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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colorectal Cancer Screening

Version 1.2018 — March 26, 2018

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NCCN Guidelines Version 1.2018 Panel Members
Colorectal Cancer Screening

* Dawn Provenzale, MD, MS/Chair ¤ Þ
Duke Cancer Institute

* Samir Gupta, MD/Vice-chair ¤
UC San Diego Moores Cancer Center

Dennis J. Ahnen, MD ¤
University of Colorado Cancer Center

Amie M. Blanco, MS, CGC Δ
UCSF Helen Diller Family
Comprehensive Cancer Center

Travis Bray, PhD ¥
Hereditary Colon Cancer Foundation

Daniel C. Chung, MD ¤ Δ
Massachusetts General Hospital
Cancer Center

Gregory Cooper, MD ¤
Case Comprehensive Cancer Center/
University Hospitals Seidman Cancer
Center and Cleveland Clinic Taussig
Cancer Institute

Dayna S. Early, MD ¤
Siteman Cancer Center at Barnes-
Jewish Hospital and Washington
University School of Medicine

James M. Ford, MD † Þ Δ
Stanford Cancer Institute

Francis M. Giardiello, MD, MBA ¤
The Sidney Kimmel Comprehensive
Cancer Center at Johns Hopkins

William Grady, MD ¤
Fred Hutchinson Cancer Research Center/
Seattle Cancer Care Alliance

Michael J. Hall, MD, MS † Δ
Fox Chase Cancer Center

Amy L. Halverson, MD ¶
Robert H. Lurie Comprehensive Cancer
Center of Northwestern University

Stanley R. Hamilton, MD ≠
The University of Texas
MD Anderson Cancer Center

Heather Hampel, MS, CGC Δ
The Ohio State University Comprehensive
Cancer Center - James Cancer Hospital
and Solove Research Institute

Jason B. Klapman, MD ¤
Moffitt Cancer Center

David W. Larson, MD, MBA¶
Mayo Clinic Cancer Center

Audrey J. Lazenby, MD ≠
Fred & Pamela Buffett Cancer Center

Xavier Llor, MD, PhD ¤ Þ
Yale Cancer Center/
Smilow Cancer Hospital

Patrick M. Lynch, MD, JD ¤
The University of Texas
MD Anderson Cancer Center

Arnold J. Markowitz, MD ¤
Memorial Sloan Kettering Cancer Center

Robert J. Mayer, MD † Þ
Dana-Farber/Brigham and Women's
Cancer Center

June Mikkelson, MS, CGC Δ
Roswell Park Cancer Institute

Reid M. Ness, MD, MPH ¤
Vanderbilt-Ingram Cancer Center

Scott E. Regenbogen, MD ¶
University of Michigan
Comprehensive Cancer Center

Thomas P. Slavin Jr, MD Δ
City of Hope Comprehensive
Cancer Center

Shajanpeter Sugandha, MD ¤
University of Alabama at Birmingham
Comprehensive Cancer Center

Jennifer M. Weiss, MD, MS ¤
University of Wisconsin
Carbone Cancer Center

NCCN
Ndiya Ogba, PhD
Mary Dwyer, MS

¤ Gastroenterology
Δ Cancer genetics
Þ Internal medicine
† Medical oncology
≠ Pathology
¶ Surgery/Surgical oncology
¥ Patient advocacy
* Discussion Writing Committee Member

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See NCCN Categories of Evidence and Consensus.

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NCCN Guidelines Version 1.2018 Updates Colorectal Cancer Screening

Updates in Version 1.2018 of the NCCN Guidelines for Colorectal Cancer Screening from Version 2.2017 include:

General

- The term "SSP with cytologic dysplasia (SSP-cd)" was changed to "SSP with dysplasia (SSP-d)."
- Footnote b, 3rd sentence was revised, "In general SSPs are managed like tubular adenomas and SSP-cds *with any grade dysplasia* are managed like high-risk adenomas..."

CSCR-1

- Risk assessment for colorectal cancer
  - Average risk, 4th bullet was revised by adding, "Negative family history for CRC *or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology)*." Also for CSCR-2.

CSCR-2

Average Risk Screening

- Screening Modality and Schedule
  - Colonoscopy, the criteria after polypectomy was revised, "Hyperplastic polyps ≥1 cm in size *or adenomas or SSP of any size*."
- Footnotes
  - Footnote c was revised: "CRC screening is recommended in adults ages 50–75 y. ~~Because the risk of colorectal screening increases with age,~~ The decision to screen between ages 76–85 y should be individualized and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. *Eligible* individuals who have not been previously screened are most likely to benefit in this age group."
  - Footnote h was added, "Based on recent evidence, FIT has been shown to have superior sensitivity to guaiac-based tests. However, guaiac-based testing has been shown to reduce mortality from CRC and high-sensitivity FOBT is a reasonable alternative if an immunochemical test cannot be used. (Rabeneck L, et al. Can J Gastroenterol 2012;26:131-147; Scholefield JH, et al. Gut 2012;61:1036-1040.)"
  - Footnote j was revised, "There are insufficient data to determine whether individuals with small *(<1 cm)* hyperplastic polyps proximal to ~~rectum or~~ sigmoid colon should be considered at increased risk and managed differently."

CSCR-3

Average Risk Screening (continued)

- Screening Modality and Schedule
  - Flexible sigmoidoscopy was revised by removing, "± interval high-sensitivity guaiac-based or immunochemical-based testing at year 3."
    - ◊ Positive stool test pathway was removed.
    - ◊ "Negative stool test" was removed from "No polyps"
    - ◊ The criteria after "Biopsy or polypectomy" was revised to be consistent with CSCR-2, "*Hyperplastic polyps ≥1 cm in size, or* adenoma/SSP *of any size*" and "Hyperplastic <1 cm *only*."
  - CTC
    - ◊ After Negative/No Polyps, the evaluation was revised as, "Rescreen *with any modality* in 5 y."
- Footnote m was added, "There are alternative strategies that have been recommended with flexible sigmoidoscopy including flexible sigmoidoscopy every 10 years with annual FIT or considering longer interval flexible sigmoidoscopy without FIT (Knudsen A, Zauber A, Rutter C, et al. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: Modeling study for the US Preventive Services Task Force. JAMA 2016;315:2595-2609)."

CSCR-4

Personal History of Adenomatous Polyp or Sessile Serrated Polyp

- Clinical Findings
  - SSP without dysplasia was separated out from low-risk polyps into "intermediate-risk polyps."
- Follow-up of Clinical Findings
  - Low-risk polyps was changed from "repeat colonoscopy within 5–10 y" to "Repeat colonoscopy between 5–10 y."
    - ◊ The follow-up for positive/adenoma or SSP was changed to "Repeat colonoscopy according to clinical findings" rather than looping back to the beginning of the algorithm. Also for High risk.
  - High risk was changed from "Repeat colonoscopy within 3 y" to "Repeat colonoscopy in 3 y."
    - ◊ The criteria for negative was revised, "Negative for adenoma or SSP ~~or~~ ± low-risk polyps."
      - – The follow-up was revised from "Repeat colonoscopy within 5 y" to "Repeat colonoscopy in 5 y."

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Updates in Version 1.2018 of the NCCN Guidelines for Colorectal Cancer Screening from Version 2.2017 include:

CSCR-5

Increased Risk Based on Personal History of Colorectal Cancer

- Footnote r was revised, "The panel recommends universal screening of all CRC tumors to maximize sensitivity for identifying individuals with LS, and to ~~simplify~~ *inform prognosis and* care processes *in patients with and without LS*. ~~However, evidence suggests an alternate option would be to limit screening to individuals with CRC diagnosed <70 y plus those >70 y meeting Bethesda guidelines~~. *The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab–based universal screening and to guide treatment decisions.*"
- References were removed, "Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555-1565" and "Evaluation of Genomic Applications in Practice and Prevention Working Group from the CDC and shown to be cost-effective (EGAPP Recommendation Statement. Genetics in Medicine 2009;11:35-41)" and are located in the Discussion.

CSCR-6

Increased Risk Based on Personal History of Inflammatory Bowel Disease

- Surveillance Modality and Schedule
  - Colonoscopy
    - ◊ 1st sub-bullet for HD-WLS/SD-WLE was revised, "Random 4 quadrant biopsies every 10 cm with >~~33~~ *32* total samples."
    - ◊ 1st sub-bullet for chromoendoscopy was revised, "If biopsies for dysplasia are not done, 2 random biopsies in every bowel segment ~~are commonly recommended~~ *may be considered* to document microscopic disease activity."

CSCR-8

Increased Risk Based on Positive Family History

- Family History Criteria
  - First criteria were revised:
    - ◊ "≥1 first-degree relative with ~~adenomatous CRC~~ *colorectal adenocarcinoma* at any age"
    - ◊ ≥1 second-degree relative with ~~CRC~~ *colorectal adenocarcinoma* aged <50 y."
  - Footnotes
    - ◊ Footnote ee was revised, "Colonoscopy intervals ~~should~~ *may* be further modified based on personal and family history as well as on individual preferences...including number and age of onset of all affected relatives, *whether relatives had an inciting cause such as inflammatory bowel disease*; size of family; completeness of the family history; participation in screening; and colonoscopy findings in family members. See Discussion."
    - ◊ Footnote ff was added, "For individuals not willing to undergo colonoscopy, there are emerging data that FIT may be a reasonable substitute."
    - ◊ Footnote was removed, "For individuals with a family history of CRC, diagnosed at a younger age, a shortened interval may be appropriate."

Screening Modality and Schedule

CSCR-A 1 of 5

- 5th bullet, last sentence was revised by adding, "If a result is determined to be a false positive *(eg, positive stool DNA test followed by a negative colonoscopy)*, clinical judgment and shared decision-making should be used regarding future patient management."

CSCR-A 3 of 5

- Colonoscopy
  - 1st bullet, a sub-bullet was removed, "Number, size, and location of polyps detected."
- Flexible sigmoidoscopy
  - Bullet was removed, "May be performed alone or in combination with high-sensitivity FOBT or FIT."

CSCR-A 4 of 5

- CTC
  - Accuracy, 2nd sub-bullet was revised, "Lesions ~~5~~ *6* –9 mm can be identified with an acceptable accuracy that is less than that identified for colonoscopy."

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RISK ASSESSMENT FOR COLORECTAL CANCER

Average risk:[a]

- Age ≥50 y
- No history of adenoma or sessile serrated polyp (SSP)[b] or colorectal cancer (CRC)
- No history of inflammatory bowel disease
- Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology)

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

Increased risk:

- Personal history
  - Adenoma or SSP[b] → See Follow-up of Clinical Findings: Adenomatous Polyp or Sessile Serrated Polyp (CSCR-4)
  - CRC → See Increased Risk Based on Personal History of Colorectal Cancer (CSCR-5)
  - Inflammatory bowel disease (ulcerative colitis, Crohn's disease) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-6)
- Positive family history → See Increased Risk Based on Positive Family History (CSCR-8)

High-risk syndromes:

- Lynch syndrome (hereditary nonpolyposis colorectal cancer [HNPCC])
- Polyposis syndromes
  - Classical familial adenomatous polyposis
  - Attenuated familial adenomatous polyposis
  - *MUTYH*-associated polyposis
  - Peutz-Jeghers syndrome
  - Juvenile polyposis syndrome
  - Serrated polyposis syndrome (rarely inherited)
  - Colonic adenomatous polyposis of unknown etiology

→ See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal

- Cowden syndrome/PTEN hamartoma tumor syndrome
- Li-Fraumeni syndrome

→ See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Breast and Ovarian

[a]See Discussion for further information on age of screening in African Americans.

[b]The terms sessile serrated polyp (SSP) and sessile serrated adenoma are synonymous; SSPs are a type of serrated polyp that are not dysplastic but they can develop foci of dysplasia and are then termed SSP with dysplasia (SSP-d). These guidelines will use "SSP" for SSPs without dysplasia and "SSP-d" for SSPs with dysplasia. In general SSPs are managed like tubular adenomas and SSP-ds with any grade dysplasia are managed like high-risk adenomas but may need even more frequent surveillance. In addition, any serrated lesions proximal to the sigmoid colon should be followed similarly to adenomatous polyps.

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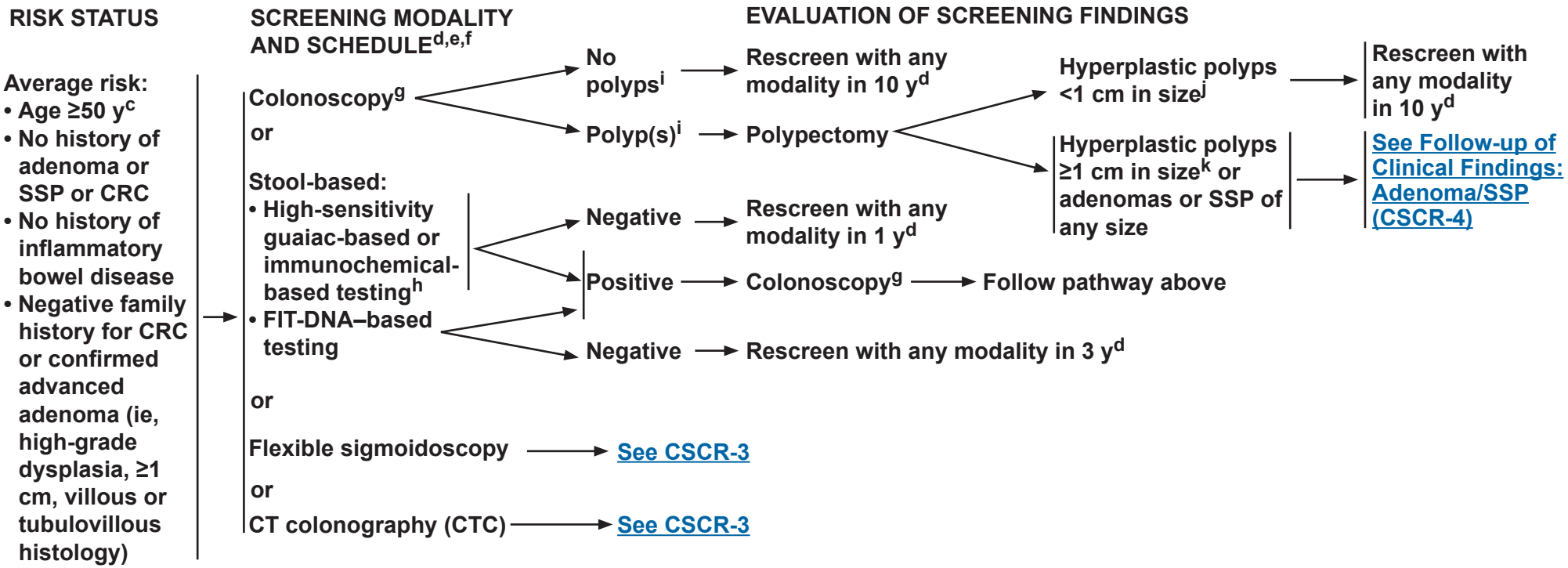

[c]CRC screening is recommended in adults ages 50–75 y. The decision to screen between ages 76–85 y should be individualized and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. Eligible individuals who have not been previously screened are most likely to benefit in this age group.

[d]See Screening Modality and Schedule (CSCR-A).

[e]A blood test that detects circulating methylated SEPT9 DNA was recently FDA-approved and may provide an option for screening for those who refuse other screening modalities, but its ability to detect CRC and advanced adenoma is inferior to other recommended screening modalities. The interval for repeating testing is unknown.

[f]Screening should be individualized and include a discussion of the risks and benefits of each modality.

[g]If colonoscopy is incomplete or preparation is suboptimal, consider other screening modality or repeat colonoscopy within 1 year (Johnson D, et al. Gastro 2014;147:903-924).

[h]Based on recent evidence, FIT has been shown to have superior sensitivity to guaiac-based tests. However, guaiac-based testing has been shown to reduce mortality from CRC and high-sensitivity FOBT is a reasonable alternative if an immunochemical test cannot be used. (Rabeneck L, et al. Can J Gastroenterol 2012;26:131-147; Scholefield JH, et al. Gut 2012;61:1036-1040.)

[i]The term "polyp" refers to both polyp and nonpolypoid (flat) lesions.

[j]There are insufficient data to determine whether individuals with small (<1 cm) hyperplastic polyps proximal to the sigmoid colon should be considered at increased risk and managed differently.

[k]There are limited data to support whether individuals with hyperplastic polyps >1 cm in size represent an increased risk group. Some data suggest that many of these polyps are in fact SSPs that have been incorrectly characterized.

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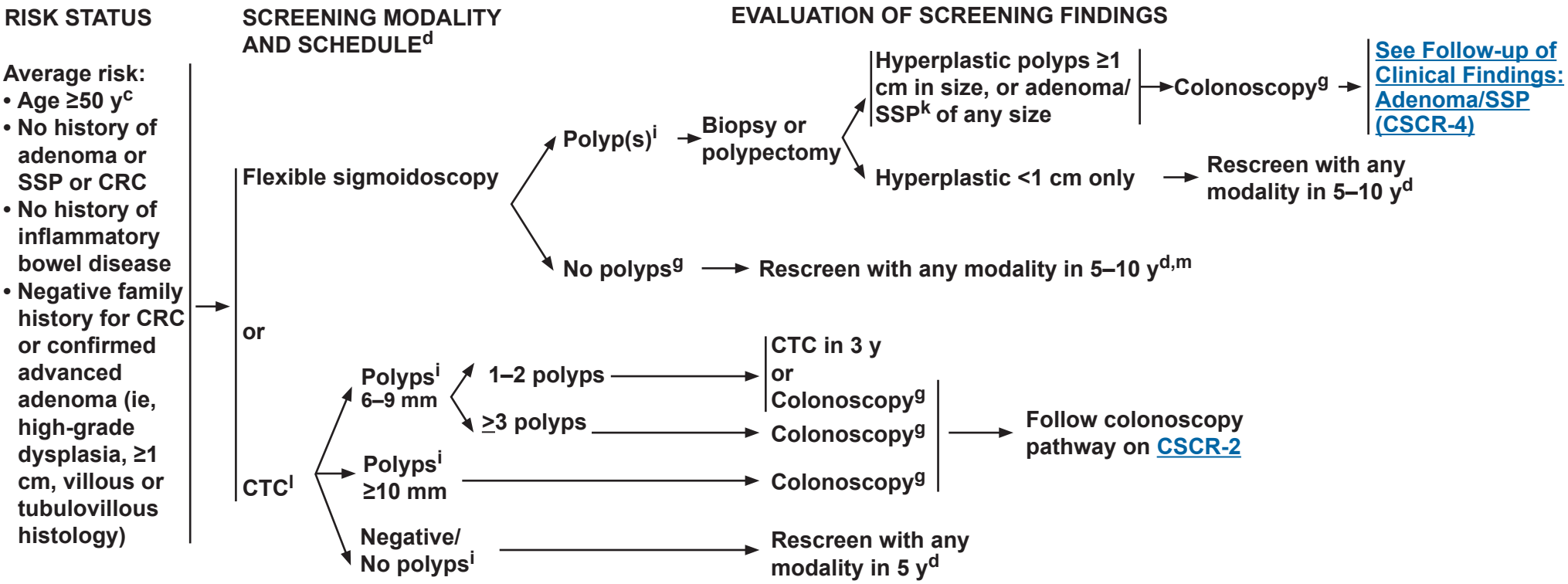

For Colonoscopy and Stool-based screening, see CSCR-2.

[c]CRC screening is recommended in adults ages 50–75 y. The decision to screen between ages 76–85 y should be individualized, and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. Eligible individuals who have not been previously screened are most likely to benefit in this age group.

[d]See Screening Modality and Schedule (CSCR-A).

[g]If colonoscopy is incomplete or preparation is suboptimal, consider other screening modality or repeat colonoscopy within 1 year (Johnson D, et al. Gastro 2014;147:903–924).

[i]The term "polyp" refers to both polyp and nonpolypoid (flat) lesions.

[k]There are limited data to support whether individuals with hyperplastic polyps >1 cm in size represent an increased risk group. Some data suggest that many of these polyps are in fact SSPs that have been incorrectly characterized.

[l]Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for evaluation of extracolonic lesions are evolving. The American College of Radiology has recommended that reporting of polyps ≤5 mm in size is not necessary. If polyp(s) of this size are reported, a decision to refer for colonoscopy with polypectomy versus surveillance CTC should be individualized.

[m]There are alternative strategies that have been recommended with flexible sigmoidoscopy, including flexible sigmoidoscopy every 10 years with annual FIT or considering longer interval flexible sigmoidoscopy without FIT (Knudsen A, Zauber A, Rutter C, et al. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: Modeling study for the US Preventive Services Task Force. JAMA 2016;315:2595-2609).

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PERSONAL HISTORY OF ADENOMATOUS POLYP OR SESSILE SERRATED POLYP[k]

RISK STATUS	CLINICAL FINDINGS	FOLLOW-UP OF CLINICAL FINDINGS[d]		
Personal history of adenomatous polyp(s) or SSPs[k] found at colonoscopy[n]	Low-risk polyps (tubular adenoma):[k] • ≤2 polyps • ≤1 cm	Repeat colonoscopy between 5–10 y[q]	Negative/ No adenoma or SSP	Repeat colonoscopy every 10 y[q]
	Intermediate-risk polyps (SSP without dysplasia [d]):[k] • ≤2 polyps • ≤1 cm	Repeat colonoscopy in 5 y[q]	Positive/ adenoma or SSP	Repeat colonoscopy according to clinical findings
	High risk (advanced or multiple polyps):[k,o] • High-grade dysplasia or SSP-ed or • Adenoma or any SSP ≥1 cm or • Villous or tubulovillous histology or • Between 3 and 10 adenomatous polyps and/or SSPs[k,o]	Repeat colonoscopy in 3 y[q]	Negative for adenoma or SSP ± low-risk polyps	Repeat colonoscopy in 5 y[q]
	More than 10 cumulative adenomatous polyps[k,o]	• Individual management • Consider a polyposis syndrome	See NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	
	Incomplete or piecemeal polypectomy[p] or polypectomy of large sessile polyps[k]	Repeat colonoscopy within 2–6 mo[q] (timing depends on endoscopic and pathologic findings)		
	Malignant polyp[k]	See NCCN Guidelines for Colon Cancer or See NCCN Guidelines for Rectal Cancer		

[d] See Screening Modality and Schedule (CSCR-A).

[k] There are limited data to support whether individuals with hyperplastic polyps >1 cm in size represent an increased risk group. Some data suggest that many of these polyps are in fact SSPs that have been incorrectly characterized.

[n] Surveillance colonoscopy is recommended in adults ages 50–75 y with a history of adenomas. Because the risk of colonoscopy increases with age, surveillance of individuals between ages 76–85 y should be individualized and include a discussion of risks and benefits of continued colonoscopy based on comorbidity status, estimated life expectancy, and findings on the last or the most recent colonoscopy.

[o] Ten 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.

[p] Ink lesion for later identification; sterile carbon black ink preferred.

[q] These intervals may be individualized based on the colonic preparation and completeness of polypectomy (based on endoscopy and pathology reports, and on histology). Surveillance at 1- to 3-year intervals for SSP-eds has been recommended because they are thought to progress rapidly to cancer (Rex D, et al. Am J Gastro 2012:107:1315-29). Other factors in determining intervals might include the results of the prior examinations and the presence of comorbid conditions. The results of the first two screening examinations may predict the patient's overall colon cancer risk. (USPSTF, Screening for colorectal cancer: U.S. Preventive Service Task Force recommendation statement. Ann Intern Med 2008;149:627-637). The recommendation for a shorter interval should include a discussion with the individual based on an assessment of individual risk, including age, family history, comorbidity, and the results of previous colonoscopies.

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INCREASED RISK BASED ON PERSONAL HISTORY OF COLORECTAL CANCER

RISK STATUS	TESTING[r]	SURVEILLANCE
Personal history of CRC →	• Lynch syndrome (LS) screening with routine tumor testing is recommended at the time of diagnosis for all individuals with CRC • For additional information on LS, see NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal	→ See NCCN Guidelines for Colon Cancer and See NCCN Guidelines for Rectal Cancer

[r]The panel recommends universal screening of all CRC tumors to maximize sensitivity for identifying individuals with LS, and to inform prognosis and care processes in patients with and without LS. The panel recommends tumor testing with IHC and/or MSI be used as the primary approach for pathology-lab–based universal screening and to guide treatment decisions.

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INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE

RISK STATUS	INITIATION OF SURVEILLANCE	SURVEILLANCE MODALITY AND SCHEDULE	
Personal history of inflammatory bowel disease[s,t] • Ulcerative colitis • Crohn's colitis	→ 8 y after onset of symptoms[u]	→ • Colonoscopy ▸ High-/standard-definition white light endoscopy (HD-WLE/SD-WLE)[v] ◊ Random 4-quadrant biopsies every 10 cm with ≥ 32 total samples ◊ Additional extensive sampling of strictures and masses OR ▸ Chromoendoscopy with targeted biopsy (high-definition colonoscopy suggested)[v] ◊ If biopsies for dysplasia are not done, 2 random biopsies in every bowel segment may be considered to document microscopic disease activity • For both colonoscopy modalities, endoscopic polypectomy when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia	→ Evaluation of Positive Surveillance Findings (CSCR-7)

[s]Information regarding the value of endoscopic surveillance of long-standing Crohn's disease is limited. Risk factors for dysplasia include ulcerative colitis; extensive colitis; colonic stricture; primary sclerosing cholangitis (PSC); family history of CRC, especially age <50 y; personal history of dysplasia; and severe longstanding inflammation postinflammatory/pseudopolyps. Confirmation by an expert GI pathologist is desirable. Patients with proctosigmoiditis, who have little or no increased risk for CRC compared with the population at large, should be managed according to standard CRC screening guidelines. Lutgens M, et al. Clinical Gastroenterol Hepatol 2015;13:148-154. Beaugerie L, et al. Risk of colorectal high grade dysplasia and cancer in a prospective observational cohort of patients with IBD Gastroenterology 2013;145:166-175.

[t]If PSC is present, annual surveillance colonoscopies should be started independent of the individual colonoscopic findings and should be initiated at time of PSC diagnosis.

[u]Shergill AK, Farraye FA. Gastrointest Endosc Clin N Am 2014;24:469-481.

[v]Endoscopy should be performed during quiescent disease states. Targeted biopsies improve detection of dysplasia, and should be considered for surveillance colonoscopies in patients with ulcerative colitis where expertise is available. Murthy Y, Kiesslich R. Gastointest Endosc 2013;77:351-359. Picco MF, et al. Inflamm Bowel Dis 2013;19:1913-20. Laine L, et al. SCENIC international consensus statement on surveillance and management of dysplasia in inflammatory bowel disease. Gastrointest Endosc 2015;81:489-501. The role of chromoendosocopy (CE) has been questioned and the natural history of dysplastic lesions identified using CE remains unknown. Marion JF, Sands BE. Gastroenterology 2015;148:462-467.

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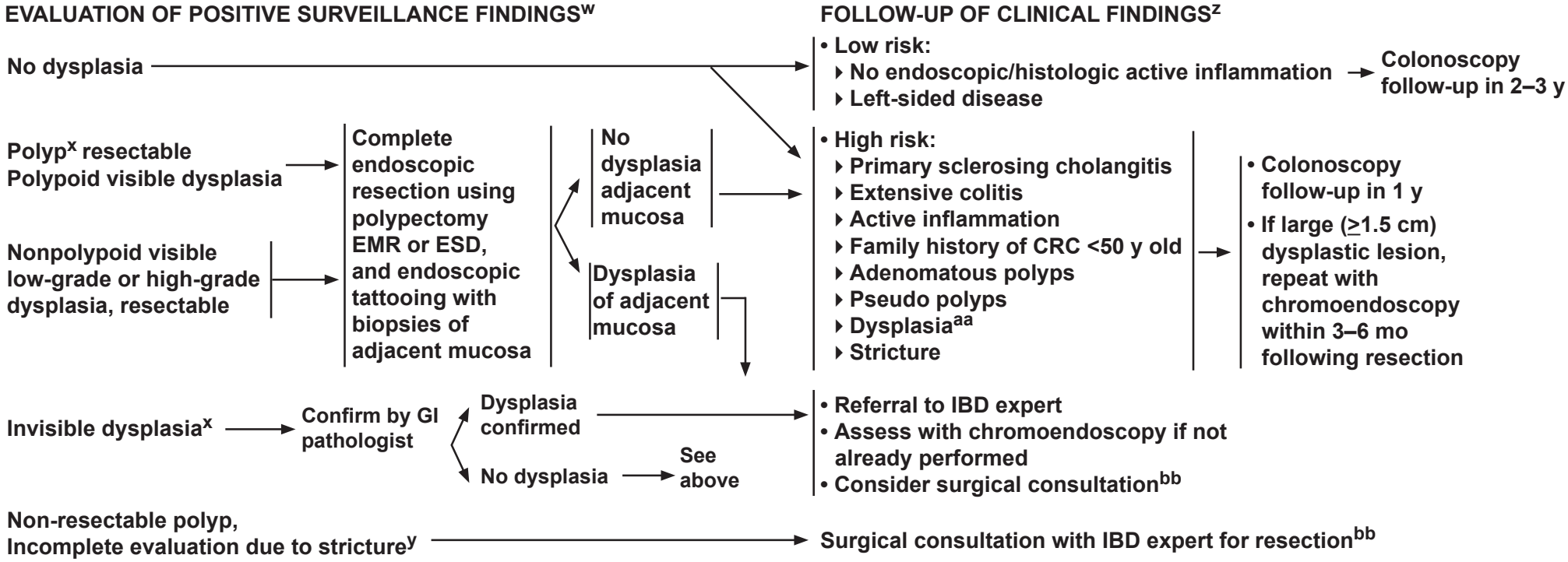
INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE



[w]Consider utilizing Paris classification to describe dysplasia. All resectable polyps and dysplasia must be performed to negative margins.

[x]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 colon and without invasive carcinoma in the polyp can be treated safely by polypectomy using ESD (endoscopic submucosal dissection) or EMR (endoscopic mucosal resection) and continued surveillance. Confirmation of all polyps and dysplasia by an expert GI pathologist is desirable.

[y]A stricture is a strong indication for colectomy because of the high rate of underlying carcinoma, especially a stricture that is symptomatic or not traversable during colonoscopy, particularly in long-standing disease.

[z]UK, Australian, and European GI societies position statements recommend risk-stratified surveillance with increased surveillance interval to 3–5 years in lowest-risk patients. (Shergill A, Faraye F. Toward a consensus on endoscopic surveillance of patients with colonic inflammatory bowel disease. Gastrointest Endosc Clin N Am 2014; 24:469-481). SCENIC consensus guidelines recommend every-3-year surveillance when colitis is in remission.

[aa]All dysplastic resected lesions should be followed up within 3–6 months with chromoendoscopy due to high risk of additional dysplastic lesions being found on follow-up (Deepak P, et al. Gastrointest Endosc 2016;83:1005-1012.)

[bb]A surgical consult may include a discussion about surveillance and colectomy based on multiple factors including other visible dysplastic lesions in the same segment, histology, and a discussion with the patient about risks and benefits of each approach (Laine L, Kaltenbach T, Barkun A, et al. Gastroenterology 2015;148:639-651 e628). In patients with endoscopically invisible dysplasia, the recommendation for referral to an endoscopist with IBD expertise for chromoendoscopy is consensus-based as data to support its use in this setting are limited.

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INCREASED RISK BASED ON POSITIVE FAMILY HISTORY
(Appropriate testing for a hereditary syndrome is non-diagnostic[cc])

FAMILY HISTORY CRITERIA[dd]	SCREENING[ee,ff]	
≥1 first-degree relative with colorectal adenocarcinoma at any age	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	Repeat every 5 y[dd,ee,gg] or if positive, repeat per colonoscopy findings
≥1 second-degree relative with colorectal adenocarcinoma aged <50 y	Colonoscopy beginning at age 50 y	Repeat every 5–10 y[dd,ee,gg] or if positive, repeat per colonoscopy findings
First-degree relative with confirmed advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology)	Colonoscopy beginning at age 40 y or at age of onset of adenoma in relative, whichever is first	Repeat every 5–10 y[ee,gg] or if positive, repeat per colonoscopy findings

[cc]If a patient meets the criteria for an inherited colorectal syndrome, see Assessment for Hereditary CRC Syndrome (HRS-1) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

[dd]Some 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. Taylor DP, Stoddard GJ, Burt RW, et al. How well does family history predict who will get colorectal cancer? Implications for cancer screening and counseling. Genet Med 2011;13:385-391. Samadder NJ, Curtin K, Tuohy TM, et al. Increased risk of colorectal neoplasia among family members of patients with colorectal cancer: a population-based study in Utah. Gastroenterology 2014;147:814-821.

[ee]Colonoscopy intervals may be further modified based on personal and family history as well as on individual preferences. Factors that modify age to begin screening and colonoscopy intervals include: age of individual undergoing screening; specifics of the family history, including number and age of onset of all affected relatives, whether relatives had an inciting cause such as inflammatory bowel disease; size of family; completeness of the family history; participation in screening; and colonoscopy findings in family members. See Discussion.

[ff]For individuals not willing to undergo colonoscopy, there are emerging data that FIT may be a reasonable substitute.

[gg]Multiple (2 or more) negative colonoscopies may support stepwise lengthening in the colonoscopy interval.

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SCREENING MODALITY AND SCHEDULE

- Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and may decrease CRC incidence by detecting and removing polyps.
- CRC screening should be performed as part of a program that includes a systematic method for identifying those who are eligible for and wish to undergo screening, standard methods for administering the screening tests at agreed upon intervals, standardized reporting of the results, and a mechanism for follow-up of those with a positive test.
- There is direct evidence from randomized controlled trials that fecal occult blood testing (FOBT)[1,2,3] and flexible sigmoidoscopy[4,5,6] will reduce mortality from CRC. There is evidence from case-control and cohort studies that colonoscopy has the potential ability to prevent CRC (with its associated morbidity) and cancer deaths.[7,8]
- Low-sensitivity guaiac-based stool testing has been shown to reduce CRC in randomized trials (category 1). Studies have demonstrated that high-sensitivity guaiac-based testing is more sensitive than low-sensitivity guaiac-based testing and that FIT testing is more sensitive than high-sensitivity guaiac-based testing.
- A multi-target stool DNA combined with a FIT test has recently been approved by the FDA as a primary screening modality for CRC.[9] At this time, there are limited data available to determine an appropriate interval between screening; however, every 3 years has been suggested.[10] The data in an average-risk individual indicate that stool DNA performs well. There are no or limited data in high-risk individuals and the use of stool DNA should be individualized. If a result is determined to be a false positive (eg, positive stool DNA test followed by a negative colonoscopy), clinical judgment and shared decision-making should be used regarding future patient management.[11]

Screening modalities that detect adenomatous polyps and cancer[12,13,14]
- Colonoscopy every 10 years
- Flexible sigmoidoscopy every 5–10 years
- CTC every 5 years[15]

Screening modalities that primarily detect cancer[12,13,14]
- Stool-based screening
  - High-sensitivity guaiac-based testing annually
  - Immunochemical-based testing annually
  - Stool DNA test (which includes high-sensitivity FIT)
    - ◊ Interval for screening is uncertain; however, every 3 years is suggested[16]

See Footnotes and References on CSCR-A 5 of 5

Continued

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SCREENING MODALITY AND SCHEDULE

Colonoscopy

- In the United States, colonoscopy is the most commonly employed CRC screening test for average- and high-risk populations. There are multiple options; however, the choice of modality should be based on patient preference and availability.
- Caveats for the 10-year interval:
  - A 10-year interval is appropriate for those who had a complete procedure with an adequate prep.
  - Repeating within 1 year may be indicated based on the quality, completeness of the colonoscopy, and 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.[17]
- Colonscopy preparation[18]
  - To determine preparation quality, a preliminary assessment should be made in the rectosigmoid colon. If an inadequate preparation would interfere with the detection of polyps >5 mm, the procedure should be rescheduled. Alternatively, additional bowel cleaning can be attempted for the colonoscopy to proceed that day.
  - In cases where colonoscopy is complete to the cecum but the preparation is ultimately considered inadequate, colonoscopy should be repeated within 1 year. A more aggressive preparation regimen should be recommended in these cases. When advanced neoplasia is detected and prep was inadequate, an interval shorter than 1 year is indicated.
- Accumulating data suggest that there is substantial variability in the quality, and by extension, the clinical effectiveness of colonoscopy. A number of quality indicators have been examined. 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
  - Adenoma detection rates
  - Withdrawal time
  - 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 prep instructions[18]
    - ◊ Split-dose prep has been shown to be superior and is recommended.
    - ◊ Preferred timing of the second dose of split-dose preparation:
      - – Start 4–6 hours before colonoscopy
      - – End at least 2 hours before colonoscopy
    - ◊ Same-day, morning-only preparation is an acceptable alternative to split-dose preparation, especially in patients scheduled for afternoon procedures.

See Footnotes and References on CSCR-A 5 of 5

Continued

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SCREENING MODALITY AND SCHEDULE

Colonoscopy (Continued)

- Standardized colonoscopy reports that contain, at a minimum:[19]
  - Patient demographic, clinical factors including comorbidities, 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, including the ileocecal valve
  - 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.

Stool-based screening

- If colonoscopy is used as the screening modality in an average-risk patient, then additional, interval stool-based testing is not indicated.
- High-sensitivity guaiac-based, nonrehydrated[20]
  - 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
- FIT
  - Non-randomized studies have demonstrated that FIT is more sensitive than guaiac-based testing[21,22,23] and also reduces mortality.[24,25]
  - Detects human globin
  - Prescribed diet is not required
  - Many brands require only a single stool annually
  - Any positive test requires further evaluation

Flexible sigmoidoscopy[20]

- Recommended every 5–10 years for average-risk screening

See Footnotes and References on CSCR-A 5 of 5

Continued

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SCREENING MODALITY AND SCHEDULE

Radiographic

CTC[15,26,27]

- Accuracy
  - >10-mm lesions can be identified by CTC with an accuracy similar to colonoscopy.
  - Lesions 6–9 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
  - When identified, lesions ≤5 mm do not need to be reported or referred for colonoscopy.
  - If 1 or 2 lesions that are 6–9 mm are found, then CTC surveillance in 3 years or colonoscopy is recommended.[28,29,30]
  - If ≥3 lesions that are 6–9 mm or any lesion ≥10 mm are found, then colonoscopy is recommended.
- The recommended performance interval of every 5 years was originally based on barium enema; however, it has been supported with more recent data.[31]
- All visualized extracolonic findings should be described and recommendations should be provided as to appropriate follow-up (including no follow-up).
- The future cancer risk of a single CTC is unknown but likely very low. No empiric data have shown increased risk at levels below an exposure of 100 mSv.[32]
- CTC interpretation should be accomplished only by those trained according to American Gastroenterological Association[26] or American College of Radiology (ACR)[27] guidelines.
- Procedure quality should be tracked and assured using current ACR practice guidelines for patient preparation, image acquisition, study interpretation, and reporting.

See Footnotes and References on CSCR-A 5 of 5

Continued

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SCREENING MODALITY AND SCHEDULE
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[1]Mandel J, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study N Engl J Med 1993;328:1365-1371.
[2]Hardcastle J, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472-1477.
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[4]Atkin W, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;375:1624-1633.
[5]Schoen R, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Eng J Med 2012;366:2345-2357.
[6]Nishihara R, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Eng J Med 2013;369:1095-1105.
[7]Kahi C, et al. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol 2009;7:770-775.
[8]Baxter N, Goldwasser M, Paszat L, et al. Association of colonoscopy and death from colorectal cancer. Ann Intern Med 2009;150:1-8.
[9]Imperiale T, Ransohoff D, Itzkowitz S, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287-1297.
[10]Berger B, Schroy P 3rd, Dinh T. Screening for colorectal cancer using a multitarget stool DNA test: Modeling the effect of the intertest interval on clinical effectiveness. Clin Colorectal Cancer 2016;15:e65-e74.
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[13] Lieberman D, Rex D, Winawer S, et al; United States Multi-Society Task Force on Colorectal Cancer. Guidelines for colonoscopy surveillance after screening and polypectomy: a consensus update by the US Multi-Society Task Force on Colorectal Cancer. Gastroenterology 2012;143:844-857.
[14]Rex D, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. Am J Gastroenterol 2009;104:739-750.
[15]Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for evaluation of extracolonic lesions are evolving. The American College of Radiology has recommended that reporting of polyps ≤5 mm in size is not necessary. If polyp(s) of this size are reported, decision to refer for colonoscopy with polypectomy versus surveillance colonoscopy should be individualized.
[16]A multi-target stool DNA combined with FIT test has recently been approved by the FDA as a primary screening modality for colorectal cancer. At this time, there are limited data available to determine an appropriate interval between screening; however, every 3 years has been suggested. The data in an average-risk individual indicate that stool DNA performs well. There are no or limited data in high-risk individuals and the use of stool DNA should be individualized. If a result is determined to be a false positive, clinical judgment and shared decision-making should be used.
[17]Singh S, Singh P, Murad M, Singh H, Samadder NJ. Prevalence, risk factors, and outcomes of interval colorectal cancers: a systematic review and meta-analysis. Am J Gastroenterol 2014;109:1375-1389.
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[19]Lieberman D, Nadel M, Smith R, 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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[26]See American Gastroenterological Association CT Colonography Standards.
[27]See American College of Radiology Practice Guideline for the Performance of Computed Tomography (CT) Colonography in Adults.
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[29]Tutein Nolthenius CJ, Boellaard TN, de Haan MC, et al. Evolution of screen-detected small (6-9 mm) polyps after a 3-year surveillance interval: assessment of growth with CT colonography compared with histopathology. Am J Gastroenterol 2015;110:1682-1690.
[30]Pickhardt PJ, Kim DH, Pooler BD, et al. Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinalstudy of natural history. Lancet Oncol 2013;14:711-720.
[31]Pickhardt PJ, Pooler BD, Mbah I, Weiss JM, Kim DH. Colorectal findings at repeat CT colonography screening after initial CT colonography screening negative for polyps larger than 5 mm. Radiology 2017;282:139-148.
[32]Health Physics Society. Radiation Risk in Perspective. Position Statement. May 2017.

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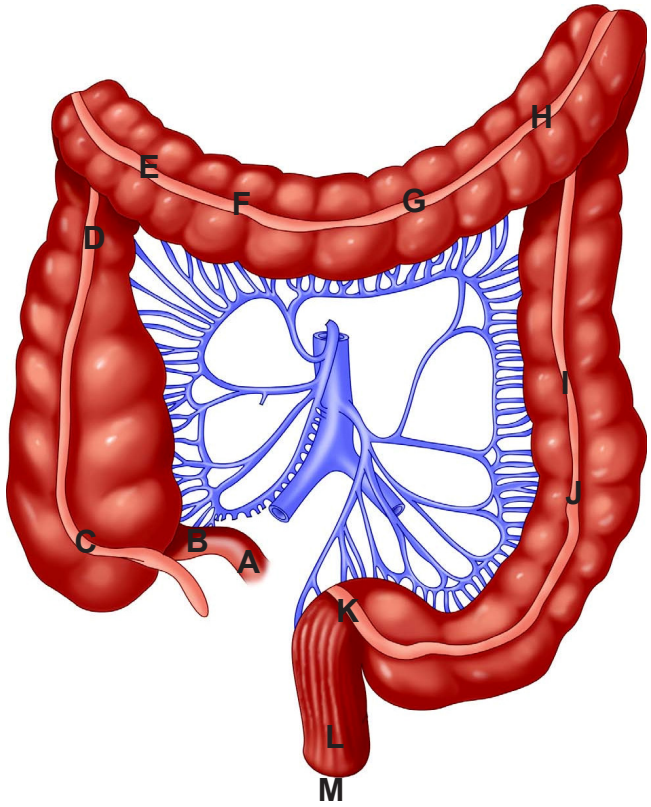
DEFINITIONS OF COMMON COLORECTAL RESECTIONS

The extent of colorectal resection depends on the location of the tumor, any underlying condition (eg, inflammatory bowel disease, hereditary syndrome), and the vascular supply to the colorectum.

Definitions of common colorectal resections are as follows:[1]



A through C	Ileocecectomy
A through F	Right hemicolectomy
A through G, H or I	Extended right hemicolectomy
E through I	Transverse colectomy
G through K	Left hemicolectomy
F through I	Extended left hemicolectomy
J through K	Sigmoid colectomy
A through K	Total colectomy
I through L	Low anterior resection with sphincter preservation
I through M	Abdominoperineal resection without sphincter preservation
A through M	Total proctocolectomy

[1]Adapted and reprinted with permission from Bullard KM and Rothenberger DA. (2005). Colon, Rectum, and Anus. In Brunicardi C (Ed.) Schwartz's Principles of Surgery, 8th Edition, page 1069. McGraw Hill: New York, NY.

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Discussion

This discussion is being updated to correspond with the newly updated algorithm. Last updated 11/14/17

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.

Discussion update in progress

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Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. In 2017, an estimated 95,520 new cases of colon cancer and 39,910 new cases of rectal cancer will occur in the United States.[1] During the same year, it is estimated that 50,260 people will die from colon and rectal cancer.[1] Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and may decrease CRC incidence by detecting and removing polyps.[2-4] Currently, patients with localized CRC have a 90% relative 5-year survival rate, whereas rates for those with regional and distant disease are 71% and 14%, respectively, demonstrating that earlier diagnosis can have a large impact on survival.[1]

Importantly, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005.[5] 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.[6] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[7] and in 2014 was down by 51% from peak mortality rates.[1] These improvements in incidence of and mortality from CRC over past years are thought, at least in part, to be a result of cancer prevention and earlier diagnosis through screening and better treatment modalities. In fact, modeling suggests that approximately 63% of CRC deaths can be attributed to non-screening.[8] According to the Centers for Disease Control and Prevention (CDC), the screening rate among U.S. adults aged 50 to 75 years has increased from approximately 42% in 2000 to 59% in 2010.[9] The National Colorectal Cancer Roundtable established the goal to increase U.S. CRC screening rates to 80% by 2018, which they estimate could prevent approximately 280,000 new CRC cases and 200,000 CRC deaths through 2030.[10]

These NCCN Guidelines for Colorectal Cancer Screening describe various colorectal screening modalities as well as recommended screening schedules for patients at average or increased risk of developing sporadic CRC. They are intended to aid physicians with clinical decision-making regarding CRC screening for patients without defined genetic syndromes. Recommendations regarding the management of inherited syndromes such as Lynch syndrome (also known as hereditary nonpolyposis colorectal cancer, or HNPCC), familial adenomatous polyposis (FAP), *MutY human homolog* (MUTYH)-associated polyposis (MAP), Peutz-Jeghers syndrome (PJS), juvenile polyposis syndrome (JPS), and serrated polyposis syndrome (SPS) are addressed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).[11-13]

Literature Search Criteria and Guidelines Update Methodology

Prior to the update of this version of the NCCN Guidelines for Colorectal Cancer Screening, an electronic search of the PubMed database was performed to obtain key literature in the field of CRC screening published between October 22, 2015 and October 10, 2016, using the following search terms: (colorectal cancer screening) or (colon cancer screening) or (rectal cancer screening) or (colorectal cancer prevention) or (colon cancer prevention) or (rectal cancer prevention) or (colonoscopy) or (fecal occult blood) or (fecal immunochemical testing) or (flexible sigmoidoscopy) or (stool DNA) or (CT colonography) or (inflammatory bowel disease cancer) or (ulcerative colitis cancer) or (Crohn's disease cancer). The PubMed database was chosen because it remains the most widely used resource for medical literature and indexes only peer-reviewed biomedical literature.[14]

The search results were narrowed by selecting studies in humans published in English. Results were confined to the following article

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types: Clinical Trial, Phase II; Clinical Trial, Phase III; Clinical Trial, Phase IV; Guideline; Practice Guidelines; Randomized Controlled Trials; Meta-Analysis; Systematic Reviews; and Validation Studies.

The PubMed search resulted in 287 citations, and their potential relevance was examined. The data from key PubMed articles and articles from additional sources deemed as relevant to these guidelines and discussed by the panel have been included in this version of the Discussion section (eg, e-publications ahead of print, meeting abstracts). Recommendations for which high-level evidence is lacking are based on the panel's review of lower-level evidence and expert opinion.

The complete details of the Development and Update of the NCCN Guidelines are available on the NCCN website (www.NCCN.org).

Risk Assessment (CSCR-1)

The NCCN Guidelines for Colorectal Cancer Screening stratify patients into 3 groups depending on their risk of getting CRC. Colorectal screening is particularly important for African Americans since they have a higher risk of incidence and mortality (see *Increased Risk*, below). Communication with the patient and referring physician of 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, those with hyperplastic polyps (described below under *Screening of Individuals at Average Risk*) less than 1 cm in size and a negative family history for CRC, no history of adenoma, CRC, or inflammatory bowel disease (IBD).

Increased Risk

Individuals with a personal history of adenomatous polyps or sessile serrated polyps (SSPs) (described below under *Screening of Individuals at Average Risk*), CRC, or IBD (ie, ulcerative colitis, Crohn's 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 and those who are obese also have a higher risk,[15,16] although these factors are not considered to affect the screening guidelines. Other factors that influence risk include age, sex, and race.[17]

In particular, registry data suggest an increased incidence for CRC in African Americans prior to age 50 years.[18] This increased risk has led some to recommend beginning population CRC screening in African Americans at age 45 years.[19] Using a microsimulation model, one study found that differences in screening accounted for 42% of disparity in CRC incidence and 19% of disparity in CRC mortality between African Americans and whites.[20] 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.[21] Therefore, based on the available data and emerging evidence, methods to further enhance access to screening in African American and other minority populations should be endorsed.

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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 the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at www.NCCN.org).

Colorectal Cancer Screening (CSCR-2)

Current technology falls into two broad categories: structural tests and stool/fecal-based tests.[22] There is direct evidence from randomized controlled trials (discussed in detail below) that fecal occult blood testing (FOBT) and flexible sigmoidoscopy reduce mortality from CRC. Colonoscopy is supported by case-control and cohort studies and has the potential ability to prevent CRC (with its associated morbidity) and cancer deaths.

In the United States, colonoscopy is the most commonly employed CRC screening test for average- and high-risk populations. However, multiple options exist, and the choice of modality should be based on patient preference and resource availability. In fact, screening completion rates are higher when FOBT is recommended or when a choice of FOBT or colonoscopy is given than when only colonoscopy is recommended (67% or 69% vs. 38%; $P < .001$ for both).[23] Overall, whereas some techniques are better established than others, panelists agree that any screening is better than none. Results of a large population-based prospective study in Australia support this supposition; participants who had received screening by FOBT, sigmoidoscopy, or colonoscopy had a 44% lower risk of developing CRC (HR, 0.56; 95% CI, 0.49–0.63) compared with those who were never screened.[24]

CRC screening should be performed as part of a program that includes a systematic method for identifying those who are eligible for and desire screening, standard methods for administering the screening tests at agreed upon intervals, standardized reporting of the results, and a mechanism for follow-up of those with a positive test.

Screening Modalities (CSCR-A)

Structural Screening Tests

Structural screening tests detect adenomatous polyps and cancer 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 a day). Endoscopic exams 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 age 66 to 95 years showed that the risks of adverse events after colonoscopy increase with age.[25]

Colonoscopy

Colonoscopy is the most complete screening procedure, allowing examination of the entire large bowel and the removal of polyps in one session. It is the required procedure for confirmation of positive findings from other tests. Colonoscopy is also considered the current gold standard for assessing the sensitivity for detecting neoplasia of other screening modalities. Although no randomized controlled trials directly demonstrate mortality reduction by colonoscopy, findings from case-control and cohort studies show significant impact of colonoscopy and polypectomy on CRC, with an estimated >50% reduction in incidence.[26-35] A large population study involving approximately 2.5 million Canadians with an age range of 50 to 90 years reported an inverse

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correlation between colonoscopy use and death from CRC.[36] For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.[36]

Interestingly, in a Canadian case-control study that matched each of the 10,292 individuals who died of CRC to 5 controls, colonoscopy was associated with lower mortality from distal CRC (adjusted conditional OR, 0.33; 95% CI, 0.28–0.39) but not proximal CRC (OR, 0.99; CI, 0.86–1.14).[37] Part of this finding may be related to significant variation in the quality of this widely used procedure in the community that can lead to variable effectiveness.[38,39] However, additional studies have also demonstrated a reduced effectiveness in the right colon.[26,40] A population-based, case-control study in Germany demonstrated that colonoscopy in the preceding 10 years gave an overall 77% decrease in the risk for CRC.[26] While risk reduction was strongest for distal cancer, a 56% risk reduction was seen for proximal disease as well. A case-control study using the SEER-Medicare database also found that colonoscopies are associated with a decrease in death from CRC and the association was strongest for distal over proximal CRC.[40]

Analysis of 2 prospective cohorts (the Nurses' Health Study and the Health Professionals Follow-up Study) followed 88,902 participants for 22 years, comparing long-term outcomes in those who had screening colonoscopies, sigmoidoscopies, or no endoscopy.[35] Death from CRC was reduced after screening sigmoidoscopy (HR, 0.59; 95% CI, 0.45–0.76) and after screening colonoscopy (HR, 0.32; 95% CI, 0.24–0.45). However, mortality from proximal colon cancer was reduced after screening colonoscopy (HR, 0.47; 95% CI, 0.29–0.76) but not after sigmoidoscopy.

The impact of colonoscopic screening on CRC mortality has been investigated in studies that have evaluated the effects of colonoscopies with concurrent polypectomies. In the National Polyp Study, the mortality of 2602 patients with adenomas removed was compared to the incidence-based mortality from CRC in the SEER database.[41] With a median follow-up of 15.8 years, 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.[41]

Another study estimated CRC mortality in 40,826 patients who underwent polypectomy in Norway.[42] Patients with high-risk adenomas were recommended for repeat colonoscopy in 10 years if they were younger than 75 years or in 5 years if 3 or more adenomas were found. No further surveillance was recommended for patients with low-risk adenomas or those older than 74 years. As compared with expected CRC mortality rates in the general population, CRC mortality of patients with low-risk adenomas removed was lower (standardized incidence-based mortality ratio [SMR], 0.75; 95% CI, 0.63–0.88) after a mean follow-up of 7.7 years.[42] On the other hand, CRC mortality was increased in patients with high-risk adenomas removed (SMR, 1.16; 95% CI, 1.02–1.31), likely because these patients are predisposed to CRC and possibly because of the relatively long 5-year screening interval recommended for these patients.[42] In addition to cancer prevention, colonoscopic screening is also expected to lead to earlier diagnosis. Supporting this supposition, a retrospective review of a prospective database compared 217 patients diagnosed with colon cancer through screening colonoscopy with 854 patients with colon cancer not diagnosed through screening.[43] Unscreened patients were at higher risk for more invasive tumors (relative risk [RR], 1.96; $P < .001$), nodal disease (RR, 1.92; $P < .001$), and metastatic disease on presentation (RR, 3.37; $P < .001$).[43] Furthermore, unscreened patients had higher rates of death and recurrence, shorter survival, and shorter disease-free intervals.

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A meta-analysis of 14 randomized controlled trials and other controlled studies found that while endoscopic surveillance detected more advanced neoplasms than stool testing, its advantage was offset by a lower participation rate.[44] Interim results of the COLONPREV study, a randomized controlled study comparing one-time colonoscopy with biennial fecal immunochemical testing (FIT; see discussion of FIT below) in asymptomatic adults aged 50 to 69 years showed that the two tests identified similar numbers of cancers in initial screening, but colonoscopy identified significantly more advanced and non-advanced adenomas.[45] The data also showed that subjects were more likely to participate in FIT compared to colonoscopy screening (34.2% vs. 24.6%; $P < .001$).[45] Subsequent analyses confirmed these observations.[46]

Colorectal Cancer Screening Programs

Colonoscopy

An optimal screening program should have an interval during which there is a low likelihood of developing cancer, and it should be cost-effective based on the duration of risk reduction following an initial negative screen. The general consensus is that a 10-year interval is appropriate for most individuals (average risk) who had a complete colonoscopic procedure with an adequate bowel preparation, although a 1-year interval may be indicated depending on the completeness and quality of the colonoscopy.[47] 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 one of 154 individuals had a polyp ≥1 cm.[48] These results suggest that an interval of repeat colonoscopy after an initial negative colonoscopy beyond 5 years is safe. Imperiale et al reported on 2436 individuals with no adenomatous polyps at baseline colonoscopy.[49] No cancers were found at rescreening at a mean of 5.3 years later. Adenomatous polyps were identified in 16% of individuals and only 1.3% had advanced adenomatous polyps. The authors recommended a rescreening interval of 5 years or longer. Lieberman and colleagues 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.[50] In this study, individuals with 1 or 2 adenomatous polyps <1 cm at baseline also had a low rate of developing advanced neoplasia.

Singh et al also assessed the time that risk reduction persists after colonoscopy.[51] This study was a population-based retrospective analysis utilizing a physician billing claims database of individuals who had a negative screening colonoscopy. Patients in the surveillance cohort were compared to 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 RR for CRC among subjects with a previous negative colonoscopy.[52] 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. The risk reduction seen following negative colonoscopy holds even for patients with a family history of CRC, but not for current smokers.[53]

Colonoscopy Quality

Recommendations made by the panel are based on the premise of complete, high-quality colonoscopies. The recommended priority quality indicators are the adenoma detection rate in asymptomatic individuals undergoing screening; the frequency at which surveillance colonoscopies follow recommended post-polypectomy and post-cancer

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resection intervals; the frequency with which 10-year intervals between screening colonoscopies are followed in average-risk patients with negative screens and adequate bowel preparation; and the frequency with which visualization of the cecum is documented using notation and photodocumentation of landmarks.[54] Other suggested indicators include incidence of perforation, management of post-polypectomy bleeding without surgery, documentation of withdrawal time, frequency of obtaining biopsies in individuals with diarrhea, frequency of documentation of appropriate recommendation for interval colonoscopy, and notification of the patient of this recommendation after review of histologic findings.[54] A 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.[55] 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 ascending colon, which gives rise to a small number of cancer cases. Data analysis of almost 315,000 colonoscopies from an integrated health care delivery organization showed that higher adenoma detection rates were associated with lower rates of interval CRC (HR, 0.52; 95% CI, 0.39–0.69), advanced-stage interval CRC (HR, 0.43; 95% CI, 0.29–0.64), and fatal interval CRC (HR, 0.38; 95% CI, 0.22–0.65).[56]

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.[57] These NCCN Guidelines list the common quality indicators of colonoscopy and minimum requirements of a colonoscopy report. Quality indicators, including withdrawal time and adenoma detection rate, are an important part of the fidelity of colonoscopy findings.[56,58-60]

Bowel Preparation for Colonoscopy

Split-dose preparation has been shown to be superior to the traditional regimen administered the day before colonoscopy and is therefore recommended.[61-63] The US Multi-Society Task Force on Colorectal Cancer also recommends split preparation.[47]

The NCCN panel and the US Multi-Society Task Force agree that a same-day, morning-only regimen is an acceptable alternative, especially in patients undergoing afternoon procedures.[64-66]

Flexible Sigmoidoscopy

Flexible sigmoidoscopy followed by colonoscopic polypectomy in patients with lesions >1 cm significantly reduced mortality risk in early case-control studies.[34,67] Evidence from randomized controlled trials have also demonstrated that flexible sigmoidoscopy reduces mortality from CRC.[35,68-74] A randomized study examined the effect of flexible sigmoidoscopy offered once between ages 55 and 64 years on CRC incidence and mortality.[68] Compared to the population that did not receive any screening, intention-to-treat analyses showed that intervention with flexible sigmoidoscopy decreased CRC incidence by 23% (HR, 0.77; 95% CI, 0.70–0.84) and CRC mortality by 31% (HR 0.69; 95% CI, 0.59–0.82).[68] In addition, the SCORE trial randomized 34,272 subjects aged 55 to 64 years to one-time sigmoidoscopy or no screening and reported incidence and mortality results after >10 years of median follow-up.[71] Per-protocol analysis demonstrated a 31% reduction in incidence and a 38% reduction in mortality.

The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening group reported CRC mortality rates from their randomized, controlled

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flexible sigmoidoscopy screening trial, which screened >64,000 participants with flexible sigmoidoscopy and 59% of those participants a second time at 3 or 5 years.[72-74] A 26% reduction in deaths from CRC was seen in the screened group (RR, 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.[72] 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.

The Norwegian Colorectal Cancer Prevention (NORCCAP) Study Group performed a randomized controlled trial of flexible sigmoidoscopy with or without an FOBT in over 98,000 participants aged 55 to 64 years.[69] After 7 years of follow-up, the researchers reported no difference in the incidence of or mortality from CRC between screened and unscreened individuals. However, after 11 years of follow-up, the hazard ratio for death from CRC was 0.73 (95% CI, 0.56–0.94).[70] Interestingly, the addition of FOBT did not affect the long-term outcomes of participants screened with sigmoidoscopy in this trial.

Meta-analyses of randomized controlled trials support the conclusion that screening by flexible sigmoidoscopy significantly reduces the incidence and mortality of CRC.[75-78] In addition, 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.[79] A similar result was seen in a nested case-control study of 4 U.S. health plans, in which the reduction of stage IIB or higher CRC was only seen in the distal colon.[80]

Compared to colonoscopy, sigmoidoscopy requires no sedation and less bowel preparation, but is limited to examination of the distal colon. An 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.[81] 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. Patients with lesions larger than 1 cm should be referred directly to colonoscopy, since they are almost always adenomatous polyps, which are associated with a risk of proximal colonic neoplasms.

Computed Tomographic Colonography

CT colonography, also known as virtual colonoscopy or CTC, is evolving as a promising technique for CRC screening. CT colonography has the advantages of being noninvasive and not requiring sedation. The risk of test-related complications is also very low, and results of a recent systematic review suggest that CT colonography may be cost effective when compared to colonoscopy.[82] However, a positive finding requires a colonoscopy, and extracolonic findings—which are present in up to 16% of patients—pose a dilemma.[83,84] These findings require further investigations and have a potential for both benefit and harm. At the present time, data to determine the clinical impact of these incidental findings are insufficient.

The accuracy of CT colonography 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 (ACR) Imaging Network.[85] In this study, 2531 participants underwent CT colonography followed by traditional optical colonoscopy. Colonoscopy identified 128 large adenomatous polyps or carcinomas in

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109 patients. CT colonography detected 90% of patients who had lesions measuring 10 mm or larger found by colonoscopy. There were also 30 lesions found on CT colonography, 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 CT colonography performance in this study (sensitivity of 90% and specificity of 86%) was better than that reported from some earlier studies[86,87] and similar to what was reported by Pickhardt and colleagues in a prospective study with a design similar to the ACRIN trial.[88]

Kim et al also compared CT colonography with colonoscopy for the detection of advanced neoplasia.[89] Although this study was not randomized, the detection rates were comparable between the two groups of >3,100 patients each (3.2% for CT colonography and 3.4% for colonoscopy).

Furthermore, a small prospective study of 47 patients with pathologically proven lateral spreading tumors found that CT colonography may not be as sensitive as colonoscopy for detecting tumors with significant lateral spread.[90]

In 2005, 2 meta-analyses reviewed the performance of CT colonography in the detection of colorectal polyps.[91,92] In one of these studies, CT colonography showed high average sensitivity (93%) and specificity (97%) for polyps ≥1 cm, both of which decreased to 86% when medium polyps (6–9 mm) were included in the analysis.[91] In the other meta-analysis, the sensitivity of CT colonography, although heterogenous, improved as the polyp size increased (48% for polyps less than 6 mm, 70% for 6 to 9-mm polyps, and 85% for polyps larger than 9 mm). The specificity was 92% to 97% for the detection of all the polyps.[92] Other studies have assessed growth rates of colorectal polyps (6–9 mm) using CT colonographic surveillance.[93,94] In a population-based CT colonography screening study, 93 individuals diagnosed with one or two polyps (6–9 mm) were examined with 3-year surveillance CT colonography to determine which polyps would progress to advanced adenomas.[94] Participants who had lesions ≥6 mm were offered colonoscopy. With a mean surveillance interval of 3.3 years (standard deviation [SD], 0.3; range, 3.0–4.6 years), 35% of the polyps progressed, 38% remained stable, and 27% regressed.[94] The study suggests that polyps that are 6 to 9 mm in size are unlikely to progress to advanced neoplasia within 3 years.[94] In a longitudinal study screening of 22,006 asymptomatic individuals, 243 adults (mean age, 57.4 years) had 306 colorectal polyps (6–9 mm).[93] With a mean surveillance interval of 2.3 years (SD, 1.4; range, 1–7 years), 22% of the polyps progressed, 50% remained stable, and 28% regressed.[93] Volumetric assessment determined that histology-established advanced adenomas grew faster than non-advanced adenomas, and only 6% of the 6 to 9-mm polyps exceeded 10 mm at follow-up.[93]

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 confidence intervals.[95] Another analysis focused only on studies of average-risk participants and found the sensitivity and specificity of CT colonography for the detection of adenomas ≥1 cm to be 87.9% and 97.6%, respectively.[96]

Importantly, CT colonography may be a more acceptable option to many individuals. A randomized study compared participation rates when members of the general population were offered CRC screening by either colonoscopy or CT colonography.[97] Significantly more people accepted the invitation for CT colonography (34% vs. 22%). While colonoscopy had a greater diagnostic yield in screened participants, the

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yields were similar when determined per the invited population. A prospective study has shown good sensitivity and specificity of laxative-free CT colonography for detecting lesions ≥1 cm.[98] This technique could present an alternative screening option to patients.

The technical aspects of CT colonography differ from study to study and have not been standardized. These details include the imaging, pre-procedure preparation, use of stool tagging, and expertise of the interpreter.[99,100] Long-term follow-up studies of patients who were screened by CT colonography are not yet available.

The issue of radiation exposure also requires consideration. The risk of undergoing a single CT colonography screening procedure is unknown but likely very low, and no empiric data have shown increased risk at levels below an exposure of 100 mSv.[101] Using the screening protocol for the ACRIN trial, Berrington de Gonzalez et al estimated the effective dose of low-dose CT colonography to be 9 mSv for women and 8 mSv for men, corresponding to 5 radiation-related cancer cases per 10,000 individuals undergoing one scan at 60 years of age.[102] Risks increase with repeated scanning. The 2014 ACR practice guidelines for the performance of CT colonography in adults recommend the use of a low-dose, non-enhanced CT technique on a multi-detector CT scanner to minimize radiation exposure to the patient.[103] Absorbed doses should not exceed 12.5 mGy total per scan.

Overall, available data indicate that CT colonography may be useful for the detection of larger polyps. Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for the evaluation of extracolonic lesions are evolving. If one or two lesions that are 6 to 9 mm are detected, CT colonographic surveillance at year 3 or colonoscopy is recommended. If more than three polyps that are 6 to 9 mm in size or lesions ≥10 cm are detected, colonoscopic surveillance is recommended. The ACR has recommended that reporting of polyps ≤5 mm in size is not necessary.[103] However, if polyps of this size are reported, the decision to refer for colonoscopy with polypectomy versus surveillance CT colonography should be individualized.

Fecal-Based Screening Tests (CSCR-A)

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

Any positive stool test needs to be followed by colonoscopy. To ensure adequate follow-up, a health care professional should coordinate testing so that the patient who has a positive result enters the health care system in a responsible way.

Fecal Occult Blood Test

Two types of FOBTs are currently available: guaiac-based and immunochemical. These tests are recommended annually when used alone, or once at 3 years when used in combination with flexible sigmoidoscopy. Annual FOBT should not be performed in combination with colonoscopy in an average-risk patient. Any positive result on FOBT, however, should be followed up with colonoscopy. It is important for FOBT alone 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 due to exceptionally low sensitivity.[104,105] Unfortunately, a

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survey of over 1000 primary care physicians 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.[106]

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. 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 non-human heme in food and blood from the upper gastrointestinal tract. To compensate for intermittent limitations, guaiac FOBT should be performed on three successive stool specimens obtained while the patient adheres to a prescribed diet.

There is direct evidence from randomized controlled trials that guaiac FOBT reduces the mortality from CRC.[107-109] In the Minnesota Colon Cancer Control Study, >46,000 participants were randomized to receive 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.[109] After 30-year follow-up, a CRC mortality benefit was seen in both the annual and biennial screening groups (RR for annual FOBT, 0.68; 95% CI, 0.56–0.82; RR for biennial FOBT, 0.78; 95% CI, 0.65–0.93).[110] Other large randomized studies have also demonstrated a CRC mortality decrease with biennial screening.[107,108] In fact, 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. Following adjustment for non-compliance, the reduction in CRC mortality was 18%.[111]

A systematic review of 4 randomized controlled trials involving more than 320,000 participants showed a 16% reduction in RR for CRC death with guaiac FOBT screening (95% CI, 0.78–0.90).[112] Another meta-analysis came to a similar conclusion, with guaiac FOBT screening reducing CRC mortality by 14% (RR, 0.86; 95% CI, 0.80–0.92).[77] The sensitivity of different guaiac FOBTs for cancer detection ranged from 37% to 79% in a study of about 8000 participants by Allison and colleagues.[113] In the UK National Health Service Bowel Cancer Screening Programme (BCSP), cancer was detected in 11.8% of individuals who had a colonoscopy following an abnormal or weak positive FOBT.[114] Adenomas were found in an additional 49.7% of participants.

The NCCN Colorectal Cancer Screening Panel recommends that only high-sensitivity guaiac tests be used. The U.S. Preventive Services Task Force (USPSTF) defines high-sensitivity FOBT as a test with a sensitivity for cancer >70% and a specificity >90%.[4] The guaiac tests that meet these criteria are newer and have not been tested in randomized controlled trials.

Fecal Immunochemical Test

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. A meta-analysis of studies that evaluated the diagnostic accuracy of FIT for CRC in average-risk patients found the sensitivity to be 79% (95% CI, 0.69–0.86) and the specificity to be 94% (95% CI, 0.92–0.95).[115]

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Comparative studies have shown that FIT is more sensitive than high-sensitivity guaiac FOBT.[116-122] For example, one study demonstrated a higher sensitivity for cancer by FIT compared to high-sensitivity guaiac FOBT Hemoccult® Sensa (82% vs. 64%).[116] A Dutch randomized study also demonstrated higher detection rates of advanced neoplasia by FIT (2.4%) than guaiac FOBT (1.1%), although both were less reliable than flexible sigmoidoscopy (8.0%).[118] In addition, as seen in other trials, FIT had a significantly higher participation rate than guaiac FOBT in this trial. Following extensive literature analysis, an expert panel in Ontario concluded that FIT is superior to guaiac FOBT in both participation rates and in detection of advanced adenomas and CRC.[123] Non-randomized studies have also shown that FIT screening reduces CRC mortality.[124,125] A large Taiwanese population-based study of 1,160,895 individuals aged 50 to 69 years were screened with 1 to 3 rounds of FIT and compared to an unscreened group. With a maximum follow-up of 6 years, there was a 10% decrease in CRC mortality in the FIT-screened population (RR, 0.90; 95% CI, 0.84–0.95).[124]

Combined Stool DNA/FIT Test

A combined stool DNA and occult blood test has emerged as a new primary screening tool for CRC. It screens for presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool, as well as occult blood. Specifically, Cologuard® (Exact Sciences) uses quantitative molecular assays for *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation, and *ACTB*, in conjunction with a hemoglobin immunoassay. A study that included 9989 participants at average risk for CRC, each of whom underwent FIT, stool DNA testing with Cologuard®, and a colonoscopy, found that the stool DNA test was more sensitive than FIT in the detection of CRC (92.3% vs. 73.8%; P = .002), advanced precancerous lesions (42.4% vs. 23.8%; P < .001), polyps with high-grade dysplasia (69.2% vs. 46.2%; P = .004), and SSPs >1 cm (42.4% vs. 5.1%; P < .001).[126] Specificity, however, was better with FIT (86.6% vs. 94.9% for FIT among participants with non-advanced or negative findings; P < .001), and many more participants were excluded because of problems with stool DNA testing (689) than because of problems with FIT (34). In August 2014, the FDA approved Cologuard® for primary screening for CRC.

The NCCN panel recommends the use of stool-based DNA/occult blood testing as a screening modality in average-risk individuals, but data to help determine an appropriate interval between screening, adherence to/participation rates of screening, and how stool-based DNA testing may fit into an overall screening program are limited. A rescreening interval of every 3 years has been suggested and is approved by the FDA.[3] Using a clinical effectiveness model, one study showed that compared with a 10-year colonoscopy interval, annual multi-target stool DNA (mt-sDNA) testing resulted in similar decreases in CRC incidence (65% vs. 63%) and mortality (73% vs. 72%).[127] At 3-year intervals, mt-sDNA testing reduced CRC incidence and mortality by 57% and 67% respectively. In addition, there are no or limited data in high-risk individuals;[128] therefore, the use of stool-based DNA/occult blood testing should be individualized. If a result is determined to be a false positive, clinical judgment and shared decision-making should be used.

Emerging Options: Blood-Based Screening Test

The methylation status of the septin9 (*SEPT9*) gene has been shown to distinguish CRC tissue from normal surrounding tissue, and circulating methylated *SEPT9* DNA in plasma is a biomarker for minimally invasive CRC.[129-132] A multicenter study compared the FIT test and a *SEPT9* DNA methylated blood test for CRC screening of 102 patients with identified CRC, and found that the sensitivity for CRC detection was not significantly different (68% vs. 73.3%, respectively).[133] A prospective arm of the study also tested for the specificity of the FIT and *SEPT9* DNA methylated blood tests in 199

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individuals who provided samples before colonoscopy screening and found higher specificity for the FIT test (97.4% vs. 81.5%, respectively).[133] Another prospective multicenter study assessed the accuracy of circulating methylated *SEPT9 DNA* at detecting CRC in 7941 asymptomatic individuals aged 50 years and older who met screening criteria for average risk.[134] Using colonoscopy as a reference standard, results from 53 CRC cases and from 1457 individuals without CRC determined the sensitivity and specificity of the methylated *SEPT9 DNA* blood-based assay to be 48.2% and 91.5%, respectively. However, the sensitivity was lower for advanced adenomas.[134] In 2016, a blood test that detects circulating methylated *SEPT9* DNA was approved by the FDA and may provide an alternative for individuals who refuse other screening modalities. However, the NCCN panel notes that its ability to detect CRC and advanced adenomas is inferior to other recommended screening modalities. The interval for repeated testing is unknown.

Screening of Individuals at Average Risk (CSCR-2)

It is recommended that screening for persons at average risk begin at 50 years of age after available options have been discussed. Currently, recommended options include: colonoscopy every 10 years; annual fecal-based tests (every 3 years with DNA-based testing); flexible sigmoidoscopy every 5 to 10 years with or without interval high-sensitivity guaiac-based or immunochemical-based testing at year 3; or CT colonography every 5 years.

If a colonoscopy is incomplete or preparation is suboptimal, other screening methods or repeat colonoscopy within 1 year should be considered. Following a negative test, rescreening at the appropriate interval can be done with any accepted modality. Some 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.[135]

The addition of guaiac-based or immunochemical-based testing to flexible sigmoidoscopy stems from data supporting a survival benefit. In one study, patients were assigned (based on calendar period on enrollment) to annual sigmoidoscopy with or without annual FOBT.[136] Of >12,000 participants, survival probability was significantly greater in the FOBT group (70% vs. 48%; $P < .001$). Microsimulation modeling has found that flexible sigmoidoscopy every 5 years with an interval FOBT likely results in similar life-years gained as colonoscopy every 10 years.[137] A survival meta-analysis of 4 randomized trials[68,70-72] comparing screening with flexible sigmoidoscopy to no screening found that it takes up to 10 years after flexible sigmoidoscopy to attain an absolute reduction in mortality related to CRC.[138]

Because the risk of colorectal screening increases with age, the decision to screen between ages 76 to 85 years should be individualized, and include a discussion of the risks and benefits based on comorbidity status and estimated life expectancy. The most benefit will likely be seen in individuals who have not been previously screened.

Interpretation of Findings

Colonoscopy is indicated as follow-up of abnormal findings from other screening modalities—stool-based tests, flexible sigmoidoscopy (biopsy-proven adenoma), or CT colonography. 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 in the ascending colon, as these tend to be associated with microsatellite instability (MSI) and hence greater cancer risk that warrants additional surveillance. Ideally, all detected polyps should be removed, but this is not always possible. Removed

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polyps should be examined for degree of dysplasia, as well as for histologic features of SSP.

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, and patients with these polyps should be followed as described below (see *Screening of Individuals at Increased Risk*). 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 they are not protruding from the colon wall.[139] More prospective studies are required to clarify their role in CRC risk. In the meantime, all flat adenomatous polyps should be removed upon identification with routine post-adenoma follow-up.

Sessile Serrated Polyps

SSPs, also known as sessile serrated adenomatous polyps, are rare forms of serrated polyps that have been associated with adenocarcinoma.[140] SSPs are not dysplastic; however, they can develop foci of dysplasia and are then termed SSP with cytologic dysplasia (SSP-cd). SSP-cds are thought to be the immediate precursors of high-frequency MSI sporadic CRC, and any dysplasia in an SSP is thought to be comparable to or more concerning than high-grade dysplasia in a conventional adenoma.[141,142] Thus, SSPs are managed like tubular adenomas, whereas SSP-cds are managed like high-risk adenomas. Some have recommended that patients with any serrated lesion proximal to the sigmoid colon should be followed similarly to those with adenomatous polyps because of potential increased risk for recurrent neoplasia.[141,143-145]

Hyperplastic Polyps

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. However, some studies suggest that a small subset of persons with multiple or large hyperplastic polyps have SPS, with a 26% to 70% risk for CRC (see *Serrated Polyposis Syndrome* in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at www.NCCN.org).[146-148] The majority of these persons had concomitant adenomatous polyps or SSP.[149] SPS is rarely reported to be inherited, and the CRC risk of individuals with affected relatives remains unclear. Furthermore, evidence suggests that some cancers with extensive DNA methylation and MSI might derive from hyperplastic polyps.[150]

Hyperplastic polyps that are <1 cm without SSP features indicate average risk for follow-up screening when they occur in the rectum and sigmoid colon. An expert panel concluded that hyperplastic polyps >5 mm occurring proximal to the sigmoid colon warrant a colonoscopic screening interval of 5 years.[141] In addition, when 4 or more hyperplastic polyps of any size are found proximal to the sigmoid colon, a 5-year colonoscopic screening interval was recommended.[141] Data to support these approaches are limited. The data to support whether individuals with hyperplastic polyps >1 cm in size represent an increased risk group are limited, and some studies suggest that many of these polyps are SSPs that have been incorrectly characterized.[151]

Screening of Individuals at Increased Risk (CSCR-4)

Personal History of Adenoma/SSP (CSCR-4)

Individuals with adenomatous polyps or SSPs are at increased risk for recurrent polyps and CRC. To minimize the risk of developing CRC, a

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surveillance program is recommended for patients with adenomatous polyps/SSP following screening colonoscopy and complete polypectomy.[144] The panel recommends surveillance colonoscopy in adults 50 to 75 years with a history of adenomas. Because risk of colonoscopy increases with age, surveillance of individuals between ages 76 and 85 years should be individualized and include a discussion of risks and benefits of continued colonoscopy based on comorbidity status, estimated life expectancy, and finding on the last or most recent colonoscopy. For patients with completely resected adenomatous polyps, the surveillance schedule depends on the risk of recurrence, which in turn is related to the number, size, and histology of adenomatous polyps. Furthermore, when there is uncertainty about the completeness of removal in large and/or sessile polyps and when the colonic preparation was suboptimal, shorter screening intervals may be necessary.

Patients are considered to have low-risk polyps when they have ≤2 tubular adenomas or SSPs that are <1 cm. In this group, colonoscopy should be repeated within 5 to 10 years. If this examination is normal, colonoscopy should be repeated every 10 years.[144] Results of the first 2 colonoscopy examinations may predict the patient's overall colon cancer risk.[4] Robertson et al reported on a study of 564 participants who had their first adenoma identified by colonoscopy and underwent 2 additional colonoscopies.[152] The study found that combining results of two 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 exam, 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).

The presence of an adenoma with high-grade dysplasia or an SSP-cd, an adenoma/SSP ≥1 cm, a polyp with villous or tubulovillous histology, or the presence of multiple (3–10) adenomatous polyps and/or SSPs have been associated with increased risk. High-grade dysplasia is defined as features of severe dysplasia (marked reduction of interglandular stromas with complex irregularity of glands, papillary infolding, and cytogenetic abnormalities) or severe architectural disturbance of glands along with cytologic features of dysplasia.[153] Carcinoma *in situ* is a term previously used by pathologists to describe colon polyps and cancer that has been replaced by the term high-grade dysplasia. A study by Golembeski and colleagues has shown that the identification of villous architecture and high-grade dysplasia is poorly reproducible among pathologists.[154] Studies reporting the association between polyp size and cancer risk 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 advanced or multiple adenomatous polyps should have repeat colonoscopy within 3 years, although some data suggest that intervals of 5 years may be appropriate. In addition, some experts recommend surveillance at 1- to 3-year intervals for SSP-cds, because they are thought to have an increased risk for CRC.[141,155] 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 prior to and following procedures.

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In individuals with more than 20 cumulative adenomatous polyps, a polyposis syndrome should be considered (see *Inherited Colon Cancer* in the Discussion section of the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at www.NCCN.org), although only a small fraction of those with no family history and low adenoma burden will have a defined hereditary syndrome. Genetic testing should be considered depending on patient age, the number of polyps, and family history. The cumulative presence of 10 polyps or fewer may occasionally be associated with an inherited polyposis syndrome, especially in patients younger than 40 years of age 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 polypectomy.[156] Hence, follow-up colonoscopy within 2 to 6 months is appropriate in this setting, or when polypectomy is suspected to be incomplete or was done in piecemeal fashion.

The NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer provide recommendations for management if a malignant polyp is found at colonoscopy (available at www.NCCN.org).

***Personal History of Colorectal Cancer* (CSCR-5)**

Individuals with a personal history of CRC should be followed according to the surveillance recommendations in the NCCN Guidelines for Colon Cancer and the NCCN Guidelines for Rectal Cancer (available at www.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 following CRC resections.[157-160] In patients with rectal cancer, local recurrence at the rectal anastomosis has been reported to occur in 5% to 36% of patients.[161-163] 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 following surgery and adjuvant chemotherapy.[164] 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 Cancer and the NCCN Guidelines for Rectal Cancer recommend a complete colonoscopy preoperatively as well as at 1 year following surgery (within 3 to 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.

Advantages of more intensive follow-up of patients with stage II and/or stage III rectal cancer have been demonstrated prospectively in several studies[158,165,166] and in 3 meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[167-169] Other studies impacting the issue of post-treatment CRC surveillance include results from an analysis of data from 20,898 patients enrolled in 18 large adjuvant colon cancer randomized trials.[159] The meta-analysis demonstrated that 80% of recurrences were in the first 3 years after surgical resection of the primary tumor. However, in the final analysis of Intergroup trial 0114, which compared bolus 5-FU to bolus 5-FU/LV in patients with surgically resectable rectal cancer, local recurrence rates continued to rise after 5 years.[170] Furthermore, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year

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relative survival rate of 15.6%), thereby providing support for more intensive post-treatment follow-up in these patients.[171] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative CRC surgery.[172,173]

Patients with a personal history of CRC should also be considered for Lynch syndrome screening with routine tumor testing using one of the following approaches: 1) all patients with CRC; or 2) all patients with CRC diagnosed prior to age 70 years plus patients diagnosed at older ages who meet the Bethesda guidelines.[174,175] Testing for Lynch syndrome is discussed in more detail in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal (available at www.NCCN.org).

Evidence is emerging that aspirin can reduce the risk of CRC incidence and mortality in high-risk groups.[176-179] Presently, the USPSTF recommends initiating low-dose aspirin use for the primary prevention of cardiovascular disease (CVD) and CRC in adults aged 50 to 59 years who have ≥10% CVD risk and are at average risk for CRC.[180] However, the preventive benefit on CRC is not apparent until 10 years after aspirin therapy.[180,181] As additional data emerge, consideration for recommending aspirin use will need to be individualized with consideration for life expectancy, comorbidities, and risk.

***Inflammatory Bowel Disease* (CSCR-6)**

It is well-recognized that individuals with a personal history of IBD (ie, ulcerative colitis, Crohn's disease) are at an increased risk for CRC, because chronic inflammation can lead to dysplasia and subsequent malignant conversion.[182-184] Evidence shows that endoscopic surveillance can detect cancer at earlier stages in patients with extensive colitis, suggesting that this likely reduces the risk of death from CRC for these patients.[185] A retrospective review of 6823 patients with IBD found that the incidence of CRC in patients without a colonoscopy in the past 3 years was significantly higher than in those with a recent colonoscopy (2.7% vs. 1.6%; OR, 0.56; 95% CI, 0.39–0.80).[186] In addition, a colonoscopy within 6 to 36 months before diagnosis of CRC was associated with reduced mortality (OR, 0.34; 95% CI, 0.12–0.95). Information regarding the value of endoscopic surveillance of long-standing Crohn's disease, on the other hand, is limited.

Risk factors for dysplasia in patients with IBD include ulcerative colitis, extensive colitis, colonic stricture, primary sclerosing cholangitis (PSC), family history of CRC (especially with diagnosis <50 years of age), personal history of dysplasia, severe longstanding inflammation, and post-inflammatory pseudopolyps.[182,187] Confirmation of these risk factors by an expert gastrointestinal pathologist is desirable. Patients with proctosigmoiditis have little or no increased risk of CRC compared with the general population and should be managed as average risk.[182,187]

The NCCN panel recommends colonoscopic surveillance by colonoscopy, initiated 8 years after the onset of symptoms in patients with a personal history of IBD involving the colon. If PSC is present, annual surveillance colonoscopies should be started independent of the disease activity and extent.[188] A 2001 meta-analysis showed that patients with pancolitis have a higher risk of developing CRC than those with less extensive disease.[189] However, a delay in surveillance for disease limited to the distal colon is not recommended, because the data suggesting a later onset of cancer in these individuals are not strong.[190,191] Colonoscopic surveillance may be performed with chromoendoscopy with targeted biopsy. Targeted biopsies have been found to improve detection of dysplasia and should be considered for surveillance colonoscopies in patients with ulcerative colitis by trained

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endoscopists.[188,192-195] During chromoendoscopy, high-definition colonoscopy is suggested. In support of this recommendation, a retrospective study of patients with colonic IBD comparing the yield of dysplastic lesions detected by standard-definition white light endoscopy with high-definition colonoscopy, determined that the latter improves targeted detection of dysplastic lesions during surveillance.[196] If biopsies for dysplasia are not done, two random biopsies in every bowl segment are commonly recommended to document microscopic disease activity.[197,198] Colonoscopic surveillance may also be performed with high-definition white light endoscopy (HD-WLE). Random four-quadrant biopsies (every 10 cm with 33 or more samples[199]) should be taken for histologic examination using large cup forceps. Strictures, particularly those in ulcerative colitis, should be evaluated thoroughly using biopsy and brush cytology. All endoscopy should be performed during quiescent disease states.[192,193,195]

For both colonoscopic surveillance modalities, endoscopic polypectomy should be performed when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia. Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy or confocal endomicroscopy and several studies indicate increased sensitivity of chromoendoscopy in detecting dysplastic lesions; however, the natural history of these lesions is unclear.[200] Targeted biopsies of strictures, mass lesions, and macroscopic abnormalities obtained can be categorized using the Paris classification.[192,201] Dysplasia is classified as endoscopically visible and identified by resection or targeted biopsies or endoscopically invisible and detected by random biopsies.[197]

Patients with ulcerative colitis develop sporadic colorectal adenomas at the same rate as the general population, and the appropriate management of adenomatous polyps in the setting of ulcerative colitis is dependent on various factors and should be based on individual risk factors such as duration of colitis, presence of dysplasia, and the number and size of adenomas. Lesions that appear endoscopically and histologically similar to a sporadic adenoma colon and without invasive carcinoma in the polyp can be treated safely by endoscopic submucosal dissection (ESD) or endoscopic mucosal resection (EMR) and continued surveillance. The confirmation of all polyps and dysplasias by an expert GI pathologist is desirable.

***Evaluation of Surveillance Findings* (CSCR-7)**

If no dysplasia is detected during surveillance, and patients present with left-sided disease and no endoscopic or histologic active inflammation, they can be considered to have low risk for CRC and receive follow-up with colonoscopy in 2 to 3 years. Several GI societies' position statements recommend risk-stratified surveillance with an increased surveillance interval to 3 to 5 years in lowest risk patients.[188] However, if patients present with any of the following high-risk factors: PSC, extensive colitis, active inflammation, adenomatous polyps, pseudo polyps, family history of CRC <50 years of age, strictures, or dysplasia, they may have increased risk for CRC. These patients receive follow-up with colonoscopy 1 year after endoscopic resection.

If dysplasia is detected, all endoscopically resectable polyps should be removed and dysplasia should be resected to ensure negative margins. Visible dysplasia is generally polypoid (lesion protruding from the mucosa into the lumen ≥2.5 mm) or nonpolypoid (lesion with little [<2.5 mm] or no protrusion above the mucosa).[192,197] For resectable visible dysplasia, that is both polypoid and nonpolypoid (low- or high-grade), complete endoscopic resection by polypectomy using EMR or ESD and endoscopic tattooing with biopsies of adjacent mucosa is recommended. If no dysplasia is detected in adjacent mucosa, the patient should undergo close endoscopic surveillance. During

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surveillance, if the patient has any high-risk factors described earlier, they should receive follow-up with colonoscopy 1 year after endoscopic resection. In addition, all resected dysplastic lesions, especially larger ones (≥1.5 cm), should be followed up within 3 to 6 months with chromoendoscopy due to the increased risk of additional dysplastic lesions being found during follow-up.[202]

If dysplasia is detected in the adjacent mucosa and confirmed by a GI pathologist, the patient should be referred to an experienced IBD expert to discuss surgical options.[192] The presence of dysplasia should also be assessed with chromoendoscopy, if this procedure has not already been performed. A surgical consultation may include a discussion about surveillance and colectomy based on multiple factors including other visible dysplastic lesions in the same colon segment, histology, and a discussion with the patient about the risks and benefits of each approach.[192]

If invisible dysplasia (low- or high-grade) is detected, the patient should be referred to an experienced IBD expert to discuss surgical options. The presence of invisible dysplasia should be confirmed with chromoendoscopy, if this procedure has not already been performed. Given that invisible dysplasia is associated with a high risk for CRC,[203,204] a colectomy should be considered over intensified surveillance if confirmed by a gastrointestinal pathologist.

If polyps are non-resectable or cannot be completely evaluated due to stricture, the patient should consult with an IBD expert for resection. A stricture is a strong indication for colectomy because of the high rate of underlying carcinoma,[205] especially a stricture that is symptomatic or not traversable during colonoscopy, particularly in long-standing disease.

Optimal management of Crohn's-related dysplasia remains undefined,[206] and patient and physician preferences should be considered; the extent of resection should be based on the individual findings. When a single focus of low-grade dysplasia is found in patients with IBD, total colectomy versus close colonoscopic surveillance should be discussed. If the patient decides against total colectomy, then a repeat colonoscopy should be performed within 3 months.

***Family History* (CSCR-8)**

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. 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 (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 as well as a date, age, cause of death, and availability of a tumor sample 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. The ASCO Cancer Genetics Subcommittee has provided guidance for taking and interpreting a family history that discusses barriers to accuracy in the process.[207]

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Positive Family History

If a patient meets the criteria for an inherited colorectal syndrome (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at www.NCCN.org), further risk evaluation and counseling, as outlined in the guidelines, is required. When any one of the revised Bethesda criteria[208] are met (listed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at www.NCCN.org), the possibility of Lynch syndrome is suggested, and immunohistochemical (IHC) staining of the four mismatch repair (MMR) proteins and/or MSI testing of the colon tumor of the youngest affected family member is warranted.

Other individuals with a family history of CRC have an increased risk for the disease themselves and should therefore undergo earlier and/or more frequent screenings.[209-211] The panel's recommendations are as follows:

- For patients with at least one affected first-degree relative with CRC at any age, colonoscopy is recommended every 5 to 10 years, beginning 10 years prior to the earliest diagnosis in the family or at age 40 years at the latest. If colonoscopy is positive, follow-up colonoscopy should be based on findings. For individuals with a family history of CRC diagnosed at a younger age, a shortened interval may be appropriate.
- When at least one second-degree relative is diagnosed with CRC prior to age 50 years, colonoscopy should begin at age 50 years, with repeat colonoscopy every 5 to 10 years or based on findings. Multiple (≥2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals.
- Individuals with a first-degree relative with a confirmed history of advanced adenoma(s) (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) should undergo colonoscopy at the relative's age of onset of adenoma or by age 40 years at the latest, with repeat colonoscopy every 5 to 10 years or based on findings. Multiple (≥2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals. Data suggesting an increased risk for CRC in this population are limited.[212,213]

Colonoscopy intervals should be modified based on personal and family history as well as on individual preferences. A population-based study analyzed more than 2 million individuals to determine RRs for the development of CRC depending on family history of CRC.[209] 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 above.

Factors that modify age to begin screening and colonoscopy intervals include: age of individual undergoing screening; and specifics of the family history, including number and age of onset of all affected relatives. A retrospective, population-based, case-control study showed that of 18,208 index patients diagnosed with CRC, the highest familial risk was found in first-degree relatives of index CRC patients who were diagnosed at an age younger than 40 years (HR, 2.53; 95% CI, 1.7–3.79).[214] However, familial risk for CRC was increased in first-degree relatives regardless of the age of diagnosis of the index patient.[214] The PLCO trial evaluated the effect of family history on CRC risk after 55 years of age, when risk of early-onset cancer has passed, and found that subjects with 1 first-degree relative had a modest increase in risk for CRC incidence and mortality.[215] Individuals with ≥2 first-degree relatives with CRC had continued increased risk in older age.[215]

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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.

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