NCCN Guidelines® Insights

Colorectal Cancer Screening, Version 1.2015

Featured Updates to the NCCN Guidelines

Dawn Provenzale, MD, MS[1,*]; Kory Jasperson, MS, CGC[2,*]; Dennis J. Ahnen, MD[3]; Harry Aslanian, MD[4]; Travis Bray, PhD[5]; Jamie A. Cannon, MD[6]; Donald S. David, MD[7]; Dayna S. Early, MD[8]; Deborah Erwin, PhD[9]; James M. Ford, MD[10]; Francis M. Giardiello, MD, MBA[11]; Samir Gupta, MD[12]; Amy L. Halverson, MD[13]; Stanley R. Hamilton, MD[14]; Heather Hampel, MS, CGC[15]; Mohammad K. Ismail, MD[16,*]; Jason B. Klapman, MD[17]; David W. Larson, MD, MBA[18]; Audrey J. Lazenby, MD[19]; Patrick M. Lynch, MD, JD[14]; Robert J. Mayer, MD[20]; Reid M. Ness, MD, MPH[21]; M. Sambasiva Rao, MD[13]; Scott E. Regenbogen, MD[22]; Moshe Shike, MD[23]; Gideon Steinbach, MD, PhD[24]; David Weinberg, MD, MSc[25]; Mary A. Dwyer, MS[26]; Deborah A. Freedman-Cass, PhD[26]; and Susan Darlow, PhD[26]

Abstract

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for Colorectal Cancer Screening provide recommendations for selecting individuals for colorectal cancer screening, and for evaluation and follow-up of colon polyps. These NCCN Guidelines Insights summarize major discussion points of the 2015 NCCN Colorectal Cancer Screening panel meeting. Major discussion topics this year were the state of evidence for CT colonography and stool DNA testing, bowel preparation procedures for colonoscopy, and guidelines for patients with a positive family history of colorectal cancer. (J Natl Compr Canc Netw 2015;13:959–968)

From [1]Duke Cancer Institute; [2]Huntsman Cancer Institute at the University of Utah; [3]University of Colorado Cancer Center; [4]Yale Cancer Center/Smilow Cancer Hospital; [5]Hereditary Colon Cancer Foundation; [6]University of Alabama at Birmingham Comprehensive Cancer Center; [7]City of Hope Comprehensive Cancer Center; [8]Siteman Cancer Center at Barnes-Jewish Hospital and Washington University School of Medicine; [9]Roswell Park Cancer Institute; [10]Stanford Cancer Institute; [11]The Sidney Kimmel Comprehensive Cancer Center at Johns Hopkins; [12]UC San Diego Moores Cancer Center; [13]Robert H. Lurie Comprehensive Cancer Center of Northwestern University; [14]The University of Texas MD Anderson Cancer Center; [15]The Ohio State University Comprehensive Cancer Center - James Cancer Hospital and Solove Research Institute; [16]St. Jude Children's Research Hospital/The University of Tennessee Health Science Center; [17]Moffitt Cancer Center; [18]Mayo Clinic Cancer Center; [19]Fred & Pamela Buffett Cancer Center; [20]Dana-Farber/Brigham and Women's Cancer Center; [21]Vanderbilt-Ingram Cancer Center; [22]University of Michigan Comprehensive Cancer Center; [23]Memorial Sloan Kettering Cancer Center; [24]Fred Hutchinson Cancer Research Center/Seattle Cancer Care Alliance; [25]Fox Chase Cancer Center; and [26]National Comprehensive Cancer Network.

*Provided content development and/or authorship assistance.

Please Note

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

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

The full and most current version of these NCCN Guidelines are available at NCCN.org.

Colorectal Cancer Screening, Version 1.2015

NCCN: Continuing Education

Accreditation Statement

This activity is designated to meet the educational needs of physicians, nurses, and pharmacists involved in the management of patients with cancer. There is no fee for this article. The National Comprehensive Cancer Network (NCCN) is accredited by the ACCME to provide continuing medical education for physicians. NCCN designates this journal-based CE activity for a maximum of 1.0 *AMA PRA Category 1 Credit*™. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

NCCN is accredited as a provider of continuing nursing education by the American Nurses Credentialing Center`s Commission on Accreditation.

NCCN designates this educational activity for a maximum of 1.0 contact hour. Accreditation as a provider refers to recognition of educational activities only; accredited status does not imply endorsement by NCCN or ANCC of any commercial products discussed/displayed in conjunction with the educational activity. Kristina M. Gregory, RN, MSN, OCN, is our nurse planner for this educational activity.

National Comprehensive Cancer Network is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education. NCCN designates this continuing education activity for 1.0 contact hour(s) (0.1 CEUs) of continuing education credit in states that recognize ACPE accredited providers. This is a knowledge-based activity. UAN: 0836-0000-15-009-H01-P

All clinicians completing this activity will be issued a certificate of participation. To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/71856;** and 4) view/print certificate.

Release date: August 18, 2015; Expiration date: August 18, 2016

Learning Objectives:

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

- Integrate into professional practice the updates to the NCCN Guidelines for Colorectal Cancer Screening
- Describe the rationale behind the decision-making process for developing the NCCN Guidelines for Colorectal Cancer Screening

Disclosure of Relevant Financial Relationships

Editor:

Kerrin M. Green, MA, Assistant Managing Editor, *JNCCN—Journal of the National Comprehensive Cancer Network*, has disclosed that she has no relevant financial relationships.

CE Planners:

Deborah J. Moonan, RN, BSN, Director, Continuing Education, NCCN, has disclosed that she has no relevant financial relationships.

Ann Gianola, MA, Manager, Continuing Education Accreditation & Program Operations, NCCN, has disclosed that she has no relevant financial relationships.

Kristina M. Gregory, RN, MSN, OCN, Vice President, Clinical Information Operations, NCCN, has disclosed that she has no relevant financial relationships.

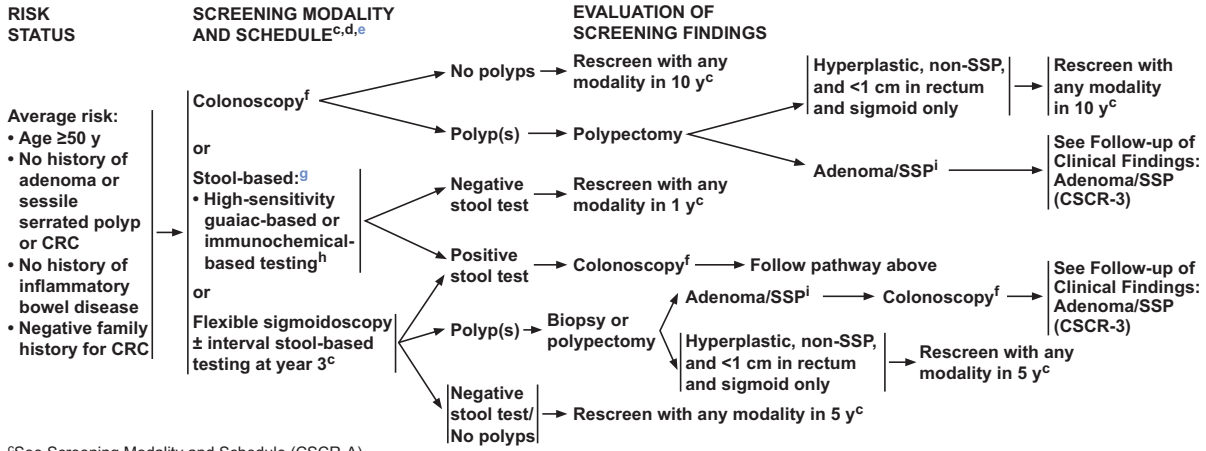
Rashmi Kumar, PhD, Senior Manager, Clinical Content, NCCN, has disclosed that she has no relevant financial relationships.

Individuals Who Provided Content Development and/or Authorship Assistance:

Dawn Provenzale, MD, MS, Panel Chair, has disclosed that she has no relevant financial relationships.
Kory Jasperson, MS, CGC, Panel Vice-Chair, has disclosed that he is an employee of Ambry Genetics.
Mohammad K. Ismail, MD, Panel Member, has disclosed that he has no relevant financial relationships.
Mary A. Dwyer, MS, Senior Manager, Guidelines, NCCN, has disclosed that she has no relevant financial relationships.
Susan Darlow, PhD, Oncology Scientist/Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.
Deborah A. Freedman-Cass, PhD, Oncology Scientist/Senior Medical Writer, NCCN, has disclosed that she has no relevant financial relationships.

Supported by an educational grant from Eisai; a contribution from Exelixis Inc.; educational grants from Bristol-Myers Squibb, Genentech BioOncology, Merck, Novartis Oncology, Novocure; and by an independent educational grant from Boehringer Ingelheim Pharmaceuticals, Inc.

Colorectal Cancer Screening, Version 1.2015



[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).

CSCR-2

NCCN Categories of Evidence and Consensus

Category 1: Based upon high-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2A: Based upon lower-level evidence, there is uniform NCCN consensus that the intervention is appropriate.
Category 2B: Based upon lower-level evidence, there is NCCN consensus that the intervention is appropriate.
Category 3: Based upon any level of evidence, there is major NCCN disagreement that the intervention is appropriate.

All recommendations are category 2A unless otherwise noted.

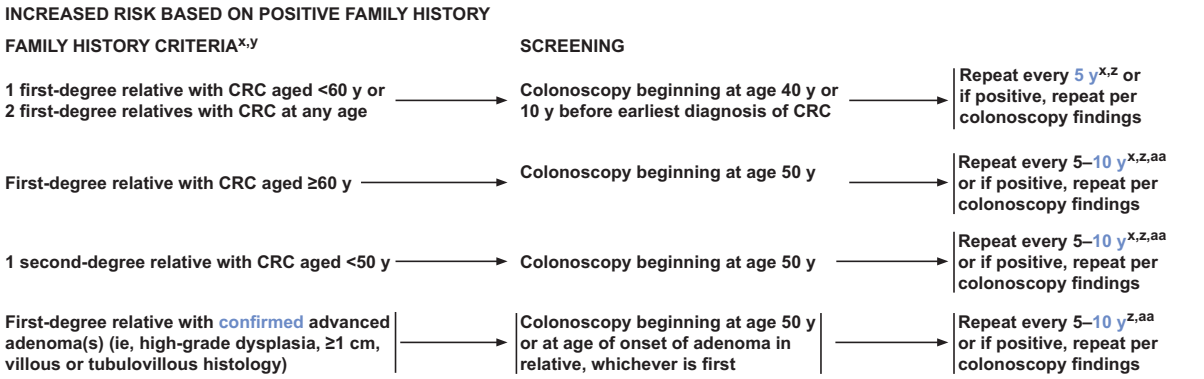
Clinical trials: NCCN believes that the best management for any cancer patient is in a clinical trial. Participation in clinical trials is especially encouraged.

Overview

Colorectal cancer (CRC) is the third most frequently diagnosed cancer and the third most frequent cause of cancer death in both US men and women.[1] 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, an estimated 49,700 people will die of colon and rectal cancer.[1] CRC mortality can be reduced through early diagnosis and cancer prevention with polypectomy.[2–4] Hence, the goal of a CRC screening program is to reduce mortality through cancer prevention and early detection. Currently, the relative 5-year survival rate for patients with localized CRC is 90.5%, whereas for those with regional and distant disease it is 71.9% and 12.5%, respectively, showing that earlier diagnosis can have a large impact on survival.[5]

The NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CRC Screening

Colorectal Cancer Screening, Version 1.2015



[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.

CSCR-6

describe various CRC screening modalities and provide recommended screening schedules for patients with an average or increased risk of developing sporadic CRC (to view the most recent version of these guidelines, visit NCCN.org). Recommendations regarding the management of inherited syndromes, such as Lynch syndrome (ie, hereditary nonpolyposis CRC), familial adenomatous polyposis, MutY human homolog (MUTYH)–associated polyposis, Peutz-Jeghers syndrome, juvenile polyposis syndrome, and serrated polyposis syndrome, are addressed in the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal available online at NCCN.org).[6–8]

Impact of CRC Screening on Mortality Rates

Mortality from CRC decreased by almost 35% from 1990 to 2007,[9] and in 2011 had decreased 47% from peak mortality rates.[1] These improvements in incidence of and mortality from CRC over past years are thought to be, at least partly, a result of cancer prevention and earlier diagnosis through screening and better treatment modalities: modeling suggests that approximately 63% of CRC deaths can be attributed to non-screening.[10] According to the CDC, the screening rate among US adults aged 50 to 75 years has increased from approximately 42% in 2000 to 59% in 2010.[11] The National Colorectal Cancer Roundtable established the goal to increase CRC screening rates in the United States to 80% by 2018, which they estimate could prevent approximately 280,000 new CRC cases and 200,000 CRC deaths through 2030.[12]

Results from the Nurses' Health Study and the Health Professionals Follow-Up Study showed that death from CRC was reduced after flexible sigmoidoscopy (hazard ratio [HR], 0.59; 95% CI, 0.45–0.76) and colonoscopy (HR, 0.32; 95% CI,

Colorectal Cancer Screening, Version 1.2015

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.

CSCR-A
3 OF 5

0.24–0.45), and that mortality from proximal colon cancer was reduced after colonoscopy (HR, 0.47; 95% CI, 0.29–0.76) but not after sigmoidoscopy.[13] Additionally, results of 5 randomized controlled trials (RCTs) provide strong evidence for the use of flexible sigmoidoscopy as a screening modality.[14–18] Recent meta-analyses of RCTs show that screening via flexible sigmoidoscopy significantly reduces CRC incidence and mortality.[19–22] Evidence from these prospective studies and reviews of RCTs shows that screening significantly reduces CRC mortality rates.

The NCCN Guidelines Panel emphasizes that the main goal of a CRC screening program is to reduce mortality through prevention and early detection. A major theme that emerged during the panel meeting is how new and/or developing screening modalities (eg, CT colonography [CTC], stool DNA testing) fit into an overall CRC screening program. The panel emphasizes the preferred conditions of a program in a footnote—specifically, that screening should include standardized methods for identifying those who are eligible for and wish to undergo screening, administering screening at agreed-upon intervals, reporting of results, and follow-up for positive results (see CSCR-2, page 961). High-quality studies that provide information about how emerging screening modalities fit into a screening program are crucial for making recommendations, such as those regarding screening intervals. However, the panel also noted the importance of patient preferences and resources: although colonoscopy may be the primary method used for screening, the patient ultimately decides which screening modality is used.

Screening Modalities

Current CRC screening technology generally falls into 2 broad categories: structural tests and stool/fecal-based tests.[23] Structural tests (ie, colonoscopy, flexible sigmoidoscopy, CTC) are able to detect

early cancer and polyps via endoscopic or radiologic imaging. However, 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 an entire day). Endoscopic examinations require informed consent, usually involve sedation, and have related risks, including perforation and bleeding. Fecal-based tests (ie, fecal occult blood test [FOBT], stool DNA test) 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 bowel cleansing is not 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 it is significantly lower than that of structural tests. Therefore, the panel recommends that any positive stool test be followed by a colonoscopy.

For the 2015 guidelines update, the panel did not discuss all possible screening modalities. Therefore, the following discussion is limited only to the modalities that were discussed (ie, colonoscopy, CTC, stool DNA testing, FOBT) during the panel meeting.

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 RCTs directly show mortality reduction by colonoscopy, findings from case-control and cohort studies show a significant impact of colonoscopy and polypectomy on CRC, with an estimated reduction in incidence of greater than 50%.[13,24–32] Rabeneck et al[33] recently reported an inverse correlation between colonoscopy use and death from CRC in a large population study involving approximately 2.5 million Canadians. For every 1% increase in colonoscopy rate, the risk of death decreased by 3%.

Colonoscopic screening, in addition to cancer prevention, is also expected to lead to earlier diagnosis. This is supported by a recent retrospective review of a prospective database comparing 217 patients diagnosed with colon cancer through screening colonoscopy and 854 patients with colon cancer not diagnosed through screening.[34] Unscreened patients were at a higher risk for more-invasive tumors (relative risk [RR], 1.96; $P<.001$), nodal disease (RR, 1.92; $P<.001$), and metastatic disease at presentation (RR, 3.37; $P<.001$). Furthermore, unscreened patients had higher rates of death and recurrence, shorter survival, and shorter disease-free intervals.

The panel enhanced its recommendations regarding bowel preparation for colonoscopy (see CSCR-A 3 of 5, page 963) based on the recently published recommendations from the US Multi-Society Task Force on Colorectal Cancer.[35] The task force recommended the use of split-dose preparation because it is superior to the traditional regimen and is administered the day before colonoscopy.[36–38] The recommended timing of the second dose of the split-dose preparation is 4 to 6 hours before colonoscopy and should end at least 2 hours before colonoscopy.[35] The panel agrees with the Multi-Society Task Force that a same-day, morning-only regimen is acceptable, particularly for patients undergoing afternoon procedures.[39–41]

The panel continues to recommend a 10-year screening interval for average-risk patients who undergo complete colonoscopy with adequate bowel preparation and have negative results. Inadequate preparation indicates a shorter screening interval. 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 larger than 5 mm, then the procedure should be rescheduled. Alternatively, additional bowel cleaning can be attempted for the colonoscopy to proceed that day.[35] For cases in which 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 preparation was inadequate, then an interval shorter than 1 year is recommended.[35]

CT Colonography

CTC is evolving as a promising technique for CRC screening, and 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 CTC may be cost-effective when compared with colonoscopy.[42] However, a positive CTC finding requires a colonoscopy, and extracolonic findings, which are present in up to 16% of patients, pose a dilemma.[43,44] These findings require further investigation and have the potential for both benefit and harm. Currently, data to determine the clinical impact of these incidental findings are insufficient.

The NCCN Guidelines Panel discussed at length how CTC might fit into a screening program. Available data indicate that CTC may be useful for the detection of larger polyps.[45–47] Further, a small prospective study of 47 patients with pathologically proven lateral spreading tumors found that CTC may not be as sensitive as colonoscopy for detecting tumors with significant lateral spread.[48] The panel noted that CTC is still an evolving technique, and currently few data are available that address screening intervals, polyp size leading to referral for colonoscopy, what follow-up is required for a patient with a positive CTC and a negative colonoscopy, and protocol for evaluating extracolonic lesions. Therefore, although it was acknowledged that CTC is a promising emerging screening modality and is currently being used in clinical practice, the panel is currently unable to provide recommendations about how CTC best fits into a screening program. The best evidence currently available seems to support repeating CTC every 5 years and referring patients with polyps larger than 5 mm for colonoscopy. The panel has revised a footnote regarding CTC for the 2015 guidelines update, reiterating this information (see CSCR-2, page 961).

Fecal Occult Blood Test

FOBTs (guaiac-based and immunochemical) are recommended annually when used alone. When used in combination with flexible sigmoidoscopy every 5 years, the panel recommends FOBT screening at year 3. 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.

Guaiac FOBT is the most common stool test used for CRC screening. A major disadvantage of this test is that it may miss tumors that bleed in smaller amounts, intermittently, or not at all. Another limitation is the high false-positive rate resulting from reaction with nonhuman heme in food and blood from the upper gastrointestinal tract. To compensate for these limitations, guaiac FOBT should be performed on 3 successive stool specimens obtained while the patient adheres to a prescribed diet. There is direct evidence from RCTs that guaiac FOBT reduces CRC mortality.[49–51] However, the panel recommends that that only high-sensitivity guaiac tests be used. The US Preventive Services Task Force defines high-sensitivity FOBT as a test with a sensitivity of greater than 70% and a specificity of more than 90% for detecting cancer[4]; guaiac tests that meet these criteria are newer and have not been tested in RCTs.

Stool DNA Testing

Stool DNA testing has emerged as a new primary screening tool for CRC, and 5 panel members raised questions about considering it as a screening option. It detects the presence of known DNA alterations during colorectal carcinogenesis in tumor cells sloughed into stool. Early tests produced relatively poor sensitivity.[52,53] However, other stool DNA tests have also been developed and tested.[54] Particularly, Cologuard 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 with average-risk CRC, each of whom underwent a fecal immunochemical test (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 larger than 1 cm (42.4% vs 5.1%; P<.001).[55] Specificity, however, was better with FIT (86.6% vs 94.9% among participants with nonadvanced or negative findings; P<.001), and more participants were excluded because of problems with stool DNA testing (n=689) than with FIT (n=34). In August 2014, the FDA approved Cologuard as the first stool DNA test for primary screening of CRC. Other stool DNA tests (eg, ColoSure, which detects methylated vimentin) are currently available in the United States, although they are not FDA-approved.[56]

Five panel members questioned whether recommendations regarding stool DNA testing should be revised because Cologuard was FDA-approved as a primary screening modality. The panel noted that, like CTC, it is not clear how stool DNA testing may fit into an overall screening program. Data are limited regarding determination of appropriate screening intervals and adherence to/participation rates in screening programs. It is not clear, for example, how stool DNA testing will compare with several rounds of annual FIT. For these reasons, the panel included a footnote in the 2015 NCCN Guidelines indicating that, although stool DNA testing has been FDA-approved as a primary screening modality, an appropriate screening interval cannot be recommended at this time because of limited available data (see CSCR-2, page 961). Therefore, the panel does not currently recommend stool DNA testing as a primary screening modality.

Screening Individuals With a Positive Family History

Individuals with a family history of CRC have an increased risk of the disease and should undergo earlier and/or more frequent screening.[57–59] The panel recommended some minor revisions to the guidelines for those with a family history of CRC, because of concerns from panel members that the previous guidelines were too aggressive. The recommendations for patients with a family history of CRC are now as follows (see CSCR-6, page 962):

- 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 before the earliest diagnosis in the family or at age 40 years at the latest. If colonoscopy results are positive, follow-up colonoscopy should be based on findings.
- For patients with one affected first-degree relative diagnosed at age 60 years or older, colonoscopy every 5 to 10 years should begin at age 50 years. If colonoscopy results are positive, follow-up colonoscopy should be based on findings. Multiple (≥2) negative colonoscopies may support stepwise lengthening of the colonoscopy interval in these individuals.
- For those with one second-degree relative diagnosed with CRC before age 50 years, colonoscopy should begin at 50 years of age, with repeat colonoscopy every 5 to 10 years or based on findings.
- Individuals with a first-degree relative with a confirmed history of advanced adenomas (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology) should undergo colonoscopy at the relative's age of onset of adenoma or 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.60,61 The panel emphasized the need to confirm family history of advanced adenoma, including obtaining documentation through medical records.

The CRC Screening Panel has also developed guidelines to screen for patients who may meet the criteria for an inherited CRC syndrome (see the NCCN Guidelines for Genetic/Familial High-Risk Assessment: Colorectal; to view the most recent version, visit NCCN.org). Further risk evaluation and counseling of these patients, as outlined in those guidelines, is required.

Summary and Conclusions

In summary, the NCCN CRC Screening Panel discussed several pertinent issues this year, and revised the 2015 recommendations to:

- Emphasize that the ultimate goal of screening is to reduce mortality through prevention and early detection;
- Enhance recommendations regarding bowel preparation for colonoscopy; and
- Revise screening guidelines for those with a positive family history.

The panel continues to monitor the potential for CTC and stool DNA testing, although it did not revise the current recommendations because of limited evidence regarding how these screening modalities fit into an overall CRC screening program.

CRC screening significantly impacts mortality rates. With continued advances in screening methods, mortality rates from CRC may continue to decrease, but there is an ongoing need for high-quality research.

Colorectal Cancer Screening, Version 1.2015

References

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2015. CA Cancer J Clin 2015;65:5–29.
2. Levin B, Lieberman DA, McFarland B, et al. Screening and surveillance for the early detection of colorectal cancer and adenomatous polyps, 2008: a joint guideline from the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology. CA Cancer J Clin 2008;58:130–160.
3. Rex DK, Johnson DA, Anderson JC, et al. American College of Gastroenterology guidelines for colorectal cancer screening 2009 [corrected]. Am J Gastroenterol 2009;104:739–750.
4. USPSTF. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. Ann Intern Med 2008;149:627–637.
5. Siegel R, Desantis C, Jemal A. Colorectal cancer statistics, 2014. CA Cancer J Clin 2014;64:104–117.
6. Burt R, Neklason DW. Genetic testing for inherited colon cancer. Gastroenterology 2005;128:1696–1716.
7. Giardiello FM, Offerhaus JG. Phenotype and cancer risk of various polyposis syndromes. Eur J Cancer 1995;31A:1085–1087.
8. Hamilton SR, Liu B, Parsons RE, et al. The molecular basis of Turcot's syndrome. N Engl J Med 1995;332:839–847.
9. Siegel R, Ward E, Brawley O, Jemal A. Cancer statistics, 2011: the impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA Cancer J Clin 2011;61:212–236.
10. Meester RG, Doubeni CA, Lansdorp-Vogelaar I, et al. Colorectal cancer deaths attributable to nonuse of screening in the United States. Ann Epidemiol 2015;25:208–213.e1.
11. Cancer screening—United States, 2010. MMWR Morb Mortal Wkly Rep 2012;61:41–45.
12. Meester RG, Doubeni CA, Zauber AG, et al. Public health impact of achieving 80% colorectal cancer screening rates in the United States by 2018 [published online ahead of print]. Cancer, doi: 10.1002/cncr.29336.
13. Nishihara R, Wu K, Lochhead P, et al. Long-term colorectal-cancer incidence and mortality after lower endoscopy. N Engl J Med 2013;369:1095–1105.
14. Atkin WS, Edwards R, Kralj-Hans I, et al. Once-only flexible sigmoidoscopy screening in prevention of colorectal cancer: a multicentre randomised controlled trial. Lancet 2010;375:1624–1633.
15. Schoen RE, Pinsky PF, Weissfeld JL, et al. Colorectal-cancer incidence and mortality with screening flexible sigmoidoscopy. N Engl J Med 2012;366:2345–2357.
16. Hoff G, Grotmol T, Skovlund E, Bretthauer M. Risk of colorectal cancer seven years after flexible sigmoidoscopy screening: randomised controlled trial. BMJ 2009;338:b1846.
17. Segnan N, Armaroli P, Bonelli L, et al. Once-only sigmoidoscopy in colorectal cancer screening: follow-up findings of the Italian Randomized Controlled Trial—SCORE. J Natl Cancer Inst 2011;103:1310–1322.
18. Holme O, Loberg M, Kalager M, et al. Effect of flexible sigmoidoscopy screening on colorectal cancer incidence and mortality: a randomized clinical trial. JAMA 2014;312:606–615.
19. Brenner H, Stock C, Hoffmeister M. Effect of screening sigmoidoscopy and screening colonoscopy on colorectal cancer incidence and mortality: systematic review and meta-analysis of randomised controlled trials and observational studies. BMJ 2014;348:g2467.
20. Elmunzer BJ, Hayward RA, Schoenfeld PS, et al. Effect of flexible sigmoidoscopy-based screening on incidence and mortality of colorectal cancer: a systematic review and meta-analysis of randomized controlled trials. PLoS Med 2012;9:e1001352.
21. Holme O, Bretthauer M, Fretheim A, et al. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. Cochrane Database Syst Rev 2013;9:CD009259.
22. Shroff J, Thosani N, Batra S, et al. Reduced incidence and mortality from colorectal cancer with flexible-sigmoidoscopy screening: a meta-analysis. World J Gastroenterol 2014;20:18466–18476.
23. Burt RW. Colorectal cancer screening. Curr Opin Gastroenterol 2010;26:466–470.
24. Brenner H, Chang-Claude J, Seiler CM, et al. Protection from colorectal cancer after colonoscopy: a population-based, case-control study. Ann Intern Med 2011;154:22–30.
25. Brenner H, Chang-Claude J, Jansen L, et al. Reduced risk of colorectal cancer up to 10 years after screening, surveillance, or diagnostic colonoscopy. Gastroenterology 2014;146:709–717.
26. Citarda F, Tomaselli G, Capocaccia R, et al. Efficacy in standard clinical practice of colonoscopic polypectomy in reducing colorectal cancer incidence. Gut 2001;48:812–815.
27. Jacob BJ, Moineddin R, Sutradhar R, et al. Effect of colonoscopy on colorectal cancer incidence and mortality: an instrumental variable analysis. Gastrointest Endosc 2012;76:355–364.e1.
28. Kahi CJ, Imperiale TF, Juliar BE, Rex DK. Effect of screening colonoscopy on colorectal cancer incidence and mortality. Clin Gastroenterol Hepatol 2009;7:770–775; quiz 711.
29. Winawer SJ, Zauber AG, Ho MN, et al. Prevention of colorectal cancer by colonoscopic polypectomy. The National Polyp Study Workgroup. N Engl J Med 1993;329:1977–1981.
30. Manser CN, Bachmann LM, Brunner J, et al. Colonoscopy screening markedly reduces the occurrence of colon carcinomas and carcinoma-related death: a closed cohort study. Gastrointest Endosc 2012;76:110–117.
31. Morois S, Cottet V, Racine A, et al. Colonoscopy reduced distal colorectal cancer risk and excess cancer risk associated with family history. Cancer Causes Control 2014;25:1329–1336.
32. Muller AD, Sonnenberg A. Prevention of colorectal cancer by flexible endoscopy and polypectomy. A case-control study of 32,702 veterans. Ann Intern Med 1995;123:904–910.
33. Rabeneck L, Paszat LF, Saskin R, Stukel TA. Association between colonoscopy rates and colorectal cancer mortality. Am J Gastroenterol 2010;105:1627–1632.
34. Amri R, Bordeianou LG, Sylla P, Berger DL. Impact of screening colonoscopy on outcomes in colon cancer surgery. JAMA Surg 2013;148:747–754.
35. Johnson DA, Barkun AN, Cohen LB, 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.
36. Enestvedt BK, Tofani C, Laine LA, et al. 4-Liter split-dose polyethylene glycol is superior to other bowel preparations, based on systematic review and meta-analysis. Clin Gastroenterol Hepatol 2012;10:1225–1231.
37. Gurudu SR, Ramirez FC, Harrison ME, et al. Increased adenoma detection rate with system-wide implementation of a split-dose preparation for colonoscopy. Gastrointest Endosc 2012;76:603–608.e1.
38. Kilgore TW, Abdinoor AA, Szary NM, et al. Bowel preparation with split-dose polyethylene glycol before colonoscopy: a meta-analysis of randomized controlled trials. Gastrointest Endosc 2011;73:1240–1245.
39. Longcroft-Wheaton G, Bhandari P. Same-day bowel cleansing regimen is superior to a split-dose regimen over 2 days for afternoon colonoscopy: results from a large prospective series. J Clin Gastroenterol 2012;46:57–61.
40. Matro R, Shnitser A, Spodik M, et al. Efficacy of morning-only compared with split-dose polyethylene glycol electrolyte solution for afternoon colonoscopy: a randomized controlled single-blind study. Am J Gastroenterol 2010;105:1954–1961.
41. Varughese S, Kumar AR, George A, Castro FJ. Morning-only one-gallon polyethylene glycol improves bowel cleansing for afternoon colonoscopies: a randomized endoscopist-blinded prospective study. Am J Gastroenterol 2010;105:2368–2374.
42. Kriza C, Emmert M, Wahlster P, et al. An international review of the main cost-effectiveness drivers of virtual colonography versus conventional colonoscopy for colorectal cancer screening: is the tide changing due to adherence? Eur J Radiol 2013;82:e629–636.
43. Kim DH, Pickhardt PJ, Taylor AJ, Menias CO. Imaging evaluation of complications at optical colonoscopy. Curr Probl Diagn Radiol 2008;37:165–177.
44. Whitlock EP, Lin JS, Liles E, et al. Screening for colorectal cancer: a targeted, updated systematic review for the U.S. Preventive Services Task Force. Ann Intern Med 2008;149:638–658.
45. Johnson CD, Chen MH, Toledano AY, et al. Accuracy of CT colonography for detection of large adenomas and cancers. N Engl J Med 2008;359:1207–1217.
46. Halligan S, Altman DG, Taylor SA, et al. CT colonography in the detection of colorectal polyps and cancer: systematic review, meta-analysis, and proposed minimum data set for study level reporting. Radiology 2005;237:893–904.
47. Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. Ann Intern Med 2005;142:635–650.
48. Togashi K, Utano K, Kijima S, et al. Laterally spreading tumors: limitations of computed tomography colonography. World J Gastroenterol 2014;20:17552–17557.

49. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. Lancet 1996;348:1472–1477.

50. Kronborg O, Fenger C, Olsen J, et al. Randomised study of screening for colorectal cancer with faecal-occult-blood test. Lancet 1996;348:1467–1471.

51. Mandel JS, Bond JH, Church TR, et al. Reducing mortality from colorectal cancer by screening for fecal occult blood. Minnesota Colon Cancer Control Study. N Engl J Med 1993;328:1365–1371.

52. Osborn NK, Ahlquist DA. Stool screening for colorectal cancer: molecular approaches. Gastroenterology 2005;128:192–206.

53. Ahlquist DA, Sargent DJ, Loprinzi CL, et al. Stool DNA and occult blood testing for screen detection of colorectal neoplasia. Ann Intern Med 2008;149:441–450, W481.

54. Ahlquist DA, Zou H, Domanico M, et al. Next-generation stool DNA test accurately detects colorectal cancer and large adenomas. Gastroenterology 2012;142:248–256; quiz e225–246.

55. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. N Engl J Med 2014;370:1287–1297.

56. Ned RM, Melillo S, Marrone M. Fecal DNA testing for colorectal cancer screening: the ColoSure test. PLoS Curr 2011;3:RRN1220.

57. 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.

58. 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.

59. Samadder NJ, Curtin K, Tuohy TM, et al. Increased risk of colorectal neoplasia among family members of patients with colorectal cancer: a population-based study in Utah. Gastroenterology 2014;147:814–821.e5; quiz e815–816.

60. Imperiale TF, Ransohoff DF. Risk for colorectal cancer in persons with a family history of adenomatous polyps: a systematic review. Ann Intern Med 2012;156:703–709.

61. Tuohy TM, Rowe KG, Mineau GP, et al. Risk of colorectal cancer and adenomas in the families of patients with adenomas: a population-based study in Utah. Cancer 2014;120:35–42.

Instructions for Completion

To participate in this journal CE activity: 1) review the learning objectives and author disclosures; 2) study the education content; 3) take the posttest with a 66% minimum passing score and complete the evaluation at **http://education.nccn.org/node/71856;** and 4) view/print certificate. After reading the article, you should be able to answer the following multiple-choice questions. Credit cannot be obtained for tests completed on paper. You must be a registered user on NCCN.org. If you are not registered on NCCN.org, click on "New Member? Sign up here" link on the left hand side of the Web site to register. Only one answer is correct for each question. Once you successfully answer all posttest questions you will be able to view and/or print your certificate. Software requirements: Internet.

Posttest Questions

1. A patient, whose biological father was diagnosed with CRC at 56 years of age, began colonoscopy screening at age 45 years. No polyps were found. At what age should this patient be screened next, according to the 2015 NCCN Guidelines for CRC Screening?
   a. 48 years
   b. 50 years
   c. 55 years
   d. No need for further screening
2. True or False: If a 6-mm polyp is found during CTC, the next step is referral for colonoscopy.
3. Which of the following is/are true regarding colonoscopy preparation and procedures, according to the 2015 NCCN Guidelines for CRC Screening:
   a. Split-dose preparation is recommended
   b. If bowel preparation is inadequate, additional bowel cleaning should not be performed to proceed with the colonoscopy that day
   c. Withdrawal time may influence quality of colonoscopy
   d. a and b
   e. a and c
   f. All of the above