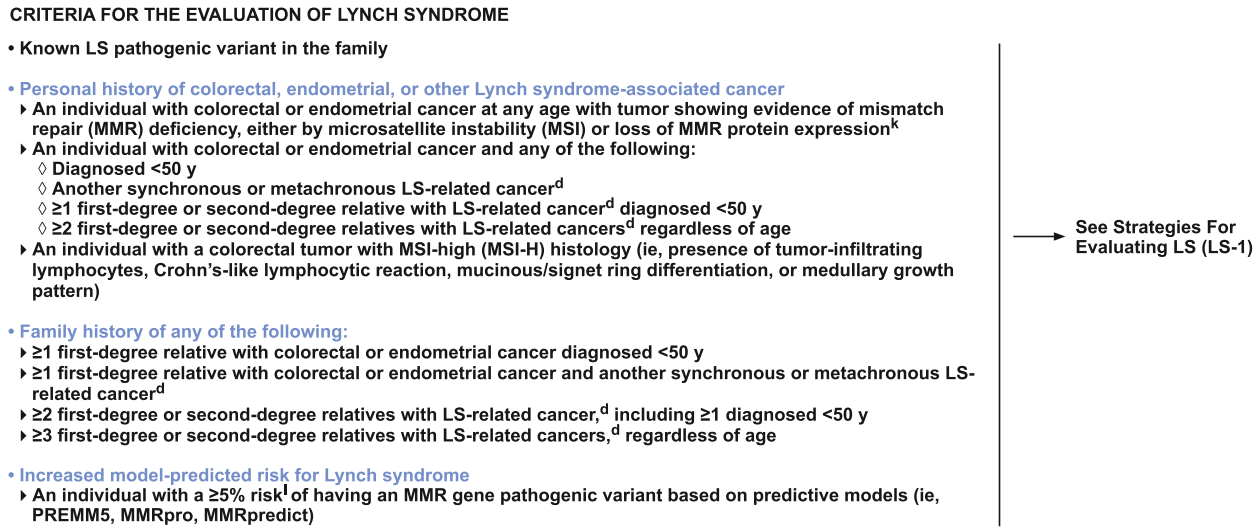


[f] See Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer (HRS-A 4 of 6).
[g] Genetic counseling/patient education is highly recommended when genetic testing is offered and after results are disclosed. A genetic counselor, medical geneticist, oncologist, gastroenterologist, surgeon, 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.
[h] If personal history of CRC and more than one syndrome might explain the presentation, consider multi-gene testing.
[i] If evaluation is based on family history of ≥1 relative with polyposis, then type of polyps in the affected relative (if known) may guide testing.
[j] Gene mutations associated with adenomatous polyposis include, but are not limited to monoallelic mutations in *GREM1*, *POLE*, *POLD1*, *AXIN2*, and biallelic mutations in *NTHL1* and *MSH3*.

HRS-2

reported that *MLH1* and *MSH2* mutations were detected in 65% of patients with MSI of colon cancer tissue who met the Bethesda criteria.[34] 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.[35] 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 fail to meet even the revised Bethesda criteria.[20] Indeed, the Amsterdam[30,36] and Bethesda[31,33] criteria, based on family and personal history of cancer alone, are limited as diagnostic tools for Lynch syndrome due to their relatively low sensitivity.[20,32,35,37,38]

To improve detection of individuals with Lynch syndrome, an alternative strategy, referred to as "universal tumor screening," is available in which all individuals newly diagnosed with CRC have either tumor-based MSI or immunohistochemistry testing for absence of DNA MMR proteins.[39–41] This approach provides a sensitivity of 100% (95% CI, 99.3%–100%) and specificity of 93.0% (95% CI, 92.0%–93.7%) for identifying individuals with Lynch syndrome.[39] An alternative approach is to test all patients with CRC diagnosed prior to age 70 years plus those diagnosed at older ages who meet the Bethesda criteria.[39] This approach gave a sensitivity of 95.1% (95% CI, 89.8%–99.0%) and 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. Expanding universal screening to include endometrial cancers has also been shown to improve the detection of Lynch syndrome.[42] Cost-effectiveness of universal screening has been established and has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention Working Group at the CDC, the US Multi-Society Task Force on Colorectal Cancer, and ESMO.[43–47] With minor qualifications, ASCO also endorses the ESMO guidelines.[48] Based on this considerable evidence and consensus to support implementation, the NCCN panel recommends universal tumor testing of individuals with CRC or endometrial cancer as a primary strategy for screening for Lynch syndrome. To complement this approach, the NCCN panel also identifies personal and family history criteria that can help identify individuals at increased risk for Lynch syndrome. Specific strategies recommended by the NCCN panel for identifying individuals with Lynch syndrome, based on either universal screening or personal/family cancer history criteria, are outlined.



[d] LS-related cancers include colorectal, endometrial, gastric, ovarian, pancreas, ureter and renal pelvis, brain (usually glioblastoma), biliary tract, small intestinal cancers, as well as sebaceous adenomas, sebaceous carcinomas, and keratoacanthomas as seen in Muir-Torre syndrome.
[k] The panel recommends tumor screening for MMR deficiency for all colorectal and endometrial cancers regardless of age at diagnosis; however, germline genetic testing is generally reserved for patients with early age at diagnosis; positive family history; or abnormal tumor testing results: MSI or loss of MMR protein expression. See LS-A for details on tumor screening for Lynch syndrome.
[l] There are recent data that resulted in a lower threshold of ≥2.5% for the PREMM5 predictive model risk for having an MMR gene pathogenic variant. Based on these data, it is reasonable for testing to be done based on the ≥2.5% score result and clinical judgment. Of note, with the lower threshold, there is an increase in sensitivity, but a decrease in specificity. It is not known how this applies to the general population of unaffected individuals.

HRS-3

Personal and Family History of CRC, Endometrial, or Other Lynch Syndrome–Associated Cancer

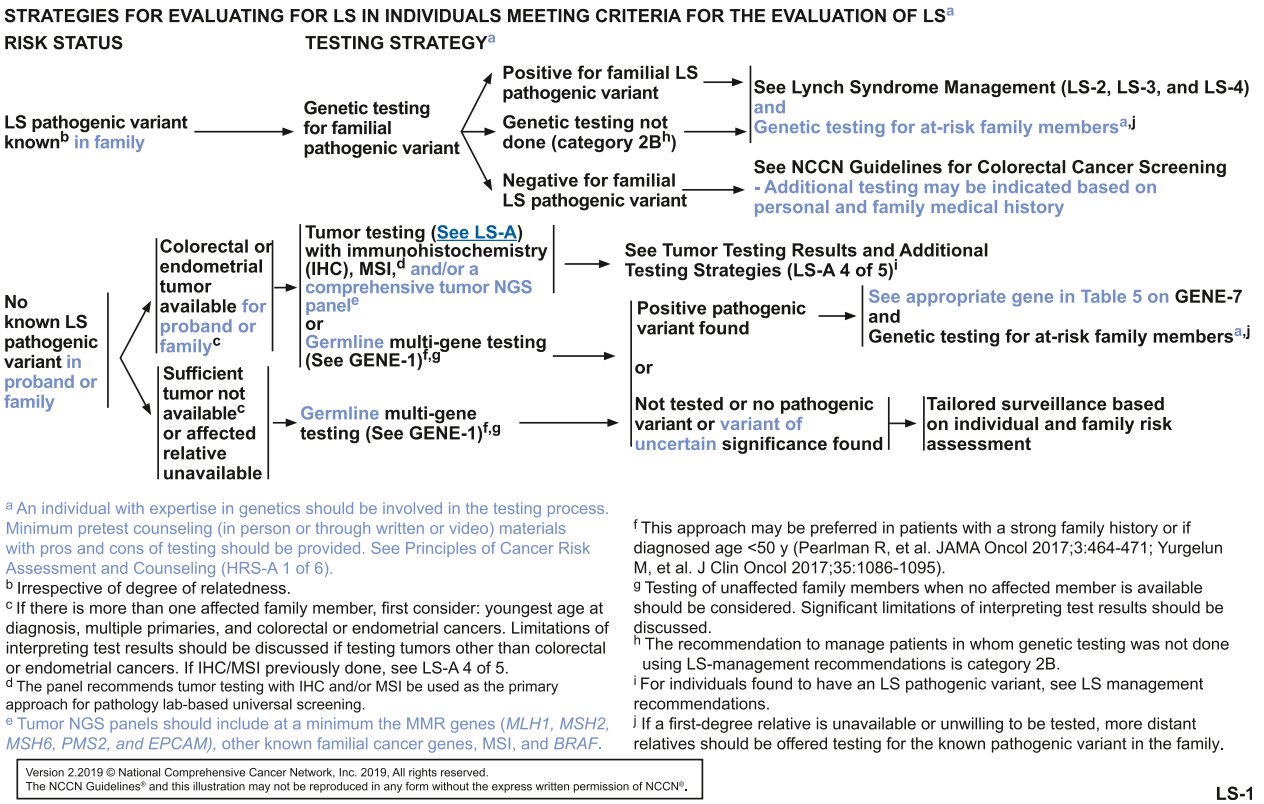
The panel recommends universal screening of all patients with CRC or endometrial cancer at any age with tumor showing evidence of MMR deficiency, either by MSI or loss of MMR protein expression, to maximize sensitivity for Lynch syndrome detection and simplify care processes.

Further genetic testing is recommended based on results of MSI and/or immunohistochemistry for DNA MMR proteins, as well as family and personal history of cancer (see LS-1 and LS-A 4 of 5, pages 1038 and 1039). The panel emphasized the importance of implementing a program for universal screening that includes a systematic method to identify those who are eligible for Lynch syndrome screening, a process for providing pretest counseling, standard methods for administering the tests and reporting their results, and a mechanism for follow-up of the results so that appropriate cancer prevention recommendations based on the test results, family history, and personal history are provided. Successful universal Lynch syndrome screening programs may require an interdisciplinary team that includes a cancer genetics expert along with the relevant specialty providers, including those from primary care, gastroenterology, surgery, oncology, pathology, and potentially others.[49]

Among individuals with a personal history of CRC or endometrial cancer, the panel provided the following additional criteria for the evaluation of Lynch syndrome (see HRS-3, above):

- An individual with CRC or endometrial cancer and any of the following:
  - Diagnosed at age <50 years
  - Another synchronous or metachronous Lynch syndrome–related cancer
  - ≥1 first- or second-degree relatives with Lynch syndrome–related cancer diagnosed at age <50 years
  - ≥2 first- or second-degree relatives with Lynch syndrome–related cancers, regardless of age
- An individual with colorectal tumor with histology typically associated with MSI-high (ie, presence of tumor-infiltrating lymphocytes, Crohn's-like lymphocytic reaction, mucinous/signet ring differentiation, or medullary growth pattern)

Among individuals with a family history of CRC, endometrial, or other Lynch syndrome–associated cancer, the following are recommended as criteria for the evaluation of Lynch syndrome (see HRS-3, above):



[a] An individual with expertise in genetics should be involved in the testing process. Minimum pretest counseling (in person or through written or video) materials with pros and cons of testing should be provided. See Principles of Cancer Risk Assessment and Counseling (HRS-A 1 of 6).
[b] Irrespective of degree of relatedness.
[c] 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 4 of 5.
[d] The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology lab-based universal screening.
[e] Tumor NGS panels should include at a minimum the MMR genes (*MLH1, MSH2, MSH6, PMS2, and EPCAM*), other known familial cancer genes, MSI, and *BRAF*.
[f] This approach may be preferred in patients with a strong family history or if diagnosed age <50 y (Pearlman R, et al. JAMA Oncol 2017;3:464-471; Yurgelun M, et al. J Clin Oncol 2017;35:1086-1095).
[g] Testing of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.
[h] The recommendation to manage patients in whom genetic testing was not done using LS-management recommendations is category 2B.
[i] For individuals found to have an LS pathogenic variant, see LS management recommendations.
[j] If a first-degree relative is unavailable or unwilling to be tested, more distant relatives should be offered testing for the known pathogenic variant in the family.

LS-1

- ≥1 first-degree relative with CRC or endometrial cancer diagnosed at age <50 years
- ≥1 first-degree relative with CRC or endometrial cancer and another synchronous or metachronous Lynch syndrome–related cancer
- ≥2 first- or second-degree relatives with Lynch syndrome–related cancer, including ≥1 diagnosed at age <50 years
- ≥3 first- or second-degree relatives with Lynch syndrome–related cancers, regardless of age

In addition to these criteria, the panel has recommended that individuals with increased risk for Lynch syndrome based on clinical prediction models should also receive further evaluation. 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.[32,50–52] These models provide probabilities of mutations and/or of the development of future cancers based on family and personal history. The $PREMM_5$ model can be applied online at https://premm.dfci.harvard.edu/ and the MMRPredict model is available at hnpccpredict.hgu.mrc.ac.uk/. MMRpro is available for free download at www4.utsouthwestern.edu/breasthealth/cagene/. Using a cutoff of 5%, one study suggests that both $PREMM_5$ and MMRPredict are effective at predicting an individual's risk of carrying MMR mutations, but they may be less effective at identifying individuals with *PMS2* mutations.[53] A study evaluating the performance of the $PREMM_5$ prediction model relative to the previous model, $PREMM_{1,2,6}$, found that $PREMM_5$ quantified the risk to an individual of carrying MMR gene mutations at a threshold of ≥2.5%, suggesting that testing can be performed based on this score threshold.[54] It is worth noting that at a threshold of ≥2.5%, there is an increase in sensitivity but a decrease in specificity. Furthermore, performance of the model in more usual care settings (eg, in consecutive primary care patients) has not been established, causing uncertainty as to whether sensitivity and particularly specificity would be similar to those observed in higher-risk populations. Regarding predictive models, the current criteria recommended by the panel for the evaluation of Lynch syndrome include (see HRS-3, page 1037) an individual with a ≥5% risk of having an MMR gene pathogenic variant based on predictive models ($PREMM_5$,[54] MMRpro, MMRPredict).

The panel notes that it is reasonable for testing to be conducted based on a $PREMM_5$ score of ≥2.5% and clinical judgment. Individuals not meeting any of

TUMOR TESTING RESULTS AND ADDITIONAL TESTING STRATEGIES[j]

Tumor Testing[a]							Plausible Etiologies	Additional Testing[d,e] NOTE: If younger than age 50 regardless of LS test results, consider genetic evaluation
IHC				MSI	*BRAF* V600E[b]	MLH1 Promoter Methylation		
MLH1	*MSH2*	*MSH6*	*PMS2*					
NL	NL	NL	NL	MSS/MSI-Low	N/A	N/A	1) Sporadic cancer 2) Other (not LS hereditary CRC syndrome)	1) None[c]
NL	NL	NL	NL	MSI-High	N/A	N/A	1) Germline pathogenic variant 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 pathogenic variant 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]
AB	NL	NL	AB	N/A	N/A	N/A	1) Sporadic cancer 2) Germline *MLH1* pathogenic variant or rarely *PMS2*	1) Consider *BRAF* pathogenic variant testing[b]/MLH1 promoter methylation 2) Germline LS genetic testing[f]
AB	NL	NL	AB	N/A	Positive	N/A	1) Sporadic cancer 2) Rarely germline *MLH1* pathogenic variant or constitutional *MLH1* epimutation	1) None, unless young age of onset or significant family history; then consider constitutional *MLH1* epimutation testing[g] and/or germline LS genetic testing[f]
AB	NL	NL	AB	N/A	Negative	Positive	1) Sporadic cancer 2) Rarely germline *MLH1* pathogenic variant or constitutional *MLH1* epimutation	
AB	NL	NL	AB	N/A	Negative	Negative	1) Germline *MLH1* pathogenic variant or rarely *PMS2* *2)* Sporadic cancer	1) Germline LS genetic testing[f] 2) If germline testing negative, consider somatic MMR genetic testing[h]
NL	AB	AB	NL	N/A	N/A	N/A	1) Germline *MSH2*/*EPCAM* pathogenic variant; or rarely germline *MSH6* pathogenic variant *2)* Sporadic cancer	
NL	NL	NL	AB	N/A	N/A	N/A	1) Germline *PMS2* pathogenic variant 2) Germline *MLH1* pathogenic variant 3) Sporadic cancer	
NL	AB	NL	NL	N/A	N/A	N/A	1) Germline *MSH2*/*EPCAM* pathogenic variant 2) Sporadic cancer	
NL	NL	AB	NL	N/A	N/A	N/A	1) Germline *MSH6* pathogenic variant 2) Germline *MSH2* pathogenic variant 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]
AB	NL	NL	NL	N/A	N/A	N/A	1) Sporadic cancer; 2) Germline *MLH1* pathogenic variant; 3) Germline *PMS2* pathogenic variant; 4) Somatic *MLH1* or *PMS2* pathogenic variant	1) *BRAF* pathogenic variant testing[b]/MLH1 promoter methylation; 2) if *BRAF*/*MLH1* methylation testing normal, germline LS genetic testing including at least the *MLH1* and *PMS2* genes; 3) If germline testing negative, consider somatic MMR sequencing of the tumor DNA
AB	AB	AB	AB	N/A	N/A	N/A	1) Germline pathogenic variant in *any* LS gene 2) Sporadic cancer	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 = Either testing was not done or results may not influence testing strategy; NL = Normal presence of positive protein staining; AB-= Abnormal/Absence (negative) protein staining

Footnotes **LS-A 4 OF 5**

the outlined criteria may be considered to have average or moderate risk for CRC, based on family history of CRC or advanced adenomas in first-degree relatives. Increased risk warranting genetic evaluation may be indicated by, but not restricted to, personal or family history of congenital hypertrophy of the retinal pigment epithelium, osteomas, supernumerary teeth, desmoid tumor, cribriform variant of papillary thyroid cancer, brain cancer (typically medulloblastoma), and hepatoblastoma.

Conclusions and Future Considerations

Comprehensive hereditary assessment is needed to identify individuals who have pathogenic variants that contribute to increased CRC risk.[7,55] The panel recommends a stepwise approach, which includes genetic counseling, using the outlined criteria based on the individual's personal and family history. During the 2019 panel review, members discussed a number of important updates to the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, including clarifying the initial approach to assessing hereditary CRC syndromes, the approach to identifying individuals with rare genetic causes of multiple adenomatous polyps, and the criteria for the evaluation of Lynch syndrome.

The panel recognized several future opportunities for research that might help inform and optimize future recommendations. Although the goal of universal tumor screening is to identify individuals at risk for Lynch syndrome, implementation of this practice has been slow, and risk assessment and referral for hereditary CRC syndromes is not widely used[55–58]; strategies to improve implementation are needed. It is also unclear whether all patients with a personal history of cancer should be offered multigene testing to screen for both Lynch syndrome and other potential hereditary causes. Research in this area is relevant now that the cost of multigene testing has become competitive with the cost of tumor-based testing (eg, with immunohistochemistry), because germline testing with blood or saliva may be convenient relative to organizing tumor-based testing, and because broader multigene testing might allow for increased opportunities for personalized prevention.[59,60]

Another area ripe for further development is whether less restrictive criteria should be used to refer patients for testing for Lynch syndrome and other causes of hereditary CRC risk. For example, for patients with a family history of CRC or endometrial cancer, the panel currently recommends evaluation for Lynch syndrome based on age of onset and number of cancers among family members. Less restrictive criteria (such as having any

family history of CRC) might improve identification of pathogenic mutation carriers but would have broad public health implications, because up to 10% of the population has a family history of CRC. Similarly, a less restrictive threshold for recommending evaluation for Lynch syndrome based on clinical prediction models could be recommended, but the impact on the general population in terms of number who would have a score triggering further evaluation requires further study. The panel also recognized a need for more evidence to inform the threshold for recommending genetic testing for adenomatous polyposis syndromes (eg cumulative >10 vs >20 lifetime adenomas), and a need for more observational research on the natural history of cancer risk among carriers of more recently identified CRC risk genes.

Ultimately, future research has great potential to further clarify and optimize the best strategies for identifying individuals at increased hereditary risk for CRC, and the best approaches to cancer risk reduction for those with identified pathogenic variants and CRC syndromes.

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2019. CA Cancer J Clin 2019;69:7–34.
2. Jasperson KW, Tuohy TM, Neklason DW, et al. Hereditary and familial colon cancer. Gastroenterology 2010;138:2044–2058.
3. Lichtenstein P, Holm NV, Verkasalo PK, et al. Environmental and heritable factors in the causation of cancer—analyses of cohorts of twins from Sweden, Denmark, and Finland. N Engl J Med 2000;343:78–85.
4. Rustgi AK. The genetics of hereditary colon cancer. Genes Dev 2007;21: 2525–2538.
5. Taylor DP, Burt RW, Williams MS, et al. Population-based family history-specific risks for colorectal cancer: a constellation approach. Gastroenterology 2010;138:877–885.
6. Committee opinion no. 634: hereditary cancer syndromes and risk assessment. Obstet Gynecol 2015;125:1538–1543.
7. Ballester V, Cruz-Correa M. How and when to consider genetic testing for colon cancer? Gastroenterology 2018;155:955–959.
8. Lynch HT, de la Chapelle A. Hereditary colorectal cancer. N Engl J Med 2003;348:919–932.
9. Samadder NJ, Baffy N, Giridhar KV, et al. Hereditary cancer syndromes—a primer on diagnosis and management, part 2: gastrointestinal cancer syndromes. Mayo Clin Proc 2019;94:1099–1116.
10. Shaco-Levy R, Jasperson KW, Martin K, et al. Gastrointestinal polyposis in Cowden syndrome. J Clin Gastroenterol 2017;51:e60–e67.
11. Boursi B, Sella T, Liberman E, et al. The APC p.I1307K polymorphism is a significant risk factor for CRC in average risk Ashkenazi Jews. Eur J Cancer 2013;49:3680–3685.
12. Locker GY, Kaul K, Weinberg DS, et al. The I1307K APC polymorphism in Ashkenazi Jews with colorectal cancer: clinical and pathologic features. Cancer Genet Cytogenet 2006;169:33–38.
13. Bellido F, Pineda M, Aiza G, et al. POLE and POLD1 mutations in 529 kindred with familial colorectal cancer and/or polyposis: review of reported cases and recommendations for genetic testing and surveillance. Genet Med 2016;18:325–332.
14. Esteban-Jurado C, Giménez-Zaragoza D, Muñoz J, et al. POLE and POLD1 screening in 155 patients with multiple polyps and early-onset colorectal cancer. Oncotarget 2017;8:26732–26743.
15. Carballal S, Rodríguez-Alcalde D, Moreira L, et al. Colorectal cancer risk factors in patients with serrated polyposis syndrome: a large multicentre study. Gut 2016;65:1829–1837.
16. Gupta S, Provenzale D, Regenbogen SE, et al. NCCN Guidelines Insights: Genetic/Familial High-Risk Assessment: Colorectal, Version 3.2017. J Natl Compr Canc Netw 2017;15:1465–1475.
17. Yurgelun MB, Allen B, Kaldate RR, et al. Identification of a variety of mutations in cancer predisposition genes in patients with suspected Lynch syndrome. Gastroenterology 2015;149:604–613.e20.
18. 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.
19. 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.
20. 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.
21. Buchanan DD, Rosty C, Clendenning M, et al. Clinical problems of colorectal cancer and endometrial cancer cases with unknown cause of tumor mismatch repair deficiency (suspected Lynch syndrome). Appl Clin Genet 2014;7:183–193.
22. 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.
23. Boland CR, Goel A. Microsatellite instability in colorectal cancer. Gastroenterology 2010;138:2073–2087.e3.
24. 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.
25. 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.
26. Baglietto L, Lindor NM, Dowty JG, et al. Risks of Lynch syndrome cancers for MSH6 mutation carriers. J Natl Cancer Inst 2010;102:193–201.
27. 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.
28. Møller P, Seppälä TT, Bernstein I, et al. Cancer risk and survival in path_MMR carriers by gene and gender up to 75 years of age: a report from the Prospective Lynch Syndrome Database. Gut 2018;67: 1306–1316.
29. Ryan S, Jenkins MA, Win AK. Risk of prostate cancer in Lynch syndrome: a systematic review and meta-analysis. Cancer Epidemiol Biomarkers Prev 2014;23:437–449.
30. Vasen HF, Watson P, Mecklin JP, et al. New clinical criteria for hereditary nonpolyposis colorectal cancer (HNPCC, Lynch syndrome) proposed by the International Collaborative Group on HNPCC. Gastroenterology 1999;116:1453–1456.
31. 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.
32. 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.
33. 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.
34. 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.
35. Piñol 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.

36. Vasen HF, Mecklin JP, Khan PM, et al. The International Collaborative Group on Hereditary Non-Polyposis Colorectal Cancer (ICG-HNPCC). Dis Colon Rectum 1991;34:424–425.
37. Green RC, Parfrey PS, Woods MO, et al. Prediction of Lynch syndrome in consecutive patients with colorectal cancer. J Natl Cancer Inst 2009;101: 331–340.
38. Sjursen W, Haukanes BI, Grindedal EM, et al. Current clinical criteria for Lynch syndrome are not sensitive enough to identify MSH6 mutation carriers. J Med Genet 2010;47:579–585.
39. Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555–1565.
40. Mvundura M, Grosse SD, Hampel H, et al. The cost-effectiveness of genetic testing strategies for Lynch syndrome among newly diagnosed patients with colorectal cancer. Genet Med 2010;12:93–104.
41. Pérez-Carbonell L, Ruiz-Ponte C, Guarinos C, et al. Comparison between universal molecular screening for Lynch syndrome and revised Bethesda guidelines in a large population-based cohort of patients with colorectal cancer. Gut 2012;61:865–872.
42. Adar T, Rodgers LH, Shannon KM, et al. Universal screening of both endometrial and colon cancers increases the detection of Lynch syndrome. Cancer 2018;124:3145–3153.
43. Evaluation of Genomic Applications in Practice and Prevention (EGAPP) Working Group. 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.
44. 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.
45. 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.
46. Balmaña J, Balaguer F, Cervantes A, et al. Familial risk-colorectal cancer: ESMO Clinical Practice Guidelines. Ann Oncol 2013;24(Suppl 6):vi73–80.
47. 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.
48. 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.
49. 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.
50. Balmaña J, Stockwell DH, Steyerberg EW, et al. Prediction of MLH1 and MSH2 mutations in Lynch syndrome. JAMA 2006;296:1469–1478.
51. Chen S, Wang W, Lee S, et al. Prediction of germline mutations and cancer risk in the Lynch syndrome. JAMA 2006;296:1479–1487.
52. 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.
53. Goverde A, Spaander MCW, Nieboer D, et al. Evaluation of current prediction models for Lynch syndrome: updating the PREMM5 model to identify PMS2 mutation carriers. Fam Cancer 2018;17:361–370.
54. Kastrinos F, Uno H, Ukaegbu C, et al. Development and validation of the $PREMM_5$ model for comprehensive risk assessment of Lynch syndrome. J Clin Oncol 2017;35:2165–2172.
55. Idos G, Gupta S. When should patients undergo genetic testing for hereditary colon cancer syndromes? Clin Gastroenterol Hepatol 2018;16: 181–183.
56. Beamer LC, Grant ML, Espenschied CR, et al. Reflex immunohistochemistry and microsatellite instability testing of colorectal tumors for Lynch syndrome among US cancer programs and follow-up of abnormal results. J Clin Oncol 2012;30:1058–1063.
57. Cragun D, DeBate RD, Vadaparampil ST, et al. Comparing universal Lynch syndrome tumor-screening programs to evaluate associations between implementation strategies and patient follow-through. Genet Med 2014; 16:773–782.
58. Shaikh T, Handorf EA, Meyer JE, et al. Mismatch repair deficiency testing in patients with colorectal cancer and nonadherence to testing guidelines in young adults. JAMA Oncol 2018;4:e173580.
59. Pearlman R, Frankel WL, Swanson B, et al. Prevalence and spectrum of germline cancer susceptibility gene mutations among patients with early-onset colorectal cancer. JAMA Oncol 2017;3:464–471.
60. Yurgelun MB, Kulke MH, Fuchs CS, et al. Cancer susceptibility gene mutations in individuals with colorectal cancer. J Clin Oncol 2017;35: 1086–1095.