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NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®)

Colorectal Cancer Screening

Version 1.2015

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Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

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Continue

NCCN Guidelines Panel Disclosures

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015 Table of Contents
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

For High-Risk Colorectal Cancer Syndromes,
see NCCN Genetic/Familial High-Risk Assessment: Colorectal

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

To find clinical trials online at NCCN Member Institutions, click here: nccn.org/clinical_trials/physician.html.

NCCN Categories of Evidence and Consensus: All recommendations are category 2A unless otherwise specified.

See NCCN Categories of Evidence and Consensus.

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015 Updates Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Updates in Version 1.2015 of the NCCN Guidelines for Colorectal Cancer Screening from Version 1.2014 include:

CSCR-1

- **Footnote "b" was changed from "There is controversy over whether SSPs should be called 'sessile serrated adenomas.' These terms are equivalent and these guidelines will use 'SSPs.' SSPs are a type of serrated polyp and should be managed the same as adenomas. However, any serrated lesions in the proximal to sigmoid colon should be followed similarly to adenomatous polyps." to "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 cytologic dysplasia (SSP-cd). These guidelines will use 'SSP' for SSPs without dysplasia and 'SSP-cd' for SSPs with dysplasia. In general SSPs are managed like tubular adenomas and SSP-cd 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."**

CSCR-2

Average Risk Screening

- **Evaluation of Screening Findings**
  - **After biopsy or polypectomy, the findings option was revised: "Hyperplastic, non-SSP, and <1 cm *in rectum and sigmoid only.*"**
- **Footnotes**
  - **Footnote "d" was revised as, "Currently there is not a consensus on the use of CT colonography *(CTC)* as a primary screening modality... *Also unclear is what follow-up is required for a patient with a positive CTC and a negative colonoscopy. CTC may also not be as sensitive as colonoscopy to detect clinically significant lateral spreading tumors (Togashi K, et al. World J Gastroenterol 2014 Dec;20:17552-7). Despite these uncertainties, CTC is being utilized in clinical practice* ~~However~~. The *current* data available suggest that if CTC is negative/no polyps, then repeat CTC in 5 y, and if positive/polyps lesions, colonoscopy should be performed."**
  - **Footnote "e" was added: "*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.*"**
  - **Footnote "f" was modified as, "If colonoscopy is incomplete or preparation is suboptimal, consider other screening modality or repeat colonoscopy in *1 y (Johnson D, et al. Gastroenterology 2014;147:903–924)* ~~a shorter interval at discretion of physician.~~"**
  - **Footnote "g" was revised as, "~~Emerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening modality~~, ~~but~~ *Stool DNA testing has recently been approved by the FDA as a primary screening modality for colorectal cancer (Imperiale TF, et al. N Engl J Med 2014;370:1287-97). At this time*, there *are* limited data *available* to determine an *appropriate* interval between screening. ~~At present, stool DNA is not considered a primary screening modality~~.**
  - **Footnote "i" was revised as, "~~SSPs are managed the same as adenomas~~ *SSPs without dysplasia are generally managed like adenomas; SSP-cd are managed like high-risk adenomas and may need even more frequent surveillance."* (Also for CSCR-3)**
  - **Footnote "e" text was moved to CSCR-A,**
    - **There is direct evidence from randomized controlled trials that fecal occult blood testing (Mandel JS, et al. N Engl J Med 1993;328:1365-71; Hardcastle JD, et al. Lancet 1996; 348:1472-77; Kronborg O, et al. Lancet 1996; 348:1467-71) and flexible sigmoidoscopy (Atkin WS, et al. Lancet 2010;375:1624-33; Schoen RE, et al. N Eng J Med 2012;366:2345-57; Nishihara R, et al. N Eng J Med; 2013;369:1095-105) will reduce mortality from colorectal cancer. There is evidence from case control and cohort studies that colonoscopy has the potential ability to prevent colorectal cancer (with its associated morbidity) and cancer deaths (Kahi CJ, et al. Clin Gastroenterol Hepatol 2009;7:770-5; Baxter NN, et al. Ann Intern Med 2009;150:1-8).**
    - **"Winawer S, et al. J Natl Cancer Inst 1993;85:1311-8 and Zauber AG, et al. Ann Intern Med 2008;149:659-69."**

Continued on next page

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015 Updates Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Updates in Version 1.2015 of the NCCN Guidelines for Colorectal Cancer Screening from Version 1.2014 include:

CSCR-3

Increased Risk Based on Personal History of Adenomatous Polyp or Sessile Serrated Polyp

- Clinical findings
  - First branch was clarified, "Low-risk ~~adenomatous~~ polyps (tubular *adenoma or SSP without cytologic dysplasia [cd]*)"
  - Second branch was clarified, "*High risk* (Advanced or multiple ~~*adenomatous*~~ polyps)
    - ◊ High-grade dysplasia *or SSP-cd or*
    - ◊ *Adenoma or any SSP* ≥1 cm *or*
    - ◊ Villous *or tubulovillous* histology ~~(Any villous features)~~ *or*
    - ◊ Between 3 and 10 adenomatous polyps *and/or SSPs*
  - Last branch was clarified, "Malignant ~~adenomatous~~ polyp"
- Follow-up of clinical findings
  - Low-risk follow-up was revised, "Repeat colonoscopy within 5–*10* y"
- Footnote "l" was modified, "Shorter intervals may be necessary when there is uncertainty about completeness of removal of large *and/or* sessile polyps, if the colonic preparation was suboptimal *and for SSP-cds. Some authorities recommend surveillance at 1- to 3-year intervals for SSP-cds because they are thought to rapidly progress to CRC (RexD, et al. Am J Gastro 2012;107:1315-29)...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.*"

CSCR-5

Increased Risk Based on Personal History of Inflammatory Bowel Disease

- Initiation of screening, the following revisions were made,
  - 8–10 y after onset of symptoms ~~of pancolitis~~
  - ~~12 y after onset of left-sided colitis~~
- Evaluation of positive screening findings
  - The findings of "incomplete evaluation due to stricture" was added.
- Footnotes
  - Footnote "o" was revised by adding, "...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. Clin Gastroenterol Hepatol 2015;13:148-54.*"
  - Footnote "q" was added, "Shergill AK, Farraye FA. Gastrointest Endosc Clin N Am 2014;24:469-481."
  - Footnote "s" was added, "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, especially in long-standing disease."
  - Footnote "v" was modified by adding, "Appropriate management of adenomatous polyps in the setting of ulcerative colitis is dependent on various factors and should be ~~at the discretion of the treating physician~~ *based on individual risk factors such as duration of colitis, presence of dysplasia, and number and size of adenomas.*"

CSCR-6

Increased Risk Based on Positive Family History

- Family history criteria
  - Fourth criteria was revised: "First-degree relative with *confirmed* advanced adenoma(s) *(ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology)*"
- Screening
  - For first-degree relative with CRC aged ≥60 y, the screening was revised, "Colonoscopy beginning at age 50 y ~~or 10 y before earliest diagnosis of CRC~~."
  - For first criteria, after colonoscopy was revised, "Repeat every ~~3-~~5 y ~~depending on individual family history~~ *or if positive, repeat per colonoscopy findings.*"
  - For second, third, and fourth criteria, after colonoscopy was revised, "Repeat every 5–*10* y or if positive, repeat per colonoscopy findings."
- Footnote "x" references were added, "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(4):814-821."

Continued on next page

National Comprehensive Cancer Network®

NCCN Guidelines Version 1.2015 Updates Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion

Updates in Version 1.2015 of the NCCN Guidelines for Colorectal Cancer Screening from Version 1.2014 include:

CSCR-A 1 of 5

Screening Modality and Schedule

- 1st bullet was revised to, "*The goal of a CRC screening program is to reduce CRC mortality through cancer prevention and early detection*" from "Colon cancer prevention and early detection with mortality reduction should be the primary goals of CRC screening program."
- Bullet was removed, "Although patient preferences and availability of resources play an important role in the selection of screening options, tests that are designed to detect both early cancer and adenomatous polyps should be encouraged."

CSCR-A 3 of 5

- Colonoscopy
  - 1st bullet was revised, "~~However, screening with any of the available modalities is preferable to no screening.~~ *There are multiple options; however, the choice of modality should be based on patient preference and availability*."
  - 2nd bullet, "Caveats for the 10-year interval," the second sub-bullet was revised, "~~Shorter intervals~~ *Repeating in 1 year* may be indicated based on..."
  - 3rd bullet regarding colonoscopy preparation was added.
  - 4th bullet,
    - ◊ Second sentence was revised, "A number of quality indicators ~~such as withdrawal time~~ have been examined."
    - ◊ Under 'Quality indicators,' the indicator of "withdrawal time" was added.
    - ◊ Appropriate prep instructions, the following changes were made:
      - – Revised, "Split dose prep has been shown to be superior and ~~should be encouraged~~ *is recommended*"
      - – Added, "*Preferred timing of the second dose of split-dose preparation:*
        - ▪ *Start 4–6 hours before colonoscopy*
        - ▪ *End at least 2 hours before colonoscopy*
      - – Added, "*Same-day, morning-only preparation is an acceptable alternative to split-dose preparation, especially in patients scheduled for afternoon procedures*."

CSCR-A 4 of 5

- Stool-based screening
  - 1st bullet was revised, "~~Annual stool occult blood testing should not be performed~~ If colonoscopy is used as the screening ~~measure~~ modality in an average-risk patient, then additional, interval stool-based testing is not indicated."
- Footnote "8" was revised by adding references, "Mandel JS, Bond JH, Church TR, et al. N Engl J Med 1993;328:1365-71. Kronborg O, Fenger C, Olsen J, et al. Lancet 1996;348:1467-71. Atkin WS, et al. Lancet 2010;375:1624-33; Schoen RE, et al. N Engl J Med 2012;366:2345-57; Nishihara R, et al. N Engl J Med; 2013;369:1095-105."
- Footnote "12" references were added, "Winawer S, et al. J Natl Cancer Inst 1993 18;85:1311-8 and Zauber A, et al. Ann Intern Med 2008;149:659-69."

MS-1

- The Discussion section was updated to reflect the changes in the algorithm.

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

→ 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-3)
  - CRC → See Increased Risk Screening Based on Personal History of Colorectal Cancer (CSCR-4)
  - Inflammatory bowel disease (ulcerative colitis, Crohn's disease) → See Increased Risk Screening Based on Personal History of Inflammatory Bowel Disease (CSCR-5)
- Positive family history → See Increased Risk Screening Based on Positive Family History (CSCR-6)

High-risk syndromes:

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

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

- Cowden 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 cytologic dysplasia (SSP-cd). These guidelines will use "SSP" for SSPs without dysplasia and "SSP-cd" for SSPs with dysplasia. In general SSPs are managed like tubular adenomas and SSP-cd 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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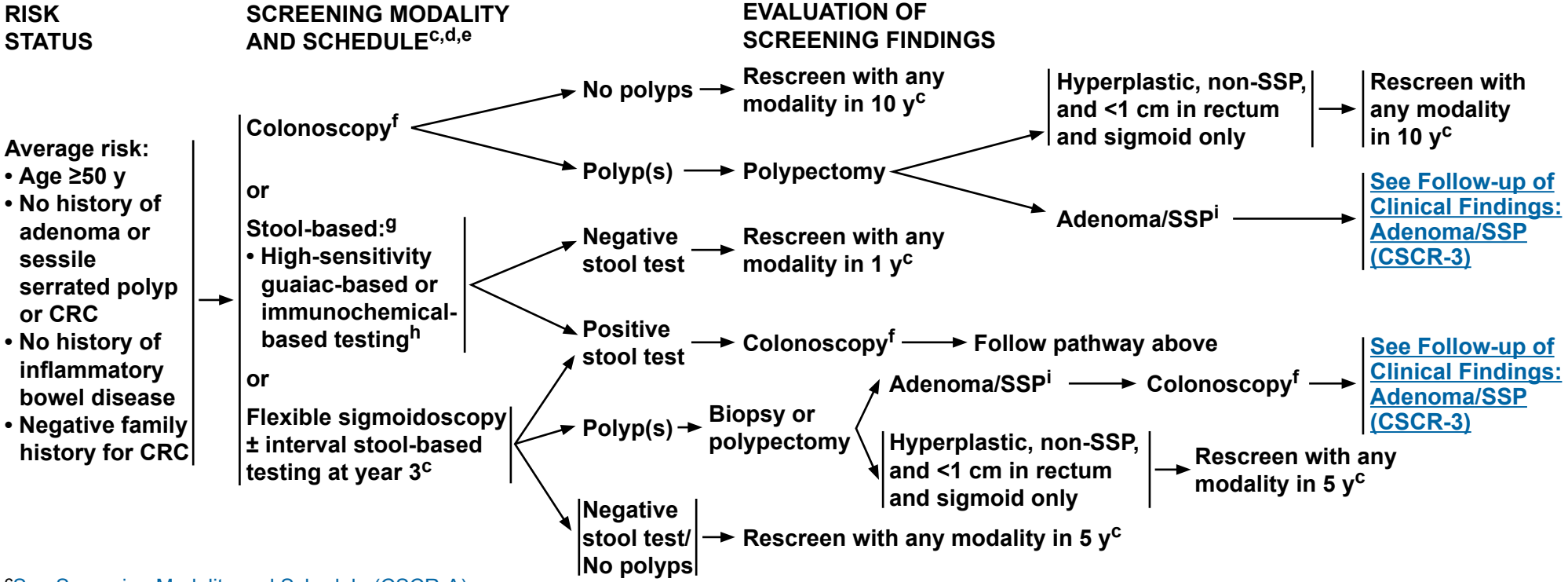
NCCN Guidelines Version 1.2015
Colorectal Cancer Screening

NCCN Guidelines Index
Colorectal Screening TOC
Discussion



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

[d] Currently there is not a consensus on the use of CT colonography (CTC) as a primary screening modality, and it is evolving with regards to recommended/ programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. Also unclear is what follow-up is required for a patient with a positive CTC and a negative colonoscopy. CTC may also not be as sensitive as colonoscopy to detect clinically significant lateral spreading tumors (Togashi K, et al. World J Gastroenterol 2014;20:17552-7). Despite these uncertainties, CTC is being utilized in clinical practice. The current data available suggest that, if CTC is negative/no polyps, then repeat CTC in 5 y, and if positive/polyps lesions, colonoscopy should be performed.

[e] 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.

[f] 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.).

[g] Stool DNA testing has recently been approved by the FDA as a primary screening modality for colorectal cancer (Imperiale TF, et al. N Engl J Med 2014;370:1287-1297). At this time, there are limited data available to determine an appropriate interval between screening.

[h] Recent studies have demonstrated that FIT is more sensitive than high-sensitivity guaiac-based testing. However, regular guaiac-based stool testing has been shown to reduce CRC mortality in randomized trials (category 1).

[i] SSPs without dysplasia are generally managed like adenomas; SSP-cd are managed like high-risk adenomas and may need even more frequent surveillance.(Rex D, et al. Am J Gastro 2012;107:1315-1329; Leiberman D, et al. Gastroenterology 2012;143:844-857).

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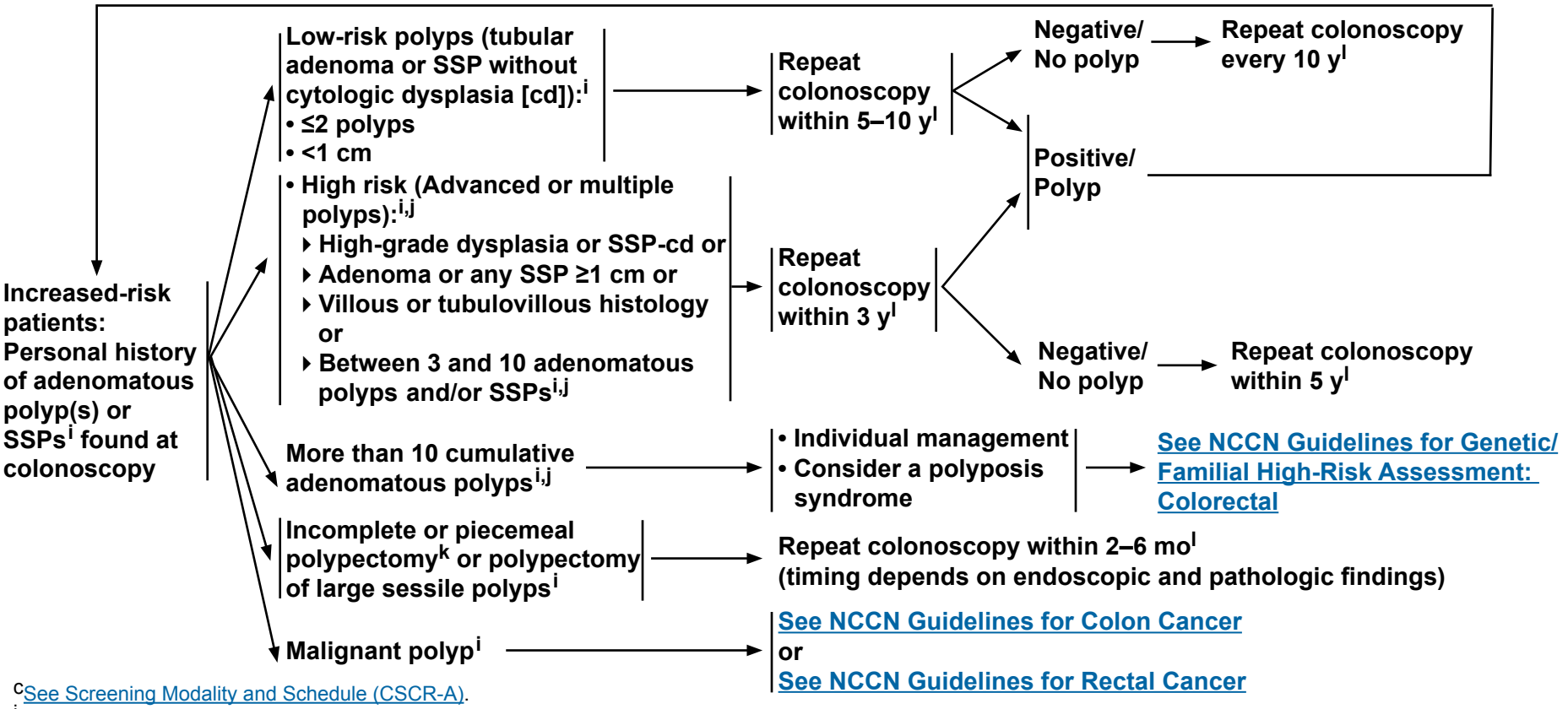
INCREASED RISK BASED ON PERSONAL HISTORY OF ADENOMATOUS POLYP OR SESSILE SERRATED POLYP[i]



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

[i] SSPs without dysplasia are generally managed like adenomas; SSPs with cytologic dysplasia (SSP-cd) are managed like high-risk adenomas and may need even more frequent surveillance (Rex D, et al. Am J Gastro 2012;107:1315-1329; Leiberman D, et al. Gastroenterology 2012;143:844-857).

[j] 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.

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

[l] Shorter intervals may be necessary when there is uncertainty about completeness of removal of large and/or sessile polyps, if the colonic preparation was suboptimal, and for SSP-cds. Some authorities recommend surveillance at 1- to 3-year intervals for SSP-cds because they are thought to rapidly progress to CRC (RexD, et al. Am J Gastro 2012;107:1315-1329). 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[m,n]	SURVEILLANCE
Personal history of CRC →	• Lynch syndrome (LS) screening with routine tumor testing is recommended at the time of diagnosis with either approach below: ▸ Individuals with CRC diagnosed at ≤70 y; and also those >70 y who meet the Bethesda guidelines or ▸ 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

[m]Moreira L, Balaguer F, Lindor N, et al. Identification of Lynch syndrome among patients with colorectal cancer. JAMA 2012;308:1555-1565.
[n]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).

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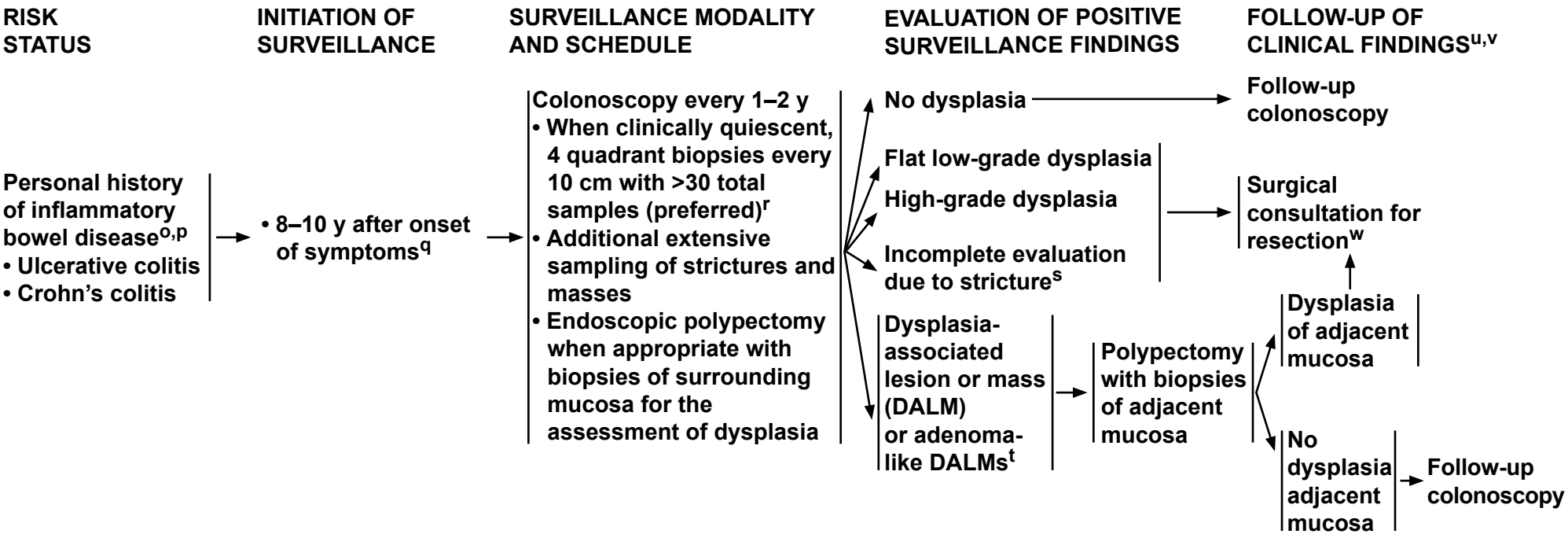
INCREASED RISK BASED ON PERSONAL HISTORY OF INFLAMMATORY BOWEL DISEASE



[o]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 colorectal cancer, 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.

[p]If PSC is present, annual surveillance colonoscopies should be started independent of the disease activity and extent.

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

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

[s]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, especially in long-standing disease.

[t]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 (adenoma-like DALMs), with no dysplasia in the flat mucosa in the surrounding area or elsewhere in the colon and without invasive carcinoma in the polyp, can be treated safely by polypectomy and continued surveillance.

[u]Optimal management of Crohn's-related dysplasia remains undefined. Patient and physician preference should be considered. Extent of resection for Crohn's-related dysplasia should be based upon the individual findings. When a single focus of low-grade dysplasia is found in patients with inflammatory bowel disease, 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.

[v]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 number and size of adenomas.

[w]See Definitions of Common Colorectal Resections (CSCR-B).

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INCREASED RISK BASED ON POSITIVE FAMILY HISTORY

FAMILY HISTORY CRITERIA[x,y]	SCREENING	
1 first-degree relative with CRC aged <60 y or 2 first-degree relatives with CRC at any age	Colonoscopy beginning at age 40 y or 10 y before earliest diagnosis of CRC	Repeat every 5 y[x,z] or if positive, repeat per colonoscopy findings
First-degree relative with CRC aged ≥60 y	Colonoscopy beginning at age 50 y	Repeat every 5–10 y[x,z,aa] or if positive, repeat per colonoscopy findings
1 second-degree relative with CRC aged <50 y	Colonoscopy beginning at age 50 y	Repeat every 5–10 y[x,z,aa] 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 50 y or at age of onset of adenoma in relative, whichever is first	Repeat every 5–10 y[z,aa] or if positive, repeat per colonoscopy findings

[x]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 Oct;147(4):814-821.

[y]If a patient meets the criteria for an inherited colorectal syndrome, see Criteria for Further Risk Evaluation for High-Risk Syndromes (HRS-1) in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal.

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

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

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SCREENING MODALITY AND SCHEDULE (1 of 5)

- **The goal of a CRC screening program is to reduce CRC mortality through cancer prevention and early detection.**
- **Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and by detecting and removing polyps. It has also been shown to be cost-effective compared to other screening programs.**
- **There is direct evidence from randomized controlled trials that fecal occult blood testing (Mandel JS, et al. N Engl J Med 1993;328:1365-71; Hardcastle JD, et al. Lancet 1996;348:1472-7; Kronborg O, et al. Lancet 1996;348:1467-71) and flexible sigmoidoscopy (Atkin WS, et al. Lancet 2010;375:1624-33; Schoen RE, et al. N Eng J Med 2012;366:2345-57; Nishihara R, et al. N Eng J Med; 2013;369:1095-105) will reduce mortality from colorectal cancer. There is evidence from case control and cohort studies that colonoscopy has the potential ability to prevent colorectal cancer (with its associated morbidity) and cancer deaths (Kahi CJ, et al. Clin Gastroenterol Hepatol 2009;7:770-5; Baxter NN, et al. Ann Intern Med 2009;150:1-8).**

Continued on next page

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SCREENING MODALITY AND SCHEDULE (2 of 5)

Screening modalities that detect adenomatous polyps and cancer[1,2,3]

- **Colonoscopy every 10 years,**
- **Flexible sigmoidoscopy every 5 years,**
- **CT colonography (CTC) every 5 years**[4]

Screening modalities that primarily detect cancer[1,2,3]

- **Stool-based screening**
  - **High-sensitivity guaiac-based testing annually**
  - **Immunochemical-based testing annually**
  - **Stool DNA test with high sensitivity (interval for screening is uncertain)**[5]

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[1]Levin B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: A joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. Gastroenterology 2008;134:1570-1595.
[2]USPSTF, Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627-637.
[3]Rex DK, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2008. Am J Gastroenterol 2009;104:739-750.
[4]Currently there is not a consensus on the use of CT colonography as a primary screening modality, and it is evolving with regards to recommended/ programmatic frequency, polyp size leading to referral for colonoscopy, and protocol for evaluating extra colonic lesions. However, the data available suggest that if CT colonography is negative/no polyps, then repeat CT colonography in 5 years, and if CT colonography is positive/polyps lesions >5 mm, colonoscopy should be performed.
[5]Emerging technologies such as stool DNA have shown increasing evidence as a reasonably accurate screening modality, but there are limited data to determine an interval between screening. At present, stool DNA is not considered a primary screening modality.

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SCREENING MODALITY AND SCHEDULE (3 of 5)

Colonoscopy

- In the United States, colonoscopy is the primary method employed for CRC screening in 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 in 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
- Colonscopy preparation[6]
  - 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[6]
    - ◊ 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.

Continued on next page

[6]Johnson DA, et. al. Optimizing adequacy of bowel cleansing for colonoscopy: recommendations from the US multi-society task force on colorectal cancer. Gastroenterology 2014;147:903-924.

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SCREENING MODALITY AND SCHEDULE (4 of 5)

Colonoscopy (Continued)

- Standardized colonoscopy reports that contain, at a minimum:[7]
  - 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
  - Estimate of quality of bowel preparation
  - Documentation of follow-up planning, including pathology results
  - Sedation administered
  - Written communication of the findings and plans to the patient and referring physician is encouraged.
- Pathology should also include polyp number, size, and location in addition to histopathology.

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[8]
  - Requires 3 successive stool specimens annually (not via digital rectal examination), prescribed diet, and coordination by health care provider
  - Any positive test requires further evaluation
- Fecal immunochemical testing (FIT)
  - Recent studies have demonstrated that FIT is more sensitive than guaiac-based testing.[9,10,11]
  - Detects human globin
  - Prescribed diet is not required
  - Many brands require only a single stool annually
  - Any positive test requires further evaluation

Flexible sigmoidoscopy[8]

Continued on next page

- May be performed alone or in combination with stool-based screening[12]
- Recommended every 5 years for average-risk screening

[7] Lieberman D, Nadel M, Smith RA, et al. Standardized colonoscopy reporting and data system: Report of the Quality Assurance Task Group of the National Colorectal Cancer Roundtable. Gastrointestinal Endoscopy 2007;65:757-6.

[8] There are category 1 data that regular (not high-sensitivity) guaiac-based fecal occult blood test (FOBT) and flexible sigmoidoscopy reduce mortality from colorectal cancer. Mandel JS, Bond JH, Church TR, et al. N Engl J Med 1993;328:1365-71. Kronborg O, Fenger C, Olsen J, et al. Lancet 1996;348:1467-71. Atkin WS, et al. Lancet 2010; 375:1624-33; Schoen RE, et al. N Eng J Med 2012;366:2345-57; Nishihara R, et al. N Eng J Med; 2013;369:1095-105.

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

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

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

[12] Winawer S, et al. J Natl Cancer Inst 1993 18;85:1311-8 and Zauber A, et al. Ann Intern Med 2008;149:659-69.

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SCREENING MODALITY AND SCHEDULE (5 of 5)

Radiographic

CTC[4,13,14]

- **Accuracy**
  - **>10 mm lesions can be identified by CTC with an accuracy similar to colonoscopy**
  - **Lesions 5–9 mm can be identified with an acceptable accuracy that is less than that identified for colonoscopy**
  - **Lesions <5 mm cannot be identified with acceptable accuracy**
- **Follow-up of identified lesions**
  - **All identified lesions >5 mm should be referred for colonoscopy**
  - **When identified, lesions <5 mm generally do not need to be referred for colonoscopy**
- **The recommended performance interval of every 5 years is based solely on computer simulation models**
- **All visualized extracolonic findings should be described and recommendations should be provided as to appropriate follow-up (including no follow-up)**
- **The increased risk of cancer arising from the performance of a single CTC is estimated to be <0.14%**
- **CTC interpretation should be accomplished only by those trained according to American Gastroenterological Association[11] or American College of Radiology (ACR)[12] guidelines**
- **Procedure quality should be tracked and assured using current ACR practice guidelines for patient preparation, image acquisition, study interpretation, and reporting**

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

[13]See American Gastroenterological Association CT Colonography Standards.

[14]See American College of Radiology Practice Guideline for the Performance of Computed Tomography (CT) Colonography in Adults.

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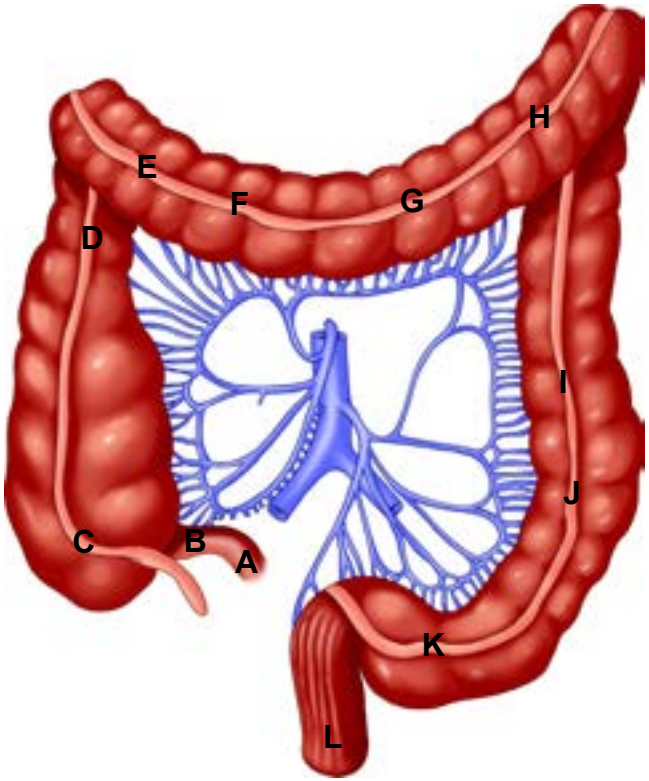
DEFINITIONS OF COMMON COLORECTAL RESECTIONS

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 D	Ascending colectomy
A through F	Right hemicolectomy
A through G	Extended right hemicolectomy
E through H	Transverse colectomy
G through I	Left hemicolectomy
F through I	Extended left hemicolectomy
J through K	Sigmoid colectomy
A through J	Subtotal colectomy
A through K	Total colectomy
K through L	Low anterior resection with sphincter preservation
K through L	Abdominoperineal resection without sphincter preservation

[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

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.

Table of Contents

Overview

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer in the United States. In 2015, an estimated 93,090 new cases of colon cancer and 39,610 new cases of rectal cancer will occur in the United States. During the same year, it is estimated that 49,700 people will die from colon and rectal cancer.[1] CRC mortality can be reduced both by early diagnosis and by cancer prevention through polypectomy.[2-4] Hence, the goal of a CRC screening program is to reduce CRC mortality through cancer prevention and early detection. Currently, patients with localized CRC have a 90.5% relative 5-year survival rate, whereas rates for those with regional and distant disease are 71.9% and 12.5%, respectively, demonstrating that earlier diagnosis can have a large impact on survival.[5]

Importantly, the incidence of colon and rectal cancers per 100,000 people decreased from 60.5 in 1976 to 46.4 in 2005.[6] 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.[7] In addition, mortality from CRC decreased by almost 35% from 1990 to 2007,[8] and in 2011 was down by 47% 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.[9] 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.[10] 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.[11]

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).[12-14]

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 15, 2013 and October 15, 2014, 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.[15]

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

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 424 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).

Colorectal Cancer Screening

Current technology falls into two broad categories: structural tests and stool/fecal-based tests.[16] 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 primary method employed. 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).[17] 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 (95% CI, 0.49–0.63) compared with those who were never screened.[18]

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. In addition, whereas rescreening can be performed with any screening modality, interval screening with additional modalities (ex, interval stool-based testing with every 10-year colonoscopies in an average-risk individual) should not be performed.

Structural Screening Tests

Structural tests are able to detect both early cancer and polyps using endoscopic or radiologic imaging. Endoscopic tests have several limitations including their relative invasiveness, the need for dietary preparation and bowel cleansing, and the time dedicated to the examination (typically 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.[19]

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 assessment of the efficacy of other screening methods. 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.[20-29] Rabeneck and colleagues recently reported an inverse correlation between colonoscopy use and death from CRC from a large population study involving close to 2.5 million Canadians.[30] For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.

Interestingly, in a Canadian case-control study that matched each of 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).[31] 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.[32,33] However, additional studies have also demonstrated a reduced effectiveness in the right colon. A recent population-based, case-controlled study in Germany demonstrated that colonoscopy in the preceding 10 years gave an overall 77% decrease in the risk for CRC.[20] While risk reduction was strongest for distal cancer, a 56% risk reduction was seen for proximal disease as well. Similar results were seen in a recent large case-control study using the SEER-Medicare database.[34]

Another recent study followed 88,902 participants in 2 prospective cohorts (the Nurses' Health Study and the Health Professionals Follow-up Study) for 22 years, comparing long-term outcomes in those who had screening colonoscopies, sigmoidoscopies, or no endoscopy.[29] 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). Mortality from proximal colon cancer was reduced after screening colonoscopy (HR, 0.47; 95% CI, 0.29–0.76) but not after sigmoidoscopy.

A recent follow-up on the National Polyp Study evaluated the long-term mortality effects of colonoscopy with polypectomy.[25,35] The mortality of 2,602 patients with adenomas removed was compared to the incidence-based mortality from CRC in the SEER database. With a median 15.8 years follow-up, 12 deaths were attributed to CRC in the screened group, compared with an expected 25.4 deaths in the general population, suggesting a 53% decrease in mortality.

Another recent study estimated CRC mortality in 40,826 patients who underwent polypectomy in Norway.[36] 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 three 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. 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. In addition to cancer prevention, colonoscopic screening is also expected to lead to earlier diagnosis. Supporting this supposition, a recent 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.[37] 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; $P < .001$). Furthermore, unscreened patients had higher rates of death and recurrence, shorter survival, and shorter disease-free intervals.

A current randomized controlled trial is comparing one-time colonoscopy with biennial fecal immunochemical testing (FIT; see discussion of FIT below) with the primary outcome of death due to CRC at 10 years. Interim results from this trial show that subjects are more likely to participate in FIT screening (34.2% vs. 24.6%; $P < .001$).[38] The two tests identified similar numbers of cancers in initial screening, but colonoscopy identified significantly more advanced and non-advanced adenomas.

A recent 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.[39]

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 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.[40] 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.[40] 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.[41] 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. Recently, analysis of data 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).[42]

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.[43] 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.[42,44-46]

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.[47-49] The US Multi-Society Task Force on Colorectal Cancer also recommends split preparation.[50]

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.[51-53]

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.[50] 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.[54] 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.[55] 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.[56] 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.[57] 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.[58] The adjusted odds ratio was 0.26 (95% CI, 0.16–0.40). The low risk was seen even if the colonoscopy had been performed up to 20 or more years previously. A recent analysis showed that the risk reduction seen following negative colonoscopy holds even for patients with a family history of CRC, but not for current smokers.[59]

Flexible Sigmoidoscopy

Flexible sigmoidoscopy followed by colonoscopic polypectomy in patients with lesions >1 cm significantly reduced mortality risk in early case-control studies.[28,60] There is now direct evidence from randomized controlled trials that flexible sigmoidoscopy reduces mortality from CRC.[29,61-67] A recent British randomized population screening study of over 110,000 individuals attributed a 23% and 31% reduction in CRC incidence and mortality, respectively, to flexible sigmoidoscopy offered once between ages 55 and 64 compared to no screening.[61] The reductions in colorectal incidence and mortality for those individuals who accepted screening were 33% and 43%, respectively. In addition, the SCORE trial randomized 34,272 subjects to one-time sigmoidoscopy or no screening and recently reported incidence and mortality results after >10 years median follow-up.[64] 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 recently reported CRC mortality rates from their randomized, controlled 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.[65-67] 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.[65] 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.[62] 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).[63] Interestingly, the addition of FOBT did not affect the long-term outcomes of participants screened with sigmoidoscopy in this trial.

Another recent study followed 88,902 participants in 2 prospective cohorts (the Nurses' Health Study and the Health Professionals Follow-up Study) for 22 years, comparing long-term outcomes in those who had screening colonoscopies, sigmoidoscopies, or no endoscopy.[29] 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). Mortality from proximal colon cancer was reduced after screening colonoscopy (HR, 0.47; 95% CI, 0.29–0.76) but not after sigmoidoscopy.

Recent meta-analyses of randomized controlled trials support the conclusion that screening by flexible sigmoidoscopy significantly reduces the incidence and mortality of CRC.[68-71] In addition, a recent analysis of a 5% random Medicare sample of the SEER database found a similar reduction in distal CRC after both colonoscopy and sigmoidoscopy, with a reduction in proximal CRC after colonoscopy but not sigmoidoscopy.[72] 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.[73]

Compared to colonoscopy, sigmoidoscopy requires no sedation and less bowel preparation, but is limited to examination of the distal colon. A recent analysis of cancers not detected by flexible sigmoidoscopy in the PLCO trial showed that 37% of undetected lesions were beyond the reach of the sigmoidoscope.[74] In fact, the authors estimated that an additional 15% to 19% of cancers may have been detected during screening had colonoscopy been used.

Flexible sigmoidoscopy should be performed using a scope 60 cm or longer. Polyps identified should be biopsied by trained personnel to determine if they are hyperplastic, adenomatous, or sessile serrated. Flat adenomatous polyps are unusual and may be missed during screening. Patients with lesions larger than 1 cm should be referred directly to colonoscopy, 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.[75] However, a positive finding requires a colonoscopy, and extracolonic findings, which are present in up to 16% of patients, pose a dilemma.[76,77] 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.[78] In this study, 2531 participants underwent CT colonography followed by traditional optical colonoscopy. Colonoscopy identified 128 large adenomatous polyps or carcinomas in 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[79,80] and similar to what was reported by Pickhardt and colleagues in a prospective study with a design similar to the ACRIN trial.[81]

Kim et al also compared CT colonography with colonoscopy for the detection of advanced neoplasia.[82] 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.[83]

In 2005, 2 meta-analyses reviewed the performance of CT colonography in the detection of colorectal polyps.[84,85] 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.[84] 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.[85]

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.[86] 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.[87]

Importantly, CT colonography may be a more acceptable option to many individuals. A recent randomized study compared participation rates when members of the general population were offered CRC screening by either colonoscopy or CT colonography.[88] Significantly more people accepted the invitation for CT colonography (34% vs. 22%). While colonoscopy had a greater diagnostic yield in screened participants, the yields were similar when determined per the invited population. More recently, laxative-free CT colonography has shown

good sensitivity and specificity for detecting lesions 1 cm or larger.[89] This technique is likely to be even more acceptable 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 the expertise of the interpreter.[90,91] 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. 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 age 60.[92] Risks increase with repeated scanning. The 2009 ACR practice guidelines for the use of CT colonography recommend the use of a multi-detector CT scanner and low-dose, non-enhanced technique to minimize radiation exposure to the patient.[93] 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. However, it is still an evolving technique, and little data address screening intervals, polyp size leading to referral for colonoscopy, what follow-up is required for a patient with a positive CT colonography and a negative colonoscopy, and protocol for evaluating extracolonic lesions. Despite these uncertainties, CT colonography is being utilized in clinical practice. The best evidence currently available seems to support repeating the procedure every 5 years and referring patients with identified polyps larger than 5 mm to colonoscopy.

Fecal-Based Screening

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

Any positive stool test 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.[94,95] Unfortunately, a recent 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.[96]

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.[97-99] In the Minnesota Colon Cancer Control Study, more than 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.[99] 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).[100] Other large randomized studies have also demonstrated a CRC mortality decrease with biennial screening.[97,98] 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%.[101]

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).[102] 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).[70] The sensitivity of different guaiac FOBT for cancer detection ranged from 37% to 79% in a study of about 8,000 participants by Allison and colleagues.[103] 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.[104] 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 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 recent 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).[105]

A recent prospective study randomized 1918 first-degree relatives of patients with CRC to 3 years of annual FIT screening or 1-time colonoscopy.[106] Follow-up colonoscopies revealed that although FIT missed 16 of 41 advanced adenomas, FIT identified all 4 incidences of CRC.

Comparative studies have shown that FIT is more sensitive than high-sensitivity guaiac FOBT.[107-113] For example, one study demonstrated a higher sensitivity for cancer by FIT compared to high-sensitivity guaiac FOBT Hemoccult® Sensa (82% vs. 64%).[107] 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%).[109] In addition, as seen in other trials, FIT had a significantly higher participation rate than guaiac FOBT in this trial. An expert panel in Ontario recently conducted an extensive literature analysis and concluded that FIT is superior to guaiac FOBT in both participation rates and in detection of advanced adenomas and CRC.[114]

Stool DNA Test

Stool DNA testing has emerged as a new primary screening tool for CRC. It detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool. Early proof-of-principle tests involving a single-target marker such as *KRAS* produced less than 40% sensitivity.[115] In an effort to improve sensitivity, newer tests with multi-panel markers were developed. In a large multicenter study of 4404 patients, eligible subjects submitted a stool specimen for DNA analysis, underwent Hemoccult® II testing, and then had a colonoscopy.[116] In a subgroup analysis, the multi-target DNA assay SDT-1 (21 mutations in *APC*, *KRAS*, and *p53* plus 2 other markers) detected 52% of CRC compared with 13% by Hemoccult® II, with specificities of 94% and 95%, respectively. The SDT-1 assay did not perform as well in another large, multicenter, prospective, triple-blinded trial that also assessed a second-generation combination test SDT-2 (mutations in *APC* and *KRAS* plus *vimentin* methylation).[117] In this study, a total of 3,764 average-risk healthy adults underwent screening colonoscopy, Hemoccult®, Hemoccult® Sensa, SDT-1, and SDT-2. Very similar sensitivities for detection of CRCs, high-grade dysplasias, and adenomas were observed for SDT-1 and Hemoccult® Sensa (20% and 21%, respectively), whereas the sensitivity of SDT-2 was 40%.

Other stool DNA tests have also been developed and tested.[118] In particular, Cologuard® (Exact Sciences) uses quantitative molecular assays for *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation, and *ACTB*, in conjunction with a hemoglobin immunoassay. A recent 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 sessile serrated polyps (SSPs) >1 cm (42.4% vs. 5.1%; $P < .001$).[119] Specificity, however, was better with FIT (86.6% vs. 94.9% 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® as the first stool DNA test for primary screening for CRC. Other stool DNA tests (eg, ColoSure™, detecting methylated *vimentin*) are currently available in the United States, although they are not FDA approved.[120]

Importantly, however, data to help determine an appropriate interval between screening, adherence to/participation rates of screening, and how stool DNA testing may fit into an overall screening program are limited. It is not clear, for example, how stool DNA testing will compare to several rounds of annual FIT. The panel therefore does not

recommend stool DNA testing as a primary screening modality at this time.

Risk Assessment

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 age 50 years or older with a negative family history and no history of adenoma, SSPs (described below), CRC, or inflammatory bowel disease.

Increased Risk

Individuals with a personal history of adenomatous polyps or SSPs, CRC, or inflammatory bowel disease, and those with a positive family history of CRC or advanced adenomatous polyps are considered to be at increased risk for developing CRC. Individuals with diabetes mellitus or a history of *BRCA*-positive breast cancer and those who are obese also have a higher risk,[121-124] although these are not considered to affect the screening guidelines. Other factors that influence risk include age, sex, and race.[125]

In particular, registry data suggest an increased incidence for CRC in African Americans prior to age 50.[126] This increased risk has led some to recommend beginning population CRC screening in African Americans at age 45.[127] 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.[128] Therefore, based on the available data, methods to further enhance access to screening in African American populations should be endorsed.

High-Risk Syndromes

Individuals with a family history of Lynch syndrome (also known as HNPCC) or with a personal or family history of polyposis syndromes are considered to be in the high-risk category (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal, available at www.NCCN.org).

Screening of Individuals at Average Risk

It is recommended that screening for persons at average risk begin at age 50 after discussions of the available options. Currently recommended options include colonoscopy every 10 years, annual fecal-based tests, or flexible sigmoidoscopy every 5 years with or without an interval stool-based test at year 3. If a colonoscopy is incomplete or preparation is suboptimal, other screening methods or repeat colonoscopy in 1 year should be considered. Following a negative test, rescreening at the appropriate interval can be done with any accepted modality. Recent data suggest that following 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.[129]

One screening option recommended by the panel is an interval stool-based test as an added option to flexible sigmoidoscopy. In one study, patients were assigned (based on calendar period on enrollment) to annual sigmoidoscopy with or without annual FOBT.[130] Of >12,000 participants, survival probability was significantly greater in the FOBT group (70% vs. 48%; *P* <.001). In addition, 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.[131]

Interpretation of Findings

Colonoscopy is indicated as follow-up of abnormal findings from other screening modalities—stool 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 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.[132] 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.[133] 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.[134,135] Thus, SSPs are managed like tubular adenomas, whereas SSP-cds are managed like high-risk adenomas but may need even more frequent surveillance. In addition, any serrated lesion proximal to the sigmoid colon should be followed similarly to adenomatous polyps because of their significant risk of neoplastic progression.[134,136-138]

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. Recent literature, however, suggests that a small subset of persons with multiple or large hyperplastic polyps have serrated polyposis syndrome (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).[139-141] The

majority of these persons had concomitant adenomatous polyps or SSP.[142] 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.[143]

Hyperplastic polyps that are <1 cm without SSP features indicate average risk for follow-up screening when they occur in 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.[134] In addition, when 4 or more hyperplastic polyps of any size are found proximal to the sigmoid colon, a 5-year colonoscopic screening interval is recommended.[134]

Screening of Individuals at Increased Risk

Personal History of Adenoma/SSP

Individuals with adenomatous polyps or SSPs are at increased risk for recurrent polyps and CRC. To minimize the risk of developing CRC, a surveillance program is recommended for patients with adenomatous polyps/SSP following screening colonoscopy and complete polypectomy.[137] 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 or fewer 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.[137] Generally the results of the first 2 screening 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.[144] 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.[145] 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.[146] 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 new data suggest that

intervals of 5 years may be appropriate and some experts recommend surveillance at 1- to 3-year intervals for SSP-cds, because they are thought to rapidly progress to CRC.[134,147] 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.

In individuals with more than 10 cumulative adenomatous polyps, a polyposis syndrome should be considered (see *Inherited Colon Cancer* in 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 presences of ten polyps or fewer may occasionally be associated with an inherited polyposis syndrome, especially in patients younger than age 40 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.[148] 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

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.[149-152] In patients with rectal cancer, local recurrence at the rectal anastomosis has been reported to occur in 5% to 36% of patients.[153-155] Furthermore, an analysis of 3,278 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.[156] 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[150,157,158] and in 3 meta-analyses of randomized controlled trials designed to compare low-intensity and high-intensity programs of surveillance.[159-161] 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.[151] 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.[162] Furthermore, a population-based report indicated that long-term survival is possible in patients treated for local recurrence of rectal cancer (overall 5-year relative survival rate of 15.6%), thereby providing support for more intensive post-treatment follow-up in these patients.[163] Nevertheless, controversies remain regarding selection of optimal strategies for following up patients after potentially curative CRC surgery.[164,165]

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.[166,167] 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).

Inflammatory Bowel Disease

It is well recognized that individuals with a personal history of inflammatory bowel disease (ie, ulcerative colitis, Crohn's disease) are at an increased risk for CRC, because chronic inflammation can lead to dysplasia and subsequent malignant conversion.[168-170] 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.[171] In fact, a recent retrospective review of 6823 patients with inflammatory bowel disease 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).[172] 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 inflammatory bowel disease 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.[173] 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.[173]

The NCCN Panel recommends surveillance by colonoscopy every 1 to 2 years, initiated 8 to 10 years after the onset of symptoms in patients with a personal history of inflammatory bowel disease. This screening should be performed by an endoscopist who is familiar with the appearance of ulcerative colitis or Crohn's disease.[174] If PSC is present, annual surveillance colonoscopies should be started independent of the disease activity and extent.[174] A 2001 meta-analysis showed that patients with pancolitis have a higher risk of developing CRC than those with less extensive disease.[175] 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.[176,177] Several other groups have also developed evidence-based guidelines for surveillance endoscopy in inflammatory bowel disease.[174]

When inflammatory bowel disease is clinically quiescent, multiple four-quadrant biopsies (every 10 cm with 30 or more samples) 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. Biopsies can be better targeted to abnormal-appearing mucosa using chromoendoscopy or confocal endomicroscopy. Targeted biopsies have been found to improve detection of dysplasia and should be considered for surveillance colonoscopies in patients with ulcerative colitis.[178] Any masses, including so-called dysplasia-associated lesions (discussed in more detail below), are of extreme concern. Endoscopic polypectomy should be performed when appropriate with biopsies of surrounding mucosa for the assessment of dysplasia.

Interpretation of dysplasia or intraepithelial neoplasia can be difficult. Pathologists experienced in interpreting inflammatory bowel disease lesions should evaluate biopsies. Most findings of high-grade or low-grade dysplasia place the patient with ulcerative colitis at high risk for developing CRC. These patients should be referred to an experienced inflammatory bowel disease surgeon to discuss surgical options. In addition, a stricture, especially one that is symptomatic or not traversable during colonoscopy or that is associated with long-standing disease, is a strong indication for colectomy because of the high rate of underlying carcinoma.

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. Dysplasia-associated lesions or masses (DALMs) or lesions that appear endoscopically and histologically similar to sporadic adenoma (adenoma-like DALMs) can be treated safely by polypectomy and continued surveillance if no dysplasia is present in the flat mucosa in the surrounding area or elsewhere in the colon and if there is no invasive carcinoma in the polyp. If the mucosa adjacent to the DALM or adenoma-like DALM is dysplastic, however, surgical consultation is warranted.

Optimal management of Crohn's-related dysplasia remains undefined,[179] 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 inflammatory bowel disease, 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

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.[180]

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[181] 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 screening.[182-184] The panel's recommendations are as follows:

- For patients with an affected first-degree relative diagnosed before age 60 years or 2 first-degree relatives with CRC at any age, colonoscopy is recommended every 5 years, beginning 10 years prior to the earliest diagnosis in the family or at age 40 at the latest. If colonoscopy is positive, follow-up colonoscopy should be based on findings.
- For those with one affected first-degree relative diagnosed at age 60 years or older, colonoscopy every 5 to 10 years should begin at age 50. If colonoscopy is positive, follow-up colonoscopy should be based on findings. Multiple (≥2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals.
- When one second-degree relative is diagnosed with CRC prior to age 50, colonoscopy should begin at age 50 years, with repeat colonoscopy every 5 to 10 years or based on findings.
- 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 50 years at the latest, with repeat colonoscopy every 5 to 10 years or based on findings. Data suggesting an increased risk for CRC in this population are limited.[185,186]

Colonoscopy intervals should be modified based on personal and family history as well as on individual preferences. A recent population-based study analyzed more than 2 million individuals to determine RRs for the development of CRC depending on family history of CRC.[182] 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. 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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