NCCN

Colorectal Cancer Screening

Clinical Practice Guidelines in Oncology

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Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. In 2012, an estimated 102,480 new cases of colon cancer and 40,340 new cases of rectal cancer will occur in the United States. During the same year, an estimated 50,830 people will die of colon and rectal cancers.¹ Importantly, the incidence of colon and rectal cancers per 100,000 decreased from 60.5 in 1976 to 46.4 in 2005.² The incidence of CRC continued to trend downward, with an average annual percentage change of -2.7% in men and -2.1% in women from 2004 to 2008.³ In addition, mortality from CRC de-

Abstract

Mortality from colorectal cancer can be reduced by early diagnosis and by cancer prevention through polypectomy. These NCCN Guidelines for Colorectal Cancer Screening describe various colorectal screening modalities and recommended screening schedules for patients at average or increased risk of developing colorectal cancer. In addition, the guidelines provide recommendations for the management of patients with high-risk colorectal cancer syndromes, including Lynch syndrome. Screening approaches for Lynch syndrome are also described. (*JNCCN* 2013;11:1538–1575)

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.

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 Colorectal Cancer Screening are not printed in this issue of JNCCN but can be accessed online at NCCN.org.**

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Disclosures for the NCCN Colorectal Cancer Screening 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 Colorectal Cancer Screening Panel members can be found on page 1575. (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.

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creased by almost 35% from 1990 to 2007,⁴ likely because of earlier diagnosis through screening and better treatment modalities. Currently, patients with stage I localized colon cancer have a 96% relative 5-year survival rate.⁵

CRC often occurs sporadically, but familial cancer syndromes are also commonly associated with this disease. Genetic susceptibility to CRC includes well-defined inherited syndromes such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer [HNPCC]), familial adenomatous polyposis (FAP), and *MutY human homolog*-associated polyposis (MAP). Other entities include Muir-Torres, Turcot, Gardner, Cowden, Bannayan-Riley-Ruvalcaba, Peutz-Jeghers, and juvenile polyposis syndromes, and serrated polyposis syndrome (SPS).⁶⁻⁸

CRC mortality can be reduced through early diagnosis and cancer prevention via polypectomy.⁹⁻¹¹ Hence, the goals of CRC screening are to detect cancer at an early, curable stage and to detect and remove adenomatous polyps. According to the Centers for Disease Control and Prevention (CDC), the screening rate among US adults aged 50 to 75 years has increased from approximately 42% in 2000 to 59% in 2010.¹²

These guidelines describe various colorectal screening modalities and recommended screening schedules for patients at average or increased risk of developing CRC. In addition, the guidelines provide recommendations for the management of patients with high-risk syndromes, including Lynch syndrome, FAP, MAP, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and SPS.

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RISK ASSESSMENT FOR COLORECTAL CANCER

Average risk:^a

- Age ≥50 y
- No history of adenoma or colorectal cancer (CRC)
- No history of inflammatory bowel disease
- Negative family history

→ See Average-Risk Screening and Evaluation (CSCR-2)

Increased risk:

- Personal history

➤ Adenoma/sessile serrated polyp (SSP)^b → See Follow-up of Clinical Findings: Adenomatous Polyp or Sessile Serrated Polyp (CSCR-3)

➤ CRC → See Increased Risk Screening Based on Personal History of Colorectal Cancer (CSCR-4)

➤ Inflammatory bowel disease (ulcerative colitis, Crohn disease) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-5)

• Positive family history → See Increased Risk Screening Based on Positive Family History (CSCR-6)

High-risk syndromes:

- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC]) (LS-1)
- Polyposis syndromes
 - Classical familial adenomatous polyposis (FAP-1)
 - Attenuated familial adenomatous polyposis (AFAP-1)
 - MUTYH-associated polyposis (MAP-1)
 - Peutz-Jeghers syndrome (PJS-1)
 - Juvenile polyposis syndrome (JPS-1)
 - Serrated polyposis syndrome (SPS-1) (rarely inherited)
- Cowden syndrome
- Li-Fraumeni syndrome

→ See Criteria for Further Risk Evaluation for High-Risk Syndromes (HRS-1)

→ See NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Genetics/Familial High-Risk Assessment: Breast and Ovarian*

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

^aSee Discussion for further information on age of screening in African Americans.

^bSSP is synonymous with sessile serrated adenoma but does not include classical hyperplastic polyp.

CSCR-1

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^cSee Screening Modality and Schedule (CSCR-A).

^dCurrently there is not a consensus on the use of CT colonography as a primary screening modality, and it is evolving with regard to recommended/programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available suggest that, if CT colonography is negative/no polyps, then repeat CT colonography in 5 y, and if positive/polyps lesions, colonoscopy should be performed.

^eThere is direct evidence from randomized controlled trials that fecal occult blood testing (Mandel JS, et al. N Engl J Med 1993;328:1365-1371; Hardcastle JD, et al. Lancet 1996;348:1472-1477; Kronborg O, et al. Lancet 1996;348:1467-1471) and flexible sigmoidoscopy (Atkin WS, et al. Lancet 2010;375:1624-1633; Schoen RE, et al. N Engl J Med 2012;366:2345-2357) will reduce mortality from colorectal cancer. Given the available evidence from case control and cohort studies, however, it is the consensus opinion of the panel that colonoscopy should be the preferred method of screening, due to its potential ability to prevent colorectal cancer (with its associated morbidity) and cancer deaths (Kahi CJ, et al. Clin Gastroenterol Hepatol 2009;7:770-775; Baxter NN, et al. Ann Intern Med 2009;150:1-8).

^fIf colonoscopy is incomplete or preparation is suboptimal, consider other screening modality or repeat colonoscopy at discretion of physician.

^gEmerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening modality, but there are limited data to determine an interval between screening. Currently, stool DNA is not considered a primary screening modality.

^hRecent studies have demonstrated that FIT is more sensitive than guaiac-based testing.

ⁱSSPs are managed the same as adenomas. Rex et al. Am J Gastroenterol 2012;107:1315-1329.

^jControversy exists over whether SSPs should be called "sessile serrated adenomas." These terms are equivalent and these guidelines will use "SSPs." However, any serrated lesions in the proximal colon should be followed similarly to adenomatous polyps.

^kLeft-sided includes splenic flexure, descending colon, sigmoid colon, and rectum. Right-sided includes cecum, ascending colon, and transverse colon.

CSCR-2

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INCREASED RISK BASED ON PERSONAL HISTORY OF ADENOMATOUS POLYP OR SESSILE SERRATED POLYPⁱ

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

^cSee Screening Modality and Schedule (CSCR-A).

ⁱSSPs are managed the same as adenomas. Rex et al. Am J Gastroenterol 2012;107:1315-1329.

^lTen or fewer polyps in the setting of a strong family history or younger age (<40 y) may sometimes be associated with an inherited polyposis syndrome.

^mInk lesion for later identification, sterile carbon black ink preferred.

ⁿShorter intervals may be necessary when there is uncertainty about completeness of removal of large and/or sessile polyps or if the colonic preparation was suboptimal. Other factors in determining intervals might include the results of the prior examinations and the presence of comorbid conditions. Generally, the results of the first 2 screening examinations may predict the patient's overall colon cancer risk. (U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Service Task Force recommendation statement. Ann Intern Med 2008;149:627-637).

CSCR-3

Clinical trials: NCCN believes that the best management of any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged. All recommendations are category 2A unless otherwise indicated.

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INCREASED RISK BASED ON PERSONAL HISTORY OF COLORECTAL CANCER

RISK STATUS	TESTING	SURVEILLANCE
Personal history of CRC →	<ul style="list-style-type: none"> • Recommend Lynch syndrome (LS) screening at the time of diagnosis with either approach below: <ul style="list-style-type: none"> ➤ All CRC patients or ➤ CRC patients diagnosed at <70 y and also those ≥70 y who meet the Bethesda guidelines (See LS-B) • LS screening is done by:^o <ul style="list-style-type: none"> ➤ Microsatellite instability (MSI) testing and/or ➤ Immunohistochemistry (IHC) for the 4 mismatch repair proteins (MLH1, MSH2, MSH6, and PMS2) followed by BRAF testing or MLH1 promoter methylation testing if MLH1 is not expressed by IHC ➤ For patients with high MSI or abnormal IHC tumors that do not have a BRAF mutation or MLH1 promoter methylation, the patient should be referred to cancer genetics for follow-up counseling and further testing 	→ See NCCN Guidelines for Colon Cancer and See NCCN Guidelines for Rectal Cancer (to view the most recent versions of these guidelines, visit NCCN.org)

INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

RISK STATUS	INITIATION OF SCREENING	SCREENING MODALITY AND SCHEDULE	EVALUATION OF POSITIVE SCREENING FINDINGS	FOLLOW-UP OF CLINICAL FINDINGS ^{t,u}
Personal history of inflammatory bowel disease ^p <ul style="list-style-type: none"> • Ulcerative colitis • Crohn's disease, especially if pancolitis 	→ <ul style="list-style-type: none"> • 8-10 y after onset of symptoms of pancolitis^q • 12 y after onset of left-sided colitis^q 	→ <ul style="list-style-type: none"> • Colonoscopy every 1-2 y <ul style="list-style-type: none"> • When clinically quiescent, 4 quadrant biopsies every 10 cm with >30 total samples (preferred)^r • Additional extensive sampling of strictures and masses • Endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia 	→ <ul style="list-style-type: none"> • Dysplasia/intraepithelial neoplasia <ul style="list-style-type: none"> ➤ Confirmation by an expert GI pathologist is desirable • Sporadic colorectal adenoma^s 	→ Surgical consultation for resection ^v

^o See Principles of IHC and MSI Testing for Lynch Syndrome (LS-A).

^p Information regarding the value of endoscopic surveillance of long-standing Crohn disease is limited. Surveillance is at the discretion of the physician.

^q Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008;58:130-160.

^r Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy, narrow-band imaging, autofluorescence, or confocal endomicroscopy. Targeted biopsies have been found to improve detection of dysplasia, and should be considered for surveillance colonoscopies in patients with ulcerative colitis.

^s Patients with ulcerative colitis develop sporadic colorectal adenomas at the same rate as the general population. Lesions that appear endoscopically and histologically similar to a sporadic adenoma, with no dysplasia in the flat mucosa in the surrounding area or elsewhere in the colon and without invasive carcinoma in the polyp, can be treated safely by polypectomy and continued surveillance.

^t Optimal management of Crohn-related dysplasia remains undefined. Patient and physician preference should be considered. Extent of resection for Crohn-related dysplasia needs to be based on the individual findings.

^u Appropriate management of adenomatous polyps in the setting of ulcerative colitis is dependent on various factors and should be at the discretion of the treating physician.

^v See Definitions of Common Colorectal Resections (available online, in these guidelines, at NCCN.org [CSCR-B]).

CSCR-4/CSCR-5

INCREASED RISK BASED ON POSITIVE FAMILY HISTORY

FAMILY HISTORY CRITERIA ^{w,x}	SCREENING	
1 first-degree relative with CRC aged <50 y ^y or 2 first-degree relatives with CRC at any age ^y	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	Repeat every 3-5 y depending on individual family history ^{aa}
First-degree relative with CRC aged ≥50 y ^z	Colonoscopy beginning at age 50 y or 10 y before earliest diagnosis of CRC	Repeat every 5 y ^{aa,bb}
1 second-degree relative with CRC aged <50 y	Colonoscopy beginning at age 50 y	Repeat per colonoscopy findings
First-degree relative with advanced adenoma(s)	Colonoscopy beginning at age 50 y or at age of onset, whichever is first	Repeat per colonoscopy findings

^wSome combinations of affected first-, second-, and third-degree relatives may increase risk sufficiently to alter screening guidelines. 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.

^xIf a patient meets the criteria for an inherited colorectal syndrome, see Criteria for Further Risk Evaluation for High-Risk Syndromes (HRS-1).

^yIn this circumstance or if any one of the revised Bethesda criteria (see LS-B) are met, IHC/MSI testing should be performed on the colon tumor of the youngest family member with available colorectal cancer tissue. Also see Lynch syndrome guidelines (LS-1).

^zThe 50-59 y subgroup is associated with a somewhat higher risk than the >60 y group and requires more intensive risk assessment.

^{aa}Colonoscopy intervals should be further modified based on personal and family history as well as on individual preferences. Factors that modify colonoscopy intervals include specifics of the family history, including number and age of onset of affected second- and third-degree relatives; size of family; completeness of the family history; and participation in screening and colonoscopy findings in family members.

^{bb}Multiple (≥2) negative colonoscopies may support stepwise lengthening in the colonoscopy interval.

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SCREENING MODALITY AND SCHEDULE (1 of 3)

- Colon cancer prevention and early detection should be the primary goals of CRC screening.
- Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and by detecting and removing adenomas. It has also been shown to be cost-effective compared with other screening programs.
- Although patient preferences and availability of resources play an important role in the selection of screening options, tests that are designed to detect both early cancer and adenomatous polyps should be encouraged.

Screening modalities that detect adenomatous polyps and cancer^{1,2,3}

- Colonoscopy every 10 years,
- Flexible sigmoidoscopy every 5 years,
- CT colonography (CTC) every 5 years⁴

Screening modalities that primarily detect cancer^{1,2,3,5}

- Stool-based screening
 - Guaiac-based testing annually,
 - Immunochemical-based testing annually,
 - Stool DNA test with high sensitivity (interval for screening is uncertain)⁶

¹Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. *Gastroenterology* 2008;134:1570-1595.

²U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627-637.

³Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. *Am J Gastroenterol* 2009;104:739-750.

⁴Currently there is not a consensus on the use of CTC as a primary screening modality, and it is evolving with regards to recommended/ programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available suggest that if CTC is negative/no polyps, then repeat CTC in 5 years, and if CTC is positive/polyps lesions, colonoscopy should be performed.

⁵Annual stool-based testing with every-5-year flexible sigmoidoscopy can be used in combination for screening.

⁶Emerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening modality, but limited data are available to determine an interval between screening. Currently, stool DNA is not considered a primary screening modality, except in specific circumstances.

CSCR-A

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SCREENING MODALITY AND SCHEDULE (2 of 3)

Colonoscopy

- In the United States, colonoscopy is the primary method employed for CRC screening in average- and high-risk populations. However, screening with any of the available modalities is preferable to no screening.
- Caveats for the 10-year interval:
 - A 10-year interval is appropriate for average-risk patients who had an optimal procedure.
 - Shorter intervals may be indicated based on the quality and completeness of the colonoscopy.
 - Individual risk factors and physician judgment should be included in the interval determination.
 - The number and characteristics of polyps as well as family history and medical assessment should influence judgment regarding the interval between colonoscopies.
 - Colonoscopy has limitations and may not detect all cancers and polyps.
- Accumulating data suggest that there is substantial variability in the quality, and by extension, the clinical effectiveness of colonoscopy. Several quality indicators have been examined, such as withdrawal time. Quality indicators for colonoscopy are an important part of the fidelity of findings. Improving the overall impact of screening colonoscopy requires a programmatic approach that addresses quality issues at several levels. These colonoscopy quality indicators may include:
 - Cecal intubation rates
 - Withdrawal time
 - Adenoma detection rates
 - Appropriate intervals between endoscopic studies based on family and personal history and number and histologic type of polyps on last colonoscopy
 - Minor and major complication rates
 - Pre-procedure medical evaluation
 - Appropriate preparation instructions
- Standardized colonoscopy reports that contain, at a minimum:⁷
 - Patient demographic, clinical factors, adenoma and cancer history, and GI family history
 - Procedure indications
 - Endoscopic findings, including polyp number, size, location, and method of excision
 - Photographic documentation of endoscopic landmarks
 - Estimate of quality of bowel preparation
 - Documentation of follow-up planning, including pathology results
 - Sedation administered
 - Written communication of the findings and plans to the patient and referring physician is encouraged
- Pathology should also include polyp number, size, and location in addition to histopathology.

⁷Lieberman D, Nadel M, Smith RA, et al. Standardized colonoscopy reporting and data system: report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable. *Gastrointest Endosc* 2007;65:757-766.

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SCREENING MODALITY AND SCHEDULE (3 of 3)

Flexible sigmoidoscopy⁸

- May be performed alone or in combination with stool-based screening
- Issues surrounding sigmoidoscopy are similar to colonoscopy except the colon is only examined distal to the splenic flexure
- Recommended every 5 years for average-risk screening

Stool-based screening

- Annual stool occult blood testing should not be performed if colonoscopy is used as a screening measure in an average-risk patient.
- Guaiac-based, nonhydrated⁸
 - Requires 3 successive stool specimens annually (not via digital rectal examination), prescribed diet, and coordination by health care provider
 - Any positive test requires further evaluation
- Fecal immunochemical testing (FIT)
 - Detects human globin
 - Prescribed diet is not required
 - Many brands require only a single stool annually
 - Any positive test requires further evaluation
 - Recent studies have shown that FIT is more sensitive than guaiac-based testing^{9,10,11}

RadiographicCTC^{12,13,14}

- Accuracy
 - >10 mm lesions can be identified by CTC with an accuracy similar to colonoscopy
 - Lesions 5-9 mm can be identified with an acceptable accuracy that is less than that identified for colonoscopy
 - Lesions <5 mm cannot be identified with acceptable accuracy
- Follow-up of identified lesions
 - All identified lesions >5 mm should be referred for colonoscopy
 - When identified, lesions <5 mm generally do not need to be referred for colonoscopy
- The recommended performance interval of every 5 years is based solely on computer simulation models
- All visualized extracolonic findings should be described and recommendations should be provided as to appropriate follow-up
- The increased risk of cancer arising from the performance of a single CTC is estimated to be <0.14%
- CTC interpretation should be accomplished only by those trained according to American Gastroenterological Association¹² or American College of Radiology (ACR)¹³ guidelines
- Procedure quality should be tracked and assured using current ACR practice guidelines for patient preparation, image acquisition, study interpretation, and reporting

⁸Category 1 data show that guaiac-based fecal occult blood test (FOBT) and flexible sigmoidoscopy reduce mortality from colorectal cancer.

⁹Imperiale, TF. Noninvasive screening tests for colorectal cancer. Dig Dis 2012;30:16-26.

¹⁰Park DI, Ryu S, Kim YH, et al. Comparison of guaiac-based and quantitative immunochemical fecal occult blood testing in a population at average risk undergoing colorectal cancer screening. Am J Gastroenterol 2010;105:2017-2025.

¹¹Parra-Blanco A, Gimeno-García AZ, Quintero E, et al. Diagnostic accuracy of immunochemical versus guaiac faecal occult blood tests for colorectal cancer screening. J Gastroenterol 2010;45:703-712.

¹²See American Gastroenterological Association CT Colonography Standards (available at: Standards for Gastroenterologists for Performing and Interpreting Diagnostic Computed Tomographic Colonography; [www.gastrojournal.org/article/S0016-5085\(07\)0114-6/fulltext](http://www.gastrojournal.org/article/S0016-5085(07)0114-6/fulltext)).

¹³See American College of Radiology Practice Guideline for the Performance of Computed Tomography (CT) Colonography in Adults (available at: http://www.acr.org/~media/ACR/Documents/PGTS/guidelines/CT_Colonography.pdf).

¹⁴Currently there is not a consensus on the use of CT colonography as a primary screening modality, and it is evolving with regards to recommended/programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available suggest that if CT colonography is negative/no polyps, then repeat CT colonography in 5 years, and if CT colonography is positive/polyps lesions >5 mm, colonoscopy should be performed.

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HIGH-RISK SYNDROMES

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CRITERIA FOR FURTHER RISK
EVALUATION FOR HIGH-RISK
SYNDROMES

Individual meeting the revised Bethesda guidelines^a (See LS-B)

or

Individual from a family meeting Amsterdam criteria (See LS-C)

or

>10 adenomas in same individual (See APC/MUTYH-1*)

or

Individual with multiple GI hamartomatous polyps (See PJS-1* and JPS-1*) or serrated polyposis syndrome (See SPS-1*)

or

Individual from a family with a known high-risk syndrome associated with CRC, with or without a known mutation (See appropriate high-risk syndrome)

or

Individual with a desmoid tumor

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)Peutz-Jeghers syndrome (PJS)^d (See PJS-1*)Juvenile polyposis syndrome (JPS)^d (See JPS-1*)

Serrated polyposis syndrome (SPS) (See SPS-1*)

No syndromes, but familial risk present

See APC and *MUTYH* Genetic Testing Criteria (APC/MUTYH-1*)

See Positive Family History (CSCR-6) or Colonic Adenomatous Polyposis of Unknown Etiology (CPUE-1*)

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

^aEndometrial cancer <50 y is not included in the revised Bethesda guidelines; however recent, evidence suggests that these individuals should be evaluated for LS.

^bSee Obtaining a Comprehensive Assessment for Hereditary Colorectal Cancer (HRS-A*).

^cA genetic counselor and/or medical geneticist should be involved early in counseling patients who (potentially) meet criteria for an inherited syndrome. Genetic counseling is advised when genetic testing is offered.

^dReferral to a specialized team is recommended.

HRS-1

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LYNCH SYNDROME

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^aIHC and/or MSI screening of all colorectal and endometrial cancers, regardless of age at diagnosis or family history, has been implemented at some centers to identify individuals at risk for LS. This approach was recently endorsed for colorectal cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost-effective (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). An infrastructure needs to be in place to handle the screening results.

^bIf 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.

^cFor individuals found to have a deleterious LS mutation, see LS surveillance recommendations (LS-2 and LS-3). In addition, individuals with loss of *MSH2* and/or *MSH6* protein expression via immunohistochemistry, regardless of germline mutation status, should be followed as though they have LS.

^dTesting of unaffected family members when no affected member is available should be considered. Significant limitations of interpreting test results should be discussed.

^eAn 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.

LS-1

LYNCH SYNDROME

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SURVEILLANCE FOR MLH1 AND MSH2 MUTATION CARRIERS^{f,g}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; however, at this time the data are not sufficiently robust to make a recommendation for its standard use.

Extracolonic:

- 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.
 - No clear evidence supports screening for endometrial cancer for LS. However, annual office endometrial sampling is an option.
 - Although 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 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.
- Gastric and small bowel cancer: No clear evidence supports screening for gastric, duodenal, and small bowel cancer for LS. Selected individuals or families or those of Asian descent^h may consider esophagogastroduodenoscopy with extended duodenoscopy (to distal duodenum or into the jejunum) every 3-5 y beginning at age 30-35 y.
- Urothelial cancer: Consider annual urinalysis starting at 25-30 y.
- Central nervous system cancer: Annual physical 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, due to limited data, no screening recommendation is possible at this time.

→ See Follow-up
of Surveillance
Findings (LS-4)

SURVEILLANCE FOR MSH6 AND PMS2 MUTATION CARRIERS^fMSH6

- Colon cancer:
 - Colonoscopy at age 30-35 y (may need to be earlier in some families, depending on ages of cancers observed) every 2-3 y, and then after age 40 y every 1-2 y
- Extracolonic:
 - Consider prophylactic hysterectomy and BSO in women who have completed childbearing.
 - The risk of other LS-related cancers is reportedly low;^f however, due to limited data, no screening recommendation is possible at this time.

PMS2

- Colon cancer:
 - Colonoscopy at age 35-40 y (may need to be earlier in some families, depending on ages of cancers observed) every 2-3 y, and then after age 50 y every 1-2 y
- Extracolonic:
 - The risk of other LS-related cancers is reportedly low;^f however, due to limited data, no screening recommendation is possible at this time.

→ See Follow-up
of Surveillance
Findings (LS-4)

^fSee Cancer Risk Up to Age 70 Years in Individuals with Lynch Syndrome Compared With the General Population (LS-D).

^gOther than those for colon and endometrial cancer, screening recommendations are expert opinion rather than evidence-based.

^hVasen 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.

LS-2

LS-3

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LYNCH SYNDROME

SURVEILLANCE FINDINGS

FOLLOW-UP

ⁱMay consider subtotal colectomy if patient is not a candidate for optimal surveillance.

^jThe 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 (available online, in these guidelines, at NCCN.org [CSCR-B]).

LYNCH SYNDROME

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PRINCIPLES OF IHC AND MSI TESTING FOR LYNCH SYNDROME

General

- Immunohistochemistry (IHC) and MSI analyses are screening tests (either by themselves or in conjunction) that are typically done on colon cancer tissue to identify individuals at risk for LS.
- The Bethesda criteria were developed in response to the emerging understanding of the pathologic spectrum and molecular characteristics of LS-related tumors. These criteria were intended to help identify colon cancer patients whose tumors should be tested for MSI, thereby identifying patients with a greater chance of having LS. The revised Bethesda guidelines (see LS-B) are now widely used to identify tumors that should be tested for mismatch repair defects, either by MSI and/or IHC analysis. Although the revised Bethesda guidelines are more sensitive than the Amsterdam criteria (see LS-C), up to 30% of patients with LS fail to meet even these.

IHC

- IHC refers to staining tumor tissue for protein expression of the 4 mismatch repair genes known to be mutated in LS: *MLH1*, *MSH2*, *MSH6*, and *PMS2*. A normal IHC test implies all 4 mismatch repair proteins are normally expressed, and thus no underlying mismatch repair 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 mismatch repair genes guides genetic testing (mutation detection) to the gene for which protein expression is not observed.
- A total of 10%-15% of sporadic colon cancers exhibit abnormal IHC, often due to abnormal methylation of the *MLH1* gene promoter, but occasionally due to an inherited mutation of one of the mismatch repair genes. Thus, the presence of an abnormal IHC test increases the possibility of LS but does not make a definitive diagnosis. Individuals with abnormal IHC or MSI results should preferably be referred for genetic counseling so that the appropriate follow-up testing can be offered to the patient. In some cases, this would include testing for abnormal methylation of the *MLH1* promoter, and in others, it would include germline genetic testing of ≥ 1 of the mismatch repair genes. Most patients will be found to have sporadic colon cancer and not a germline mutation. Those with a germline mutation are then identified as having LS.
- There is a 5%-10% false-negative rate with IHC testing.

MSI

- MSI-H (microsatellite instability-high) in tumors refers to changes in 2 or more of the 5 microsatellite markers in the NCI-recommended panel. Its significance, use, and implications are similar to that of IHC, although the tests are slightly complementary.
- There is a 5%-10% false-negative-rate with MSI testing.

- Recommend LS screening at the time of diagnosis of CRC with either approach: All CRC patients or CRC patients diagnosed at age < 70 y and also those aged ≥ 70 y who meet the Bethesda guidelines (see LS-B). IHC and/or MSI screening of all patients with newly diagnosed CRCs and endometrial cancers, regardless of age at diagnosis or family history, have been implemented at some centers to identify individuals at risk for LS. This approach has been endorsed for colon cancer by the Evaluation of Genomic Applications in Practice and Prevention Working Group from the Centers for Disease Control and Prevention (Genet Med 2009;11:35-41) and has been shown to be cost-effective. An infrastructure needs to be in place to handle the screening results.

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LYNCH SYNDROME

REVISED BETHESDA GUIDELINES
FOR TESTING CRC FOR THE LYNCH SYNDROME BY IHC and/or MSI¹

Tumors from individuals should be tested for MSI in the following situations:

- CRC² diagnosed in a patient aged <50 y.
- Presence of synchronous, or metachronous, colorectal or other LS-related tumors,³ regardless of age.
- CRC with the MSI-H histology⁴ diagnosed in a patient aged <60 y.
- CRC diagnosed in a patient with one or more first-degree relatives with an LS-related cancer,³ with one of the cancers being diagnosed at age <50 y.
- CRC diagnosed in a patient with ≥2 first- or second-degree relatives with LS-related cancers,³ regardless of age.

¹Adapted 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.

²Endometrial cancer in patients aged <50 y is not included in the revised Bethesda guidelines; however, recent evidence suggests that these individuals should be evaluated for LS.

³LS-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.

⁴Presence of tumor-infiltrating lymphocytes, Crohn-like lymphocytic reaction, mucinous/signet-ring differentiation, or medullary growth pattern.

MINIMUM CRITERIA FOR CLINICAL DEFINITION OF LS
(AMSTERDAM CRITERIA I)^{1,2}

At least 3 relatives with CRC; all of the following criteria should be present:

- One should be a first-degree relative of the other 2;
- At least 2 successive generations must be affected;
- At least 1 of the relatives with CRC must have received the diagnosis before the age of 50 years;
- FAP should be excluded;
- Tumors should be verified by pathologic examination.

REVISED MINIMUM CRITERIA FOR CLINICAL DEFINITION OF LS
(AMSTERDAM CRITERIA II)^{1,2}

At least 3 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 2;
- At least 2 successive generations must be affected;
- At least 1 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.

¹From Vasen HF. Clinical diagnosis and management of hereditary colorectal cancer syndromes. J Clin Oncol 2000;18(21 Suppl):81s-92s

²Approximately 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 origin.

LS-B
LS-C

LYNCH SYNDROME

Colorectal Cancer Screening, Version 2.2013

Cancer Risk Up to Age 70 Years in Individuals With Lynch Syndrome Compared With the General Population

Cancer	General Population Risk ¹	<i>MLH1</i> and <i>MSH2</i> ^{1,2}		<i>MSH6</i> ²		<i>PMS2</i> ³	
		Risk	Mean Age of Onset	Risk	Mean Age of Onset	Risk	Mean Age of Onset
Colon	5.5%	40%-80%	44-61 y	10%-22%	54 y	15%-20%	61-66 y
Endometrium	2.7%	25%-60%	48-62 y	16%-26%	55 y	15%	49 y
Stomach	<1%	1%-13%	56 y	3%	63 y	†	70-78 y
Ovary	1.6%	4%-24% ⁵	42.5 y	1%-11%	46 y	†	42 y
Hepatobiliary tract	<1%	1.4%-4.0%	50-57 y	Not reported	Not reported	†	Not reported
Urinary tract	<1%	1%-4%	54-60 y	<1%	65 y	†	Not reported
Small bowel	<1%	3%-6%	47-49 y	Not reported	54 y	†	59 y
Brain/CNS	<1%	1%-3%	~50 y	Not reported	Not reported	†	45 y
Sebaceous neoplasms	<1%	1%-9%	Not reported	Not reported	Not reported	Not reported	Not reported
Pancreas ⁴	<1%	1%-6%	Not reported	Not reported	Not reported	Not reported	Not reported

¹Adapted from Kohlmann W, Gruber SB (Updated September 20, 2012). Lynch Syndrome. In: GeneReviews at GeneTests: Medical Genetics Information Resource (database online). Copyright, University of Washington, Seattle. 1997-2013. Available at <http://www.genetests.org>. Accessed February 14, 2013.

²Bonadona V, Bonaïti B, Olschwang S, et al; French Cancer Genetics Network. Cancer risks associated with germline mutations in *MLH1*, *MSH2*, and *MSH6* genes in Lynch syndrome. *JAMA* 2011;305:2304-2310.

³Senter L, Clendenning M, Sotamaa K, et al. The clinical phenotype of Lynch syndrome due to germ-line *PMS2* mutations. *Gastroenterology* 2008;135:419-428.

⁴Kastrinos F, Mukherjee B, Tayob N, et al. Risk of pancreatic cancer in families with Lynch syndrome. *JAMA* 2009;302:1790-1795.

⁵The 24% risk reported in Bonadona et al. (Cancer risks associated with germline mutations in *MLH1*, *MSH2*, and *MSH6* genes in Lynch syndrome. *JAMA* 2011;305:2304-2310) included wide confidence intervals (1%-65% for *MLH1*; 3%-52% for *MSH2*).

†The combined risk for renal pelvic, stomach, ovary, small bowel, ureter, and brain cancers is 6% to age 70 y (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).

LS-D

Text cont. from page 1539.

CRC Screening

Current technology falls into 2 broad categories: structural tests and stool/fecal-based tests.¹³ Direct evidence from randomized controlled trials suggests that fecal occult blood testing (FOBT) and flexible sigmoidoscopy (discussed in detail later) reduce mortality from CRC. Given the available evidence from case-control and cohort studies, however, the panel consensus is that colonoscopy should be the preferred method of screening because of its potential to prevent development of CRC (with its associated morbidity) and CRC-related death. Screening tests that can detect both early cancer and adenomatous polyps are encouraged, although the panel recognizes that patient preference and resource accessibility play a large role in test selection. Overall, although some techniques are better established than others, panelists agree that any screening is better than none.

Structural Screening Tests

Structural tests are able to detect both early cancer and adenomatous polyps using endoscopic or radiologic imaging. Endoscopic tests have several limitations, including their relative invasiveness, the need for dietary preparation and bowel cleansing, and the time dedicated to the examination (typically 1 day). Endoscopic examinations require informed consent and usually the need for sedation and have related risks, including perforation and bleeding. A large cohort study of 53,220 Medicare patients between ages 66 and 95 years showed that the risks of adverse events after colonoscopy increase with age.¹⁴

Colonoscopy: Colonoscopy is the most complete screening procedure, allowing examination of the entire large bowel and removal of polyps in one session. It is currently the preferred screening method and is the required procedure for confirmation of positive findings from other tests. Colonoscopy is also considered the current gold standard for assessing the efficacy of other screening methods. Although no randomized controlled trials have directly shown mortality reduction from colonoscopy, findings from case-control and cohort studies show significant impact of colonoscopy and polypectomy on CRC, with an estimated greater than 50% reduction in incidence.^{15–19} Rabeneck et al²⁰ recently reported an inverse correlation between colonoscopy use and death from CRC from a large population study in-

volving close to 2.5 million Canadians. For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.

Interestingly, in a Canadian case-control study that matched each of 10,292 individuals who died of CRC to 5 controls, colonoscopy was associated with lower mortality from left-sided CRC (adjusted conditional odds ratio [OR], 0.33; 95% CI, 0.28–0.39) but not right-sided CRC (OR, 0.99; CI, 0.86–1.14).²¹ Part of this finding may be related to significant variation in the quality of this widely used procedure in the community, which can lead to variable effectiveness.^{22,23} Another study, in which CRC mortality of 715 patients who underwent colonoscopy over a median follow-up period of 8 years was compared with expected rates of CRC mortality based on the SEER database, found a 65% relative reduction in CRC mortality after colonoscopy.²⁴

A recent follow-up on the National Polyp Study evaluated the long-term mortality effects of colonoscopy with polypectomy.^{17,25} The mortality of 2602 patients with adenomas removed was compared with the incidence-based mortality from CRC in the SEER database. With a median 15.8 years' follow-up, 12 deaths were attributed to CRC in the screened group, compared with an expected 25.4 deaths in the general population, suggesting a 53% decrease in mortality.

In addition, a population-based, case-controlled study in Germany showed that colonoscopy in the preceding 10 years was associated with an overall 77% decrease in the risk for CRC.²⁶ Although risk reduction was strongest for left-sided cancer, a 56% risk reduction was also seen for right-sided disease. Similar results were seen in a recent large case-control study using the SEER-Medicare database.²⁷

A current randomized controlled trial is comparing one-time colonoscopy with biennial fecal immunochemical testing (FIT; see later discussion) with the primary outcome of death from CRC at 10 years. Interim results from this trial show that subjects are more likely to participate in FIT screening (34.2% vs 24.6%; $P < .001$).²⁸ The 2 tests identified similar numbers of cancers in initial screening, but colonoscopy identified significantly more advanced and nonadvanced adenomas.

A recent meta-analysis of 14 randomized controlled trials and other controlled studies found that although endoscopic surveillance detected more ad-

Colorectal Cancer Screening

vanced neoplasms than stool testing, its advantage was offset by a lower participation rate.²⁹

Recommendations made by the panel are based on the premise of complete, high-quality colonoscopies, as reflected by 1) colonoscopy to cecum; 2) rectal retroflexion; 3) excellent preparation or endoscopic clearing of residual stool; 4) sufficient distention and full 360° view of front and back side of all folds; 5) withdrawal time greater than 10 minutes; and 6) complete excision of polyps (may require extra snare/biopsy or cautery after initial polypectomy).

A recent European report on a screening program involving more than 45,000 subjects confirmed that the endoscopist's rate of adenoma detection is an important predictor of the risk of interval CRC ($P=.008$), highlighting the need for meticulous inspection of the large intestinal tract.³⁰ The study did not demonstrate statistical significance with cecal intubation rate, another widely recognized quality indicator. One explanation is that the importance of this factor is restricted to the right colon, which gives rise to a small number of cancer cases.

In an effort to enhance screening quality, the Quality Assurance Task Group of the National Colorectal Cancer Roundtable developed a standardized reporting system for colonoscopy.³¹ The algorithm lists the common quality indicators of colonoscopy and minimum requirements of a colonoscopy report. Quality indicators, including withdrawal time, are an important part of the fidelity of colonoscopy findings.

An optimal screening protocol should have an interval during which patients have a low likelihood of developing cancer, and it should be cost-effective based on the duration of risk reduction after an initial negative colonoscopy. The general consensus is that a 10-year interval is appropriate for most individuals (average risk), although shorter intervals may be indicated depending on the completeness and quality of the colonoscopy. The panel emphasized the importance of family history in the screening scheme. Individual risk factors, the number or characteristics of polyps found, and physician judgment should also be included in the interval determination. A 1996 study reported that 27% of individuals had adenomatous polyps identified on repeat colonoscopy a mean of 66 months after an initial negative colonoscopy, but none had colon cancer and only 1 of 154 individuals had a polyp 1 cm or larger.³² These re-

sults suggest that an interval of repeat colonoscopy after an initial negative colonoscopy beyond 5 years is safe.

Imperiale et al³³ reported on 2436 individuals with no adenomatous polyps at baseline colonoscopy. No cancers were found at rescreening at a mean of 5.3 years later. Adenomatous polyps were identified in 16.0% of individuals, and only 1.3% had advanced adenomatous polyps. The authors recommended a rescreening interval of 5 years or longer. Lieberman et al³⁴ reported that advanced adenomatous polyps were found in only 2.4% of individuals on repeat colonoscopy within 5.5 years after a baseline normal colonoscopy. In this study, individuals with 1 or 2 adenomatous polyps less than 1 cm at baseline also had a low rate of developing advanced neoplasia.

Singh et al³⁵ assessed the time that risk reduction persists after colonoscopy. This study was a population-based retrospective analysis using a physician billing claims database of individuals who had a negative screening colonoscopy. Patients in the surveillance cohort were compared with the general population regarding incidence of CRC. A negative colonoscopy was associated with a standardized incidence ratio of 0.28 (95% CI, 0.09–0.65) at 10 years. A similar study calculated the adjusted relative risk for CRC among subjects with a previous negative colonoscopy.³⁶ The adjusted odds ratio was 0.26 (95% CI, 0.16–0.40). The low risk was seen even if the colonoscopy had been performed up to 20 or more years previously. A recent analysis showed that the risk reduction seen after negative colonoscopy holds even for patients with a family history of CRC, but not for current smokers.³⁷

Flexible Sigmoidoscopy: Flexible sigmoidoscopy followed by colonoscopic polypectomy in patients with lesions smaller than 1 cm significantly reduced mortality risk in early case-control studies.^{19,38} Direct evidence from randomized controlled trials now suggests that flexible sigmoidoscopy reduces mortality from CRC.³⁹ A recent British randomized population screening study of more than 110,000 individuals attributed a 23% and 31% reduction in CRC incidence and mortality, respectively, to flexible sigmoidoscopy offered once between ages 55 and 64 years compared with no screening.³⁹ The reductions in colorectal incidence and mortality for those individuals who accepted screening were 33% and 43%,

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respectively. In addition, the SCORE trial randomized 34,272 subjects to one-time sigmoidoscopy or no screening and recently reported incidence and mortality results after more than 10 years' median follow-up.⁴⁰ Per-protocol analysis showed a 31% reduction in incidence and a 38% reduction in mortality.

On the other hand, the Norwegian Colorectal Cancer Prevention Study Group performed a randomized controlled trial of flexible sigmoidoscopy in more than 55,000 participants aged 55 to 64 years.⁴¹ After 7 years of follow-up, the researchers reported no difference in the incidence of CRC between individuals screened once compared with unscreened participants. However, a nonsignificant trend toward reduced mortality from CRC was observed in the screened arm, and longer follow-up may reveal a mortality benefit.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening group recently reported CRC mortality rates from their randomized, controlled flexible sigmoidoscopy screening trial, which screened more than 64,000 participants with flexible sigmoidoscopy and 59% of those participants a second time at 3 or 5 years.⁴²⁻⁴⁴ A 26% reduction in deaths from CRC was seen in the screened group (relative risk, 0.74; 95% CI, 0.63-0.87; $P < .001$), with a 50% reduction seen in mortality from distal disease and no mortality from proximal disease.⁴² This strong effect was seen despite an estimated 46% contamination rate of sigmoidoscopy or colonoscopy in the control arm, suggesting that the true benefit of screening is even greater.

A recent meta-analysis of randomized controlled trials (including the PLCO trial) supports the conclusion that screening with flexible sigmoidoscopy significantly reduces the incidence and mortality of CRC.⁴⁵

A recent analysis of a 5% random Medicare sample of the SEER database found a similar reduction in distal CRC after both colonoscopy and sigmoidoscopy, with a reduction in proximal CRC after colonoscopy but not sigmoidoscopy.⁴⁶ A similar result was seen in a nested case-control study of 4 US health plans, in which the reduction of stage IIB or higher CRC was only seen on the left side.⁴⁷

Compared with colonoscopy, sigmoidoscopy requires no sedation and less bowel preparation but is limited to examination of the lower half of the colon tract. A recent analysis of cancers not detected

by flexible sigmoidoscopy in the PLCO trial showed that 37% of undetected lesions were beyond the reach of the sigmoidoscope.⁴⁸ In fact, the authors estimated that an additional 15% to 19% of cancers may have been detected during screening had colonoscopy been used.

Flexible sigmoidoscopy should be performed using a scope 60 cm or longer. Polyps identified should be biopsied by trained personnel to determine if they are hyperplastic, adenomatous, or sessile serrated (flat adenomatous polyps are unusual and may be missed during screening). Patients with lesions larger than 1 cm should be referred directly to colonoscopy, because these are almost always adenomatous polyps associated with a risk of proximal colonic neoplasms.

CT Colonography: CT colonography (CTC), also known as virtual colonoscopy, is evolving as a promising technique for CRC screening. CTC has the advantages of being noninvasive and not requiring sedation. The risk of test-related complications is also very low. However, a positive finding requires a colonoscopy, and extracolonic findings, which are present in up to 16% of patients, pose a dilemma.^{49,50} These findings require further investigations and have a potential for both benefit and harm. Currently, no sufficient data are available to determine the clinical impact of these findings.

The accuracy of CTC in detecting polyps or cancers measuring 10 mm or more was assessed in the National CT Colonography Trial (ACRIN 6664) organized by the American College of Radiology Imaging Network.⁵¹ In this study, 2531 participants underwent CTC followed by traditional optical colonoscopy. Colonoscopy identified 128 large adenomatous polyps or carcinomas in 109 patients. CTC detected 90% of patients who had lesions measuring 10 mm or larger found on colonoscopy. Thirty lesions were also found on CTC, but not colonoscopy, for which 15 of 27 participants underwent a subsequent colonoscopy. Five of 18 lesions were confirmed: 4 adenomatous polyps and 1 inflammatory polyp. The CTC performance in this study (sensitivity of 90% and specificity of 86%) was better than that reported in some earlier studies^{52,53} and similar to what was reported by Pickhardt et al⁵⁴ in a prospective study with a similar design as the ACRIN trial.

Kim et al⁵⁵ also compared CTC with colonoscopy for the detection of advanced neoplasia. Although this study was not randomized, the detection

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rates were comparable between the 2 groups of more than 3100 patients each (3.2% for CTC and 3.4% for colonoscopy).

In 2005, 2 meta-analyses reviewed the performance of CTC in the detection of colorectal polyps.^{56,57} In one of these studies, CTC showed high average sensitivity (93%) and specificity (97%) for polyps 1 cm and larger, both of which decreased to 86% when medium-sized polyps (6–9 mm) were included in the analysis.⁵⁶ In the other meta-analysis, the sensitivity of CTC, although heterogenous, improved as the polyp size increased (48% for polyps <6 mm, 70% for 6- to 9-mm polyps, and 85% for polyps >9 mm). The specificity was 92% to 97% for the detection of all the polyps.⁵⁷

Two additional meta-analyses were published in 2011. An analysis of 49 studies found the sensitivities for detection of CRC by colonography and colonoscopy to be 96.1% and 94.7%, respectively, with overlapping CIs.⁵⁸ Another analysis focused only on studies of average-risk participants and found the sensitivity and specificity of CTC for the detection of adenomas 1 cm or larger to be 87.9% and 97.6%, respectively.⁵⁹

Importantly, CTC may be a more acceptable option to many individuals. A recent randomized study compared participation rates when members of the general population were offered CRC screening with either colonoscopy or CTC.⁶⁰ Significantly more people accepted the invitation for CTC (34% vs 22%). Although colonoscopy had a greater diagnostic yield in screened participants, the yields were similar when determined per the invited population. More recently, laxative-free CTC has shown good sensitivity and specificity for detecting lesions 1 cm or larger.⁶¹ This technique is likely to be even more acceptable to patients.

The technical aspects of CTC differ from study to study and have not been standardized. These details include the imaging, preprocedure preparation, use of stool tagging, and expertise of the interpreter.^{62,63} Long-term follow-up studies of patients who were screened with CTC are not yet available.

The issue of radiation exposure also requires consideration. Using the screening protocol for the ACRIN trial, Berrington de Gonzalez et al⁶⁴ estimated the effective dose of low-dose CTC to be 9 mSv for women and 8 mSv for men, corresponding to 5 radiation-related cancer cases per 10,000 individuals undergoing 1 scan at age 60 years. Risks increase

with repeated scanning. The 2009 American College of Radiology practice guidelines for the use of CTC recommend the use of a multidetector CT scanner and low-dose nonenhanced technique to minimize radiation exposure to the patient.⁶⁵ Absorbed doses should not exceed 12.5 mGy total per scan.

Overall, available data indicate that CTC may be useful for the detection of larger polyps. However, it is still an evolving technique, and few data exist regarding screening intervals, polyp size leading to referral for colonoscopy, and protocol for evaluating extracolonic lesions. The best evidence currently available seems to support repeating the procedure every 5 years and referring patients with identified polyps larger than 5 mm to colonoscopy. The panel views colonoscopy as the preferred screening modality, and a lack of consensus exists on the use of CTC as a primary screening tool.

Fecal-Based Screening Tests

Fecal tests are designed to detect signs of CRC in stool samples, specifically occult blood or, more recently, alterations in exfoliated DNA. In contrast to structural tests, they are noninvasive and no bowel clearance is necessary. However, stool tests are less likely to detect adenomatous polyps for cancer prevention. Also, sensitivity can be limited by inadequate specimen collection or suboptimal processing and interpretation and is significantly lower than that of structural tests.

Any positive stool test must be followed by colonoscopy. To ensure adequate follow-up, a health care professional should coordinate testing so that patients with a positive result enter the health care system in a responsible way.

FOBT: Two FOBTs are currently available: guaiac-based and immunochemical. These tests are recommended annually alone, or in combination with flexible sigmoidoscopy every 5 years. Annual FOBTs should not be performed in combination with colonoscopy in an average-risk patient. Any positive result on an FOBT, however, should be followed up with colonoscopy. It is important for FOBTs to be performed annually, because the sensitivity in detecting advanced adenomas in a single test is fairly low.

FOBT of a single specimen obtained at digital rectal examination is not recommended because of its exceptionally low sensitivity.^{66,67} Unfortunately, a recent survey of more than 1000 primary care physi-

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cians revealed that inappropriate in-office testing is still widely used (25% used in-office testing only and 53% used both in-office and home testing), suggesting the need for strengthened education.⁶⁸

Guaiac FOBT: Based on the pseudoperoxidase activity of heme in human blood, guaiac FOBT is the most common stool test in use for CRC screening. Direct evidence from randomized controlled trials suggests that guaiac FOBT reduces the mortality from CRC.^{69–71} In the Minnesota Colon Cancer Control Study, more than 46,000 participants were randomized to receive an FOBT once a year, once every 2 years, or no screening. The 13-year cumulative mortality from CRC per 1000 was 5.88 and 8.83 in the annual and unscreened groups, respectively, and this 33% difference was statistically significant.⁷¹ Although this study did not show a decrease in CRC mortality with biennial screening, other large randomized studies have.^{69,70} In fact, a recently published long-term follow-up of the Nottingham trial showed that individuals randomized to the biennial guaiac FOBT screening arm had a 13% reduction in CRC mortality at a median follow-up of 19.5 years (95% CI, 3%–22%), despite a 57% participation rate. After adjustment for noncompliance, the reduction in CRC mortality was 18%.⁷²

A systematic review of 4 randomized controlled trials involving more than 320,000 participants showed a 16% reduction in relative risk for CRC death with guaiac FOBT screening (95% CI, 0.78–0.90).⁷³ The sensitivity of different guaiac FOBTs for cancer detection ranged from 37% to 79% in a study of approximately 8000 participants by Allison et al.⁷⁴ In the UK National Health Service Bowel Cancer Screening Programme, cancer was detected in 11.8% of individuals who had a colonoscopy after an abnormal or weak-positive FOBT.⁷⁵ Adenomas were found in an additional 49.7% of participants.

One major disadvantage for guaiac FOBT is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. Another limitation is the high false-positive rate resulting from reaction with nonhuman heme in food and blood from the upper gastrointestinal tract. To compensate for intermittent limitations, guaiac FOBT should be performed on 3 successive stool specimens obtained while the patient adheres to a prescribed diet.

Fecal Immunochemical Test: The FIT, approved by the FDA in 2001, directly detects human globin within

hemoglobin. Unlike guaiac FOBT, FIT does not require dietary restrictions, and a single testing sample is sufficient. However, sensitivity (11%–58% for detecting any adenoma) and specificity (59%–97%) vary widely for FIT, as illustrated by a 2009 German study that assessed 6 different FIT methods on 1319 participants.⁷⁶ More recent comparative studies have shown that FIT is more sensitive than guaiac FOBT.^{77–81} For example, one study showed FIT had a higher sensitivity for detecting cancer than Hemoccult Sensa (82% vs 64%).⁷⁷ A Dutch randomized study also showed that FIT had higher detection rates for advanced neoplasia (2.4%) than guaiac FOBT (1.1%), although both were less reliable than flexible sigmoidoscopy (8.0%).⁷⁸ An expert panel in Ontario recently conducted an extensive literature analysis and concluded that FIT is superior to guaiac FOBT in both participation rates and detection of advanced adenomas and CRC.⁸²

Stool DNA Test: Stool DNA testing is an emerging screening tool for CRC. It detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool. Early proof-of-principle tests involving a single-target marker such as KRAS produced less than 40% sensitivity.⁸³ In an effort to improve sensitivity, newer tests with multipanel markers were developed. In a large multicenter study of 4404 patients, eligible subjects submitted a stool specimen for DNA analysis, underwent Hemoccult II testing, and then had a colonoscopy.⁸⁴ In a subgroup analysis, the multitarget DNA assay SDT-1 (21 mutations in APC, KRAS, and p53 plus 2 other markers) detected 52% of CRC compared with 13% by Hemoccult II, with specificities of 94% and 95%, respectively. The SDT-1 assay did not perform as well in another large, multicenter, prospective, triple-blinded trial that also assessed a second-generation combination test SDT-2 (mutations in APC and K-ras plus vimentin methylation).⁸⁵ In this study, a total of 3764 average-risk healthy adults underwent screening colonoscopy, Hemoccult, Hemoccult Sensa, SDT-1, and SDT-2. Very similar sensitivities for detecting CRCs, high-grade dysplasias, and adenomas were observed for SDT-1 and Hemoccult Sensa (20% and 21%, respectively), whereas the sensitivity of SDT-2 was 40%. Other stool DNA tests are being developed and tested.⁸⁶

For persons unwilling or unable to have screening colonoscopy, increasing evidence suggests that a

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stool DNA test may provide a valuable noninvasive option. More research is necessary to determine the optimal testing interval. Only one stool DNA test is currently available in the United States: ColoSure, which detects methylated *vimentin*.⁸⁷ However, stool DNA testing has not yet been approved by the FDA, and is currently not considered a first-line screening tool.

Risk Assessment

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colorectal Cancer Screening stratify patients into 3 groups depending on their risk of developing CRC. Colorectal screening is particularly important for African Americans, because they have a higher risk of incidence and mortality (see “Increased Risk,” below). Communication with the patient and referring physician regarding any updated CRC risk assessment and screening plan based on family history, colonoscopy, and pathology findings is highly encouraged.

CRC risk assessment in persons without a known family history is advisable by age 40 years to determine the appropriate age for initiating screening.

Average Risk: Individuals at average risk of developing CRC are those aged 50 years or older with a negative family history and no history of adenoma, CRC, or inflammatory bowel disease.

Increased Risk: Individuals with a personal history of adenomatous polyps/sessile serrated polyps (SSPs; described later), CRC, or inflammatory bowel disease, and those with a positive family history of CRC or advanced adenomatous polyps are considered to be at increased risk for developing CRC. Individuals with diabetes mellitus or a history of BRCA-positive breast cancer also have a higher risk,^{88–90} although these conditions are not considered to affect the screening guidelines.

Registry data suggest an increased incidence of CRC in African Americans younger than 50 years.⁹¹ This increased risk has led some investigators to recommend beginning population CRC screening in African Americans at age 45 years.⁹² However, mortality from CRC is multifactorial and is related to host factors, tumor biology, environmental exposures, disparities in access to screening, differences in stage at diagnosis, and treatments received. In addition, mortality from CRC has been decreasing in African Americans and whites since 1999.⁹³ Therefore, based on the available data, methods to further

improve access to screening in African-American populations should be endorsed.

High-Risk Syndromes: Individuals with a family history of Lynch syndrome (also known as HNPCC) or with a personal or family history of polyposis syndromes are considered to be in the high-risk category (see “Inherited Colon Cancer,” page 1564).

Screening of Individuals at Average Risk

Screening beginning at age 50 years is recommended for persons at average risk, after discussions of the available options. Currently recommended options include colonoscopy every 10 years, annual fecal-based tests, flexible sigmoidoscopy every 5 years using a 60-cm or longer scope, a combination of annual fecal tests and sigmoidoscopy every 5 years, or CTC every 5 years. If available, colonoscopy is the preferred screening modality for individuals at average risk. However, any screening is better than none. Recent data suggest that after one negative colonoscopy, following up with less-invasive tests, such as annual fecal tests, provides approximately the same benefit, with lower risks and costs than colonoscopy.⁹⁴

If a colonoscopy is incomplete or preparation is suboptimal, other screening methods or repeat colonoscopy should be considered based on physician judgment.

Interpretation of Findings: Colonoscopy is indicated for follow-up of abnormal findings from other screening modalities—stool tests, flexible sigmoidoscopy (biopsy-proven adenoma), or CTC. During colonoscopy, any polyps found should be removed, and follow-up strategies should be based on the endoscopic and pathologic findings. Special attention should be paid to polyps located on the right side of the colon tract, because these tend to be associated with microsatellite instability (MSI), and hence greater cancer risk that warrants additional surveillance.

Adenoma/Adenomatous Polyps: Adenomas or adenomatous polyps (most often found to be tubular), the most common form of polyps, are associated with an increased risk for CRC (see next section on “Screening of Individuals at Increased Risk,” facing page). Villous adenomatous polyps have a greater risk of harboring cancer and finding additional adenomatous polyps or cancer on follow-up.

Flat Adenoma: Flat adenomatous polyps are unusual and can be easily missed during colonoscopy because

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they are not protruding from the colon wall.⁹⁵ More prospective studies are required to clarify their role in CRC risk. In the meantime, all flat adenomatous polyps should be removed on identification, with routine postadenoma follow-up.

Serrated Polyps: SSPs, also known as *sessile serrated adenomatous polyps*, are rare forms of polyps that have been associated with adenocarcinoma. Any serrated lesions in the proximal colon should be followed similarly to adenomatous polyps, because of their significant risk of neoplastic progression.^{96–98}

Hyperplastic polyps are another type of serrated polyp. A large body of literature indicates that hyperplastic polyps are not associated with a significantly increased risk for CRC, and supports the recommendation that persons with hyperplastic polyps be screened as average risk. Recent literature, however, suggests that a small subset of persons with multiple or large hyperplastic polyps have SPS (see “Serrated Polyposis Syndrome,” available online, in these guidelines, at NCCN.org [MS-29]), with a 26% to 70% risk for CRC.^{99–101} Most of these persons had concomitant adenomatous polyps or SSP.¹⁰² Additionally, evidence suggests that some cancers with extensive DNA methylation and MSI might derive from hyperplastic polyps.¹⁰³

Ideally, all detected polyps should be removed, but this is not always possible. Removed polyps should be examined for degree of dysplasia and for histologic features of SSP. Hyperplastic polyps that are less than 1 cm without SSP features indicate average risk for follow-up screening when they occur on the left side (ie, splenic flexure, descending colon, sigmoid colon, rectum), whereas those on the right side (ie, cecum, ascending colon, transverse colon) should be followed with repeat colonoscopy in 5 years. Larger polyps and SSPs should be followed as adenomas.⁹⁷ SPS is rarely reported to be inherited, and the CRC risk in individuals with affected relatives remains unclear (see “Serrated Polyposis Syndrome,” available online, in these guidelines, at NCCN.org [MS-29]).

Screening of Individuals at Increased Risk

Personal History of Adenoma/SSP: Individuals with adenomatous polyps are at increased risk for recurrent adenomatous polyps and CRC. To minimize the risk of developing CRC, a surveillance program is recommended for patients with adenomatous polyps after screening colonoscopy and complete polypectomy.¹⁰⁴ For patients with completely resected ade-

nomatous polyps, the surveillance schedule depends on the risk of recurrence, which in turn is related to the number, size, and histology of the adenomatous polyps. Furthermore, when uncertainty exists about the completeness of removal in large and/or sessile polyps and when the colonic preparation was suboptimal, shorter screening intervals may be necessary.

Low-risk adenomatous polyps are tubular, 2 or fewer, and less than 1 cm. In this group, colonoscopy should be repeated within 5 years, although emerging data suggest that longer intervals may be appropriate. If this examination is normal, colonoscopy should be repeated every 10 years.¹⁰⁵ Generally, the results of the first 2 screening examinations may predict the patient's overall colon cancer risk.¹¹ Robertson et al¹⁰⁶ reported on a study of 564 participants who had their first adenoma identified by colonoscopy and underwent 2 additional colonoscopies. The study found that combining results of 2 prior colonoscopies can help predict the likelihood of high-risk findings (advanced adenomatous polyps or cancers) on the third screen. If no adenomas were found on the second examination, results of the first screening predicted results of the third. In this case, if the first colonoscopy showed only low-risk findings, then the chance of high-risk findings on the third colonoscopy was 4.9%, whereas high-risk findings on the first colonoscopy gave a 12.3% risk of high-risk findings on the third colonoscopy ($P=.015$).

Advanced or multiple adenomatous polyps (3–10 polyps, ≥ 10 mm, with $>25\%$ villous histology or high-grade dysplasia) have been associated with increased risk. High-grade dysplasia is defined as an adenoma that shows features of severe dysplasia (marked reduction of interglandular stromas with complex irregularity of glands, papillary infolding, and cytogenetic abnormalities) or high-grade dysplasia (severe architectural disturbance of glands along with cytologic features of dysplasia).¹⁰⁷ *Carcinoma in situ* is a term used previously by pathologists to describe colon polyps and cancer that has been replaced by the term *high-grade dysplasia*. A study by Golembeski et al¹⁰⁸ showed that the identification of villous architecture and high-grade dysplasia is poorly reproducible among pathologists. Individuals with advanced or multiple adenomatous polyps should have repeat colonoscopy within 3 years, although new data suggest that intervals of 5 years may be appropriate.¹⁰⁹

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Because studies have used 1 cm as the standard measure, data are lacking on the relative significance of intermediate-size adenomatous polyps (size 5–10 mm). Individuals with high-risk adenomatous polyps are advised to repeat colonoscopy within 3 years. Subsequent surveillance colonoscopies are recommended within 5 years, depending on colonoscopic findings. Longer intervals are recommended for persons with normal follow-up colonoscopies. It is appropriate to reassess risk, including contributing medical and personal factors, number and characteristics of adenomatous polyps, and family history at each interval before and after procedures.

Individuals with more than 10 cumulative adenomatous polyps are recommended to undergo evaluation for a polyposis syndrome (see “Inherited Colon Cancer,” page 1564), although only a small fraction of those with no family history and low adenoma burden will have a defined hereditary syndrome. Ten polyps or fewer may infrequently be associated with an inherited polyposis syndrome, especially in patients younger than 40 years or with a strong family history. Hence, a detailed family history is crucial in patients with multiple adenomatous polyps. Individual management is emphasized.

Polypectomy of large sessile polyps is associated with a high rate of recurrence, attributed to the presence of residual adenoma tissue at the time of the procedure.¹¹⁰ Hence, follow-up colonoscopy within 2 to 6 months is appropriate in this setting or when polypectomy is suspected to be incomplete.

The NCCN Guidelines for Colon Cancer provide recommendations for management if a malignant polyp is found at colonoscopy (to view the most recent version of these guidelines, visit NCCN.org).

Personal History of CRC: Individuals with a personal history of CRC should be followed according to the surveillance recommendations in the NCCN Guidelines for Colon and Rectal Cancers (available at NCCN.org). These patients are at increased risk for recurrent adenomatous polyps and cancer. Studies have found a high recurrence rate in the 4 to 5 years after CRC resections.^{111–114} In patients with rectal cancer, local recurrence at the rectal anastomosis has been reported to occur in 5% to 36% of patients.^{115–117} Furthermore, an analysis of 3278 patients with resected stage II and III CRC in the Intergroup 0089 study found that the rate of second primary CRC is especially high in the immediate 5 years after

surgery and adjuvant chemotherapy.¹¹⁸ These results suggest that intense surveillance should be considered during that period, even though this analysis did not exclude patients with Lynch syndrome, who are at greater than 30% risk for synchronous and metachronous cancers.

The NCCN Guidelines for Colon and Rectal Cancers recommend a complete colonoscopy preoperatively and at 1 year after surgery (within 3–6 months if preoperative colonoscopy was incomplete). If this examination is normal, colonoscopy should be repeated in 3 years, then every 5 years. Shorter intervals (1 year) are recommended if adenomatous polyps or SSPs are found. Subsequent colonoscopic intervals are individualized and generally should not exceed 5 years.

In addition to colonoscopy, patients with rectal cancer also should undergo periodic endoscopic evaluation of the rectal anastomosis to identify local recurrence, which has been reported to occur in 5% to 36% of patients.^{115–117} Expert opinion supports repeat evaluation for patient status every 3 to 6 months for 2 years after low anterior resection, then every 6 months for a total of 5 years. The utility of routine endoscopic ultrasound for early surveillance is not defined.

Advantages of more intensive follow-up of patients with stage II and/or stage III rectal cancer have been shown prospectively in several studies^{112,119,120} and in 3 meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.^{121–123} Other studies impacting the issue of posttreatment CRC surveillance include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials.¹¹³ The meta-analysis showed that 80% of recurrences occurred in the first 3 years after surgical resection of the primary tumor. However, in the final analysis of Intergroup trial 0114 comparing bolus 5-FU with bolus 5-FU/leucovorin in patients with surgically resectable rectal cancer, local recurrence rates continued to increase after 5 years.¹²⁴ Furthermore, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive posttreatment follow-up in these patients.¹²⁵ Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative CRC surgery.^{126,127}

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Patients with a personal history of CRC should also be considered for Lynch syndrome testing using one of the following approaches: 1) all patients with CRC; or 2) all patients with CRC diagnosed before age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines. Testing for Lynch syndrome is discussed in more detail below (see “Molecular Workup and Genetic Testing for Lynch Syndrome,” page 1565).

Inflammatory Bowel Disease: Individuals with a personal history of inflammatory bowel disease (ie, ulcerative colitis, Crohn disease) are well recognized to be at an increased risk for CRC.^{128,129} Screening by colonoscopy every 1 to 2 years should be initiated 8 to 10 years after the onset of symptoms of pancolitis or 12 years after onset of left-sided colitis and should be performed by an endoscopist who is familiar with the appearance of ulcerative colitis or Crohn disease.⁹ A 2001 meta-analysis showed that patients with pancolitis have a higher risk of developing CRC than those with less extensive disease.¹³⁰ It should be noted, however, that separate guidelines from the American College of Gastroenterology and the American Gastroenterological Association do not recommend a delay in screening when disease is limited to the left side, because the data suggesting a later onset of cancer in these individuals are not strong.^{131,132}

When inflammatory bowel disease is clinically quiescent, multiple 4-quadrant biopsies (every 10 cm with ≥ 30 samples) should be taken for histologic examination using large-cup forceps. Strictures, particularly those in ulcerative colitis, that are suggestive should be evaluated thoroughly using biopsy and brush cytology. Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy, narrow-band imaging, autofluorescence, or confocal endomicroscopy. Targeted biopsies have been found to improve detection of dysplasia and should be considered for surveillance colonoscopies in patients with ulcerative colitis.¹³³ Any masses, including so-called dysplasia-associated lesions, are of extreme concern. Endoscopic polypectomy should be performed when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia.

Interpretation of dysplasia or intraepithelial neoplasia can be difficult. Pathologists experienced in interpreting inflammatory bowel disease lesions should evaluate biopsies. Lesions in patients with

ulcerative colitis that look endoscopically and histologically similar to sporadic adenoma, with no dysplasia in the flat mucosa in the surrounding area or elsewhere in the colon and without invasive carcinoma in the polyp, can be treated safely with polypectomy and continued surveillance. Most findings of high-grade, multifocal, or repeat low-grade dysplasia place patients with ulcerative colitis at high risk for developing CRC. Prophylactic proctocolectomy with ileoanal anastomosis is preferred for these patients. All other individuals with positive findings should be referred to an experienced inflammatory bowel disease surgeon to discuss surgical options.

Family History: Family history is one of the most important risk factors for CRC. It is essential to obtain a detailed family history, including first-degree relatives (parents, siblings, and offspring), second-degree relatives (aunts, uncles, grandparents, and half-siblings), and additional relatives with cancer (cousins, great-grandparents, nieces, and nephews). Sometimes a great deal of information can be obtained by looking at first cousins. Grandchildren are often not old enough to manifest any of the clinical phenotypes of cancer syndromes.

For each of the relatives, current age and age at diagnosis of any cancer, and a date, age, and availability of a tumor sample and cause of death are very important for discerning whether relatives were at risk for developing cancer, how long they were at risk, and what type of cancer they had. It is particularly important to note the occurrence of multiple primary tumors. Other inherited conditions and birth defects should be included in this family history. Ethnicity and country of origin are also important.

It is recommended that risk assessment be individualized and include a careful family history to determine whether a familial clustering of cancers is present in the extended family. If a patient meets the criteria for an inherited colorectal syndrome (see later discussion), further risk evaluation and counseling, as outlined in the guidelines, is required.

When any one of the revised Bethesda criteria¹³⁴ are met (listed on LS-B, page 1553), the possibility of Lynch syndrome is suggested, and immunohistochemical (IHC) staining for the four mismatch repair (MMR) proteins and/or MSI testing on the colon tumor of the youngest affected family member is warranted (see “Molecular Workup and Genetic Testing for Lynch Syndrome,” page 1565, for more

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information on this topic).

Positive Family History: Individuals with a family history of CRC have an increased risk for the disease themselves and should therefore undergo earlier and/or more frequent screening.¹³⁵ The panel's recommendations are as follows:

- For patients with an affected first-degree relative diagnosed before age 50 years or 2 first-degree relatives with CRC at any age, colonoscopy is recommended every 3 to 5 years, beginning 10 years before the earliest diagnosis in the family or at age 40 years at the latest.
- For those with one affected first-degree relative diagnosed at age 50 years or later, colonoscopy every 5 years should begin at age 50 or 10 years earlier than the age of diagnosis of the relative. Multiple (≥ 2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals.
- When 1 second-degree relative is diagnosed with CRC before age 50 years, colonoscopy should begin at age 50 years, with repeat colonoscopy based on findings.
- Individuals with a first-degree relative with a history of advanced adenomas should undergo colonoscopy beginning 10 years before the relative's age of onset or age 50 years at the latest, with repeat colonoscopy based on findings. Data suggesting an increased risk for CRC in this population are limited.¹³⁶

Colonoscopy intervals should be modified based on personal and family history and on individual preferences. A recent population-based study analyzed more than 2 million individuals to determine relative risks for the development of CRC depending on family history of CRC.¹³⁵ Results showed that some combinations of affected first-, second-, and third-degree relatives may increase risk sufficiently to alter screening guidelines from the recommendations listed earlier. Other factors that modify colonoscopy intervals include the size of the family, completeness of the family history, participation of family members in screening, and colonoscopic findings in family members.

Inherited Colon Cancer

Genetic susceptibility to CRC includes well-de-

fined inherited syndromes such as Lynch syndrome (HNPCC), FAP, MAP, and other less common syndromes. Understanding the potential genetic basis for cancer in the family is critical in inherited syndromes. If a concern exists about the presence of a hereditary syndrome, the guidelines recommend referring the patient to a genetic service or genetic counselor.

After evaluation, those with Lynch syndrome, FAP, or MAP are managed as described in the following sections. Referral to a specialized team is recommended for those with Peutz-Jeghers syndrome or juvenile polyposis; surveillance guidelines for these patients and for those with SPS are outlined in the algorithm. Individuals with a familial risk and no syndrome should be managed as described earlier for those with a positive family history, or following the newly developed recommendations for "Colonic Adenomatous Polyposis of Unknown Etiology," in these guidelines, available online, at NCCN.org [CPUE-1]).

Lynch Syndrome (HNPCC)

Lynch syndrome is the most common form of genetically determined colon cancer predisposition, accounting for 2% to 4% of all CRC cases.¹³⁷⁻¹⁴⁰ This hereditary syndrome usually results from a germline mutation in 1 of 4 DNA MMR genes (*MLH1*, *MSH2*, *MSH6*, or *PMS2*), although possible associations with 3 other genes (*MLH3*, *PMS1*, and *EXO1*) have also been found.¹⁴¹ Recent evidence has shown that 3 deletions in the *EPCAM* gene, which lead to hypermethylation of the *MSH2* promoter and subsequent *MSH2* silencing, are an additional cause of Lynch syndrome.^{142,143} *EPCAM* deletions likely account for 20% to 25% of cases in which *MSH2* protein is not detected by IHC (see later discussion) but germline *MSH2* mutations are not found.¹⁴³ MMR mutations are detected in more than half of persons meeting the clinical criteria of Lynch syndrome, and the lifetime risk for CRC approaches 80% in affected individuals carrying a mutation in one of these genes.¹⁴⁴ MSI occurs in 80% to 90% of resulting colorectal tumors.^{145,146} Surveillance in patients with Lynch syndrome has been shown to reduce the risk for CRC and may be of benefit in the early diagnosis of endometrial cancer, which is also common in these patients.^{147,148} Site-specific evaluation and heightened attention to symptoms is also advised for other cancers that occur with increased frequency

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in affected persons, including gastric, ovarian, pancreatic, urethral, brain (glioblastoma), and small intestinal cancers, and sebaceous gland adenomatous polyps and keratoacanthomas. However, efficacy of surveillance for these sites has not been clearly demonstrated (reviewed by Lindor et al¹⁴⁸).

Risk factors for the presence of Lynch syndrome related to the extended family history in an individual are listed in the guidelines. Because of the high risk for CRC in a person with the syndrome, intensive screening is essential, although the optimal interval has not been fully established in clinical trials. The recommendations in this area are based on the best evidence available to date, but more data are still needed.

Molecular Workup and Genetic Testing for Lynch Syndrome: Although identifying a germline mutation in an MMR gene (*MLH1*, *MSH2*, *MSH6*, and *PMS2*) by sequencing is definitive for Lynch syndrome, patients with CRC usually undergo 2 rounds of selection before sequencing: the first based on family history or age and the second based on results of initial tests on tumor tissue. As discussed in more detail later, many institutions now proceed directly to initial tests on tumor tissue in all patients regardless of age and family history.

Criteria for Lynch Syndrome Testing: Several different sets of criteria have been developed to identify patients who should be tested for possible Lynch syndrome. The first version of the minimum criteria for clinical definition of Lynch syndrome (Amsterdam criteria) was introduced in 1991, and these criteria were modified (Amsterdam II criteria) in 1999.¹⁴⁹ Approximately 50% of families meeting the Amsterdam II criteria have a mutation in an MMR gene.¹⁵⁰ These criteria are very stringent, however, and miss as many as 68% of patients with Lynch syndrome.¹⁵¹

The classic Bethesda guidelines were later developed to provide broader criteria for testing colorectal tumors for MSI.¹⁵² The NCI introduced the revised Bethesda guidelines in 2002 to clarify selection criteria for MSI testing.¹³⁴ 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.¹⁵³ 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.¹⁵⁴ Patients fulfilling the revised Bethesda criteria had

an OR for carrying a germline mutation in *MLH1* or *MSH2* of 33.3 (95% CI, 4.3–250; $P=.001$). Screening tumors of patients meeting the Bethesda criteria for MSI was shown to be cost-effective not only for patients with newly diagnosed CRC but also when considering benefit for the siblings and children of mutation carriers.¹⁵⁵

Some newer models have also been developed to assess the likelihood that a patient carries a mutation in an MMR gene.^{151,156–158} These computer programs give probabilities of mutations and/or of the development of future cancers based on family and personal history. The PREMM_{1,2,6} model can be used online at <http://premm.dfci.harvard.edu/> and the HNPCC predict model is available for online use at <http://hnpccpredict.hgu.mrc.ac.uk/>. MMRpro is available for free download at <http://www4.utsouthwestern.edu/breasthealth/cagene/>. These models may be particularly useful when no tumor or insufficient tumor is available for IHC or MSI testing.

Many NCCN Member Institutions and other comprehensive cancer centers now perform IHC and sometimes MSI testing on all newly diagnosed colorectal and endometrial cancers regardless of family history to determine which patients should have genetic testing for Lynch syndrome.^{159,160} The cost-effectiveness of this approach, referred to as *universal* or *reflex testing*, has been confirmed for CRC, and this approach has been endorsed by the Evaluation of Genomic Applications in Practice and Prevention working group at the CDC.^{161–163} The Cleveland Clinic recently reported on their experiences implementing such a screening approach.¹⁶⁴

An alternative approach is to test all patients with CRC diagnosed before age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines.¹⁶⁵ 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 level of sensitivity was better than that of both the revised Bethesda and Jerusalem (testing all patients diagnosed with CRC at age <70 years¹⁶⁶) recommendations. Although this new selective strategy failed to identify 4.9% of Lynch syndrome cases, it resulted in approximately 35% fewer tumors undergoing MMR testing.¹⁶⁵

The NCCN CRC Screening Panel endorses using either this selective approach (testing all patients with CRC diagnosed at age <70 years plus pa-

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tients diagnosed at older ages who meet the Bethesda guidelines) or the universal testing approach to select patients with CRC for Lynch syndrome testing. An infrastructure must be in place to handle the screening results in either case. In addition, testing for Lynch syndrome is advised for individuals who meet any of the following criteria: 1) meets revised Bethesda guidelines or Amsterdam criteria; 2) diagnosed with endometrial cancer before age 50 years; 3) known Lynch syndrome in the family.

The testing strategy will depend on whether there is a known MMR mutation in the family. If so, the individual should be tested for the familial mutation (see “Definitive Testing,” opposite column). If test results are positive or if testing is not performed for any reason, the individual should follow surveillance for Lynch syndrome outlined later. Individuals whose test results are negative for the familial mutation are considered to be at average risk, not zero risk, for CRC and should follow the corresponding screening pathway. If there is no known familial MMR mutation, initial tests should be performed on available tumor tissue, as described later.

Initial Testing Methodologies: Two main initial tests are performed on CRC specimens to identify individuals who might have Lynch syndrome: 1) IHC analysis for MMR protein expression, which is often diminished because of mutation; and 2) analysis for MSI, which results from MMR deficiency.¹⁶⁷ Some studies have shown that both IHC and MSI are cost-effective and useful for selecting high-risk patients who may have *MLH1*, *MSH2*, and *MSH6* germline mutations.^{163,168,169} However, conclusive data are not yet available that establish which strategy is optimal.^{141,154,170-173} The sensitivities of MSI and IHC testing have been estimated to be 77% to 89% and 83%, respectively; specificities have been estimated to be 90% and 89%, respectively.¹⁶³ Some experts advocate for using both methods when possible.¹⁷⁴

MSI testing is particularly helpful when the family history is not strongly suggestive of Lynch syndrome. Families that meet the minimal criteria for consideration (diagnosis before the age of 50 years, but no other criteria) may not represent the disorder. A microsatellite stable tumor arising within a young-onset patient without a strong family history of colorectal/endometrial cancer is very unlikely to represent the disorder.¹⁷⁵ Proceeding with genetic testing in this setting is unlikely to yield an informa-

tive result. On the other hand, among patients who met the Amsterdam criteria with MSI-negative tumors, 29% were found to have germline MMR gene mutations. MMR gene mutations were found in 88% of patients with MSI-positive tumors who met the Amsterdam criteria.¹⁷⁵

IHC analysis is especially useful for family members who meet the Amsterdam criteria I or II, because it has a 50% to 92% chance of identifying a mutation in an MMR gene in these individuals.¹⁶⁷ IHC analysis has the advantage of predicting which gene is most likely mutated and thus the first candidate for germline sequencing.¹⁶⁷ Testing the *BRAF* gene for mutation is indicated when *MLH1* expression is absent in the tumor by IHC analysis. The presence of a *BRAF* mutation indicates that *MLH1* expression is downregulated by somatic methylation of the promoter region of the gene and not by a germline mutation.¹⁶⁷

Additional testing strategies and a table of IHC and MSI testing results are included in these NCCN Guidelines (LS-1 on page 1549, and LS-A, 2 of 2 online at NCCN.org, respectively).

Often, a patient presents with a strong family history of Lynch syndrome-associated cancer, but no tumor sample is available for testing. A recent study showed that large (≥ 10 mm) adenomatous colorectal polyps in patients with Lynch syndrome display a loss of MMR protein expression by IHC and are MSI-positive.¹⁷⁶ These results indicate that MSI and/or IHC testing of large polyps when a tumor sample is not available is justified in high-risk families.¹⁷⁷ Importantly, a negative result would not rule out Lynch syndrome. An alternative approach is to proceed directly to germline sequencing in patients determined to have a 5% or greater risk for Lynch syndrome when a tumor sample is not readily available,¹⁷⁸ with the following priority: *MLH1* and *MSH2* first, then *MSH6*, and lastly *PMS2*. Because of its rarity, testing for *PMS2* mutation is only necessary if no mutation is found in the other genes.

Definitive Testing: Initial tests do not necessarily indicate that a patient has Lynch syndrome. Patients with sporadic CRC can have abnormal results because of abnormal methylation of the *MLH1* gene promoter. A recent study estimated that 7.1% (95% CI, 2.8%–18.2%) of patients with CRC with defective MMR have germline mutations associated with Lynch syndrome.¹⁷⁹ Therefore, all individuals with abnormal IHC or MSI results should be referred for

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genetic counseling so that the appropriate follow-up testing can be offered. These tests might include one for abnormal *MLH1* promoter methylation and/or germline genetic testing of one or more of the MMR genes. If a mutation is not found through sequencing, testing for large rearrangements and deletions of MMR genes may also be performed. Most patients will be found to have sporadic CRC; those with a germline alteration are identified as having Lynch syndrome and should undergo surveillance for Lynch syndrome as described later. If no familial mutation is identified, surveillance should be tailored based on individual and family risk assessment.

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. Predictive testing can prevent people from undergoing several unnecessary procedures. It is important to consider genetic testing for at-risk family members when the family mutation is known. 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 family mutation.

Many other issues are involved in the genetic counseling process of individuals regarding presymptomatic testing for cancer susceptibility. A fair number of individuals elect not to undergo testing, and it is important to counsel these individuals so that they continue with increased surveillance.

Surveillance for Lynch Syndrome: The NCCN CRC Screening Panel has had extensive discussions on the surveillance schemes for individuals with Lynch syndrome. These patients are at an increased lifetime risk compared with the general population for CRC (10%–80% vs 5.5%), endometrial cancer (16%–60% vs 2.7%), and other cancers, including those of the stomach and ovary.^{180–185} For the 2013 version of these NCCN Guidelines, the panel devised separate cancer screening recommendations for patients with mutations in *MLH1*/*MSH2*, *MSH6*, and *PMS2*. This decision was based on emerging data that show a smaller risk for cancer in the latter groups.^{180,183,186} For example, individuals with *MSH6* and *PMS2* mutations have a 10% to 22% risk for colon cancer up to age 70 years, whereas those with *MLH1* and *MSH2* mutations have a 40% to 80% risk.

Existing screening data in the literature are mainly on colon and endometrial cancers. More data are needed to evaluate the risk and benefits of extracolonic and extra-endometrial cancer screening, and recommendations are based mainly on expert opinion.

Colon Cancer Surveillance: If Lynch syndrome with *MLH1* or *MSH2* mutation is confirmed, colonoscopy is advised to start between the ages of 20 to 25 years, or 2 to 5 years younger than the youngest diagnosis age in the family, whichever comes first, to 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.¹⁴⁸

Because the average age of colon cancer onset for *MSH6* or *PMS2* mutation carriers is somewhat older than for *MLH1* and *MSH2* mutation carriers,^{180,186} the start of colon screening may be delayed. *MSH6* carriers should begin colonoscopic surveillance at age 30 to 35 years, and *PMS2* carriers should begin at age 35 to 40 years. However, screening may need to be initiated earlier in some families, depending on ages of cancers observed in family members. This screening is recommended every 2 to 3 years until age 40 or 50 years for *MSH6* and *PMS2* mutation carriers, respectively, at which time colonoscopy should be performed every 1 to 2 years.

Endometrial and Ovarian Cancer Surveillance: Women with Lynch syndrome are at heightened risk for endometrial and ovarian cancers (up to 60% and 24%, respectively).^{148,180,182,184} Education that enhances recognition of relevant symptoms (ie, dysfunctional uterine bleeding) is advised. Total abdominal hysterectomy and bilateral salpingo-oophorectomy is an option that should be considered for risk reduction in women who have completed childbearing and carry a *MLH1*, *MSH2*, or *MSH6* mutation.^{187,188} No clear evidence supports routine screening for gynecologic cancers. Annual endometrial sampling is an option for *MLH1* or *MSH2* mutation carriers.^{187,189–192} Routine transvaginal ultrasound and serum CA-125 testing are not endorsed because they have not been shown to be sufficiently sensitive or specific,^{187,189–193} but the panel recognized that circumstances may exist in which clinicians may find these tests helpful.

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

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30% in Korea.^{148,194} Most cases occur after age 40 years, and men have a stronger predisposition. Lynch syndrome is also associated with a 3% to 6% risk for small bowel cancer.^{180,183,186,195–197} No clear evidence supports screening for gastric, duodenal, and small bowel cancer in patients with Lynch syndrome.¹⁹⁸ For selected individuals or families or those of Asian descent with *MLH1* or *MSH2* mutations, physicians may consider upper esophagogastroduodenoscopy extended to the distal duodenum or into the jejunum every 3 to 5 years starting at age 30 to 35 years.¹⁹⁹

Annual urinalysis starting at age 25 to 30 years should also be considered to screen for urothelial cancers in carriers of *MLH1* or *MSH2* mutations, providing relative ease and low cost compared with other tests. These individuals have an increased risk for pancreatic and brain cancer.^{182–185} However, no effective screening techniques have been identified for pancreatic cancer; therefore, no screening recommendation is possible at this time. Annual history and physical examination starting at age 25 to 30 years is appropriate for central nervous system cancer.

In addition, investigators have suggested an increased risk for breast cancer in the Lynch syndrome population^{200,201}; however, because of limited data, no screening recommendation is possible at this time.

Lynch Syndrome Surveillance Findings and Follow-up: If there are no pathologic findings, continued surveillance is recommended. If the patient is not a candidate for routine surveillance, subtotal colectomy may be considered. This important feature is seen clinically often because some people cannot undergo a colonoscopy or decline to have one on a regular basis.

Patients with confirmed adenocarcinoma should be treated following the appropriate disease-specific treatment guidelines (see NCCN Guidelines for Treatment of Cancer by Site, available online, at 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 the adenomatous polyps identified cannot be endoscopically resected or high-grade dysplasia is identified, total abdominal colectomy with an ileorectal anastomosis is recommended. Because surgical management is evolving, the option of segmental or ex-

tended segmental colectomy is based on individual considerations and discussion of risks. These patients should be followed with endoscopic rectal examinations every 1 to 2 years.

Chemoprevention in Lynch Syndrome: In the recent randomized CAPP2 trial, 861 participants with Lynch syndrome took either daily aspirin (600 mg) or placebo for up to 4 years; the primary end point was the development of CRC.²⁰² After a mean follow-up of greater than 4 years, participants taking daily aspirin for at least 2 years had a 59% reduction in the incidence of CRC (hazard ratio [HR], 0.41; 95% CI, 0.19–0.86; $P=.02$). These participants also saw protection from noncolorectal Lynch syndrome cancers (HR, 0.47; 95% CI, 0.21–1.06; $P=.07$). No protection was seen for participants who completed less than 2 years of the intervention. Criticisms of this trial have been published.^{203,204} At this time, the panel believes that the data are not sufficiently robust to recommend standard use of aspirin as chemoprevention in Lynch syndrome.

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