NCCN Guidelines® Insights
Colorectal Cancer Screening, Version 1.2018

Featured Updates to the NCCN Guidelines

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Abstract

The NCCN Guidelines for Colorectal Cancer (CRC) Screening outline various screening modalities as well as recommended screening strategies for individuals at average or increased-risk of developing sporadic CRC. The NCCN panel meets at least annually to review comments from reviewers within their institutions, examine relevant data, and reevaluate and update their recommendations. These NCCN Guidelines Insights summarize 2018 updates to the NCCN Guidelines, with a primary focus on modalities used to screen individuals at average-risk for CRC.

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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.

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### RISK STATUS
- **Average risk:**
  - Age ≥50 y
  - No history of adenoma or SSP or CRC
  - No history of inflammatory bowel disease
  - Negative family history for CRC or confirmed advanced adenoma (ie, high-grade dysplasia, ≥1 cm, villous or tubulovillous histology)

### SCREENING MODALITY AND SCHEDULE

<table>
<thead>
<tr>
<th>Adenoma/SSP or CRC of any size</th>
<th>Colonoscopy&lt;sup&gt;a&lt;/sup&gt; or Flexible sigmoidoscopy</th>
<th>CT colonography (CTC)</th>
</tr>
</thead>
<tbody>
<tr>
<td>No polyps&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Rescreen with any modality in 10 y&lt;sup&gt;d&lt;/sup&gt;</td>
<td>See CSCR-3</td>
</tr>
<tr>
<td>Polyp(s)&lt;sup&gt;i&lt;/sup&gt;</td>
<td>Polyectomy</td>
<td></td>
</tr>
<tr>
<td>Positive</td>
<td>Rescreen with any modality in 1 y&lt;sup&gt;d&lt;/sup&gt;</td>
<td></td>
</tr>
<tr>
<td>Negative</td>
<td>Colonoscopy&lt;sup&gt;g&lt;/sup&gt;</td>
<td>Follow pathway above</td>
</tr>
<tr>
<td>or</td>
<td>Flexible sigmoidoscopy</td>
<td></td>
</tr>
<tr>
<td>CT colonography (CTC)</td>
<td>See CSCR-3</td>
<td></td>
</tr>
</tbody>
</table>

### EVALUATION OF SCREENING FINDINGS

- **Hyperplastic polyps <1 cm in size**
- **Hyperplastic polyps ≥1 cm in size or adenomas or SSP of any size**
- **Rescreen with any modality in 10 y**
- **See Follow-up of Clinical Findings: Adenoma/SSP (CSCR-4)**

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

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**Overview**

Colorectal cancer (CRC) is the fourth most frequently diagnosed cancer and second leading cause of cancer death in the United States. In 2018, an estimated 97,220 new cases of colon cancer and 43,030 new cases of rectal cancer will occur in the United States.<sup>1</sup> During the same year, it is estimated that 50,630 people will die from CRC. CRC risk assessment in persons without a known family history is advisable by age 40 years to determine the appropriate age to initiate screening, although in general, it is currently recommended that screening for persons at average risk for CRC begin at age 50 years. Individuals at average risk are those aged ≥50 years without personal history of inflammatory bowel disease, adenomas, or CRC; without a family history of CRC or advanced adenomas; and without symptoms such as rectal bleeding. Registry data from the SEER program suggest an increased incidence of CRC in African Americans prior to age 50 years,<sup>2</sup> which led to the recommendation by some in 2005.
that CRC screening in African Americans begin earlier, at age 45 years.\textsuperscript{3,4} In addition, epidemiologic reports suggest that the incidence of CRC may be increasing in adults aged <50 years,\textsuperscript{5,6} supporting a rationale for CRC screening to possibly start before age 50 years.\textsuperscript{7} Based on statistical modeling incorporating these data which predicted potential increased benefit,\textsuperscript{8,9} the American Cancer Society recently recommended—as a qualified recommendation—that individuals at average risk of CRC begin screening at age 45 years.\textsuperscript{10} Additional data from longitudinal cohorts or population-based studies are needed to validate these analyses, and the net benefits versus harms are uncertain.

Screening of average-risk individuals can reduce CRC mortality by detecting cancer at an early, curable stage and may decrease CRC incidence by detecting and removing adenomatous polyps.\textsuperscript{4,11,12} Currently, patients with localized CRC have a 90% relative 5-year survival rate, whereas rates for those with regional and distant disease are 71% and 14%, respectively, demonstrating that earlier diagnosis can have a large impact on survival.\textsuperscript{1} Current technology for CRC screening falls into 2 broad categories: stool/fecal-based tests and structural tests.\textsuperscript{13} In the United States, colonoscopy is the most commonly used CRC screening test for average- and high-risk populations. However, multiple options exist, and the choice of screening modality may also include consideration of patient preference and resource availability. The updated NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines) for CRC Screening describe the various screening modalities currently available, as well as recommended screening schedules for patients at average or increased risk of developing CRC. The guidelines are intended to aid physicians with clinical decision-making regarding CRC screening for patients without defined genetic syndromes or a family history of CRC or advanced adenomas. These NCCN Guidelines Insights review the 2018 updates to the NCCN Guidelines, focusing on CRC screening modalities and schedules.
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Summary of 2018 Updates and CRC Screening Modalities/Schedules

Stool/Fecal-Based Screening Tests

Two types of fecal occult blood tests (FOBTs) are currently available: guaiac-based and immunochemical. More recently, a fecal test to assess for alterations in exfoliated DNA in combination with checking for occult blood has also become available. Abnormal results from any stool/fecal-based screening test are an indication for colonoscopy. The guaiac FOBT is based on the detection of pseudoperoxidase activity of heme in human blood, whereas the fecal immunochemical test (FIT) directly detects human globin within hemoglobin in stool. FIT has been shown to be superior in terms of screening participation rates and detection of CRC.\textsuperscript{14–16} However, during the meeting to update the 2018 guidelines for CRC screening, the NCCN panel elected to retain guaiac FOBT as a stool-based CRC screening option because regular use been shown to reduce mortality from CRC,\textsuperscript{17–19} and may remain a reasonable alternative when immunochemical testing is not available.

Guaiac FOBT

Direct evidence from randomized controlled trials (RCTs) shows that low-sensitivity guaiac FOBTs reduce mortality from CRC.\textsuperscript{17–19} In the Minnesota Colon Cancer Control Study, >46,000 participants were randomized to receive guaiac FOBT either annually or biennially or no screening. The study reported that the 13-year cumulative mortality from CRC per 1,000 individuals evaluated was 5.88 and 8.83 in the annual and unscreened groups, respectively; this 33% difference was statistically significant.\textsuperscript{19} After 30-year follow-up, a CRC mortality benefit was seen in both the annual and biennial screening groups (annual FOBT: relative risk [RR], 0.68; 95% CI, 0.56–0.82; biennial FOBT: RR, 0.78; 95% CI, 0.65–0.93).\textsuperscript{20} In addition, long-term follow-up from the Nottingham trial showed that individuals randomized to the biennial guaiac FOBT screening arm had a 13% reduction in CRC mortality at a median follow-up of 19.5 years (95% CI, 3%–22%), despite a 57% participation rate. After adjustment for noncompliance, the reduction in CRC mortality was estimated to be 18%.\textsuperscript{21} This reduction in CRC mortality using low-sensitivity guaiac FOBTs has been confirmed by a systematic review and meta-analysis of multiple studies.\textsuperscript{22,23}

The US Preventive Services Task Force (USPSTF) defines the high-sensitivity guaiac FOBT as having a sensitivity for cancer >70% and a specificity >90%.\textsuperscript{24} Although high-sensitivity guaiac FOBTs that meet these criteria have not been tested in RCTs, some studies have shown that high-sensitivity guaiac FOBTs have higher CRC detection rates when compared with low-sensitivity guaiac FOBTs.\textsuperscript{25–27} The NCCN CRC Screening Panel recommends that only high-sensitivity guaiac tests be used.

Fecal Immunochemical Test

Unlike guaiac FOBT, FIT does not require dietary restrictions and a single testing sample is sufficient. A meta-analysis of studies that evaluated the diagnostic accuracy of FIT for CRC in average-risk patients found the sensitivity and specificity to be 79% (95% CI, 0.69–0.86) and 94% (95% CI, 0.92–0.95), respectively.\textsuperscript{28} Comparative studies have shown that FIT is more sensitive than guaiac FOBT.\textsuperscript{26,29–33} For example, one study demonstrated a higher sensitivity for cancer by FIT compared with a high-sensitivity guaiac FOBT (82% vs 64%).\textsuperscript{26} A Dutch randomized study also demonstrated higher detection rates of advanced neoplasia using FIT (2.4%) versus guaiac FOBT (1.1%), although both were less sensitive for advanced neoplasia than flexible sigmoidoscopy (8.0%).\textsuperscript{30} In addition, as seen in other trials, FIT had a significantly higher participation rate than guaiac FOBT in this trial. Following extensive literature analysis, an expert panel in Ontario concluded that FIT is superior to guaiac FOBT in both participation rates and detection of advanced adenomas and CRC.\textsuperscript{34} Nonrandomized studies have also shown that FIT screening reduces CRC mortality.\textsuperscript{35,36} In a large Taiwanese population-based study, 1,160,895 individuals aged 50 to 69 years were screened with 1 to 3 rounds of FIT and compared with an unscreened group. With a maximum follow-up of 6 years, a 10% decrease in CRC mortality was seen in the FIT-screened population (RR, 0.90; 95% CI, 0.84–0.95).\textsuperscript{35}

After reviewing the evidence and considering the potential impact on patient access if guaiac FOBT was removed, the NCCN CRC Screening Panel decided to include a footnote in the 2018 version of the guidelines acknowledging the outlined
advantages of FIT over guaiac FOBT, but noting that guaiac FOBT has been shown to decrease mortality from CRC and that high-sensitivity guaiac FOBT can be used as an alternative to FIT (see CSCR-2, page 941).

Although an ideal interval for CRC screening with FIT is unclear, data extrapolated from a modeling analysis demonstrated similar life-years gained when annual FOBT strategies were compared with colonoscopy every 10 years.37 Currently, the guidelines recommend annual screening intervals using any modality after a negative finding by high-sensitivity guaiac FOBT and FIT. To determine whether this screening interval should be modified, the panel reviewed data from a population-based CRC study of 7,501 Dutch individuals randomly selected to receive 2 one-sample FIT screening rounds with intervals of 1, 2, or 3 years.38 The total number of advanced neoplasia detected at repeat FIT screening was not impacted by the interval length within the range of 1 to 3 years.38 The panel considered potential issues with increasing the interval, including impact on adherence to screening schedules and having discordant recommendations to those of the USPSTF and US Multi-Society Task Force (USMSTF),11,15 and decided to leave the recommended annual FIT screening interval unchanged. Future studies may shed light on this issue.

**FIT-DNA–Based or Multitarget Stool DNA Test**
A combined multitarget stool DNA and occult blood test (mt-sDNA) has emerged as an option for CRC screening (Cologuard, Exact Sciences Corp.). It screens for the presence of known DNA alterations (KRAS mutations, aberrant NDRG4 and BMP3 methylation) during colorectal carcinogenesis in tumor cells sloughed into stool, as well as occult blood as measured by immunoassay. A study that included 9,989 participants at average risk for CRC, each of whom underwent FIT, mt-sDNA testing, and a colonoscopy, found that the mt-sDNA test was more sensitive than FIT for detecting 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 serrated sessile polyps >1 cm (42.4% vs 5.1%; \( P < .001 \)).19 However, FIT had significantly higher specificity than the mt-sDNA test (94.9% vs 86.6%, respectively, among participants with nonadvanced or negative findings; \( P < .001 \)), and many more participants were excluded because of problems with mt-sDNA testing (n=689) than with FIT (n=34).

The NCCN panel recommends inclusion of mt-sDNA–based testing as a potential screening modality in average-risk individuals, but data to help determine an appropriate interval between screening, adherence to/participation rates of screening, and how mt-sDNA testing may fit into an overall screening program are limited. A rescreening interval of every 3 years has been suggested and is FDA-approved.40 Using a clinical effectiveness model, one study showed that, compared with a 10-year colonoscopy interval, annual mt-sDNA testing resulted in similar decreases in CRC incidence (65% vs 63%) and mortality (73% vs 72%).41 At 3-year intervals, such testing was predicted to reduce CRC incidence and mortality by 57% and 67%, respectively. In addition, no or limited data are available for high-risk individuals who refuse colonoscopy or have limited access to conventional screening strategies42; therefore, the use of mt-sDNA–based testing should be individualized in these cases.

**Structural-Based Screening Tests**
Structural screening tests detect both adenomatous polyps and cancer using endoscopic or radiologic imaging. Screening intervals for colonoscopy have been established for individuals at average risk of developing CRC, but intervals have been evolving for other modalities, including flexible sigmoidoscopy. During the 2018 panel meeting, the panel reviewed and discussed data related to flexible sigmoidoscopy screening strategies and schedules.

**Colonoscopy**
Colonoscopy is the most complete screening procedure and is considered the current gold standard for assessing the sensitivity of detecting neoplasia for other screening modalities. The general consensus is that a 10-year interval is appropriate for most average-risk individuals who had a normal, high-quality colonoscopy, defined as an examination complete to the cecum with bowel preparation adequate to detect polyps >5 mm.43 Although no RCTs directly demonstrate mortality reduction as a result of colonoscopy, findings from case-control and cohort studies show that colonoscopy and polypectomy have a significant impact on decreasing CRC incidence and mortality.44-47
The benefit of one-time flexible sigmoidoscopy with or without a concurrent FOBT versus no screening in >98,000 participants aged 55 to 64 years. 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 (HR) for death from CRC was 0.73 (95% CI, 0.56–0.94) in the screened groups. Interestingly, the addition of FOBT did not affect the long-term outcomes of participants screened with sigmoidoscopy in this trial.

The SCORE trial randomized 34,272 individuals aged 55 to 64 years to one-time sigmoidoscopy or no screening and reported incidence and mortality results after >10 years of median follow-up. The intention-to-treat analysis demonstrated a 18% reduction in incidence and a 22% reduction in mortality. In addition, a randomized study examined the effect of flexible sigmoidoscopy offered once between ages 55 and 64 years on CRC incidence and mortality. Compared with the population that did not receive any screening, intention-to-treat analysis showed that intervention with flexible sigmoidoscopy decreased CRC incidence by 23% (HR, 0.77; 95% CI, 0.70–0.84) and CRC mortality by 31% (HR, 0.69; 95% CI, 0.59–0.82). The benefit of one-time sigmoidoscopy demonstrating decreased CRC incidence and mortality was sustained after 17 years of follow-up. Although more data are warranted to determine the implications on screening, it is worth noting that some studies suggest that the long-term benefit of flexible sigmoidoscopy, in terms of decreased CRC incidence and mortality, may be more apparent in men and lower or undetectable in women.

Based on the relevant data, in the updated 2018 version of the guidelines the NCCN panel removed the interval screening with high-sensitivity guaiac FOBT or FIT at year 3 as a possible screening strategy. During the 2018 update meeting, the NCCN panel discussed changing the interval to annual FIT based on the results of a modeling study that proposed benefit from flexible sigmoidoscopy performed every 10 years with annual FIT. The Norwegian Colorectal Cancer Prevention (NORCCAP) Study Group performed an RCT of one-time flexible sigmoidoscopy with or without a concurrent FOBT versus no screening in >98,000 participants aged 55 to 64 years. 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 (HR) for death from CRC was 0.73 (95% CI, 0.56–0.94) in the screened groups. Interestingly, the addition of FOBT did not affect the long-term outcomes of participants screened with sigmoidoscopy in this trial.

Flexible Sigmoidoscopy
Evidence from RCTs have also demonstrated that flexible sigmoidoscopy reduces the incidence of and mortality from CRC. The Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening group reported CRC mortality rates from their RCT of flexible sigmoidoscopy screening, which screened >64,000 participants using this modality, and 59% of those participants a second time at 3 or 5 years. 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 effect on mortality from proximal disease. 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 2017 version of the NCCN Guidelines recommended flexible sigmoidoscopy with or without interval high-sensitivity guaiac FOBT or FIT at year 3 as a possible screening strategy. During the 2018 update meeting, the NCCN panel discussed changing the interval to annual FIT based on the results of a modeling study that proposed benefit from flexible sigmoidoscopy performed every 10 years with annual FIT. The Norwegian Colorectal Cancer Prevention (NORCCAP) Study Group performed an RCT of one-time flexible sigmoidoscopy with or without a concurrent FOBT versus no screening in >98,000 participants aged 55 to 64 years. 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 (HR) for death from CRC was 0.73 (95% CI, 0.56–0.94) in the screened groups. Interestingly, the addition of FOBT did not affect the long-term outcomes of participants screened with sigmoidoscopy in this trial.

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Emerging Options: Blood-Based Screening Test

The methylation status of the septin9 (SEPT9) gene has been shown to distinguish CRC tissue from normal surrounding tissue, and circulating methylated SEPT9 DNA in plasma is a biomarker for CRC.\(^{74–77}\) A multicenter study compared the FIT test and a SEPT9 DNA methylated blood test for CRC screening in 102 patients with identified CRC, and found that the sensitivity for CRC detection was not significantly different (68% vs 73.3%, respectively).\(^{78}\) The PRESEPT study, a prospective multicenter study, assessed the accuracy of circulating methylated SEPT9 DNA at detecting CRC in 7,941 asymptomatic individuals aged ≥50 years who met screening criteria for average risk, and determined the sensitivity and specificity of the methylated SEPT9 DNA blood-based assay to be 48.2% and 91.5%, respectively.\(^{79}\) An independent clinical performance analysis was conducted on plasma samples from the PRESEPT study using an updated SEPT9 DNA assay and determined that the sensitivity for detecting CRC was 68%,\(^{80}\) an improvement over the previous report,\(^{79}\) and the specificity was 80%.\(^{80}\) Factors that may potentially negatively impact the performance of the SEPT9 DNA test have been suggested, including early-stage disease, age >65 years, diabetes, arteriosclerosis, and arthritis.\(^{81}\)

A blood test that detects circulating methylated SEPT9 DNA is currently FDA-approved and may provide a potential alternative for individuals who refuse other screening modalities. However, a limitation remains the lack of sensitivity for advanced adenomas. Further, the interval for repeat testing is uncertain. On balance, the NCCN panel felt that there was insufficient evidence to recommend routine use of this assay.

Conclusions

Clinical decisions regarding recommendations for CRC screening modalities and schedules involve consideration of multiple factors, including age to initiate screening, efficacy, adherence, cost, and
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patient preference. During the 2018 meeting, the NCCN panel enacted important updates to the NCCN Guidelines for CRC Screening. Based on existing data, the panel agreed that FIT was superior to low-sensitivity guaiac FOBT, but also recognized the wealth of data supporting the benefits of guaiac FOBT in decreasing CRC incidence and mortality. Emerging data suggest long-term benefit of one-time flexible sigmoidoscopy, but more data are needed to consider screening intervals longer than 10 years. Overall, the availability of multiple screening modalities and evolving screening schedules may offer additional opportunities to decrease CRC incidence and mortality.

References

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Posttest Questions
1. In what ways are guaiac FOBTs and FITs comparable/equivalent?
   a. They both have similar sensitivities for detecting advanced carcinomas and CRC.
   b. They both have equivalent patient participation rates.
   c. They both employ use of a single testing sample.
   d. They both decrease colorectal cancer mortality.
   e. All of the above.

2. Recent data supports longer intervals for flexible sigmoidoscopy. During the 2018 update of the NCCN Guidelines for CRC Screening, which changes were applied to the screening schedule for flexible sigmoidoscopy?
   a. Flexible sigmoidoscopy + biennial FIT was added
   b. Flexible sigmoidoscopy once every 10 years was added
   c. Flexible sigmoidoscopy + FIT at year 3 was removed
   d. b and c
   e. All of the above

3. True or False: In the 2018 version of the NCCN Guidelines for CRC Screening, if polyps >10mm are detected with CTC, colonoscopy is an effective follow-up strategy.