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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Release date: August 10, 2018; Expiration date: August 10, 2019

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

The NCCN staff listed below discloses no relevant financial relationships:

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Samir Gupta, MD, Panel Vice Chair, has disclosed that he receives grant/research support from Epigenomics AG.

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

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

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

^fScreening should be individualized and include a discussion of the risks and benefits of each modality.

^gIf 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).

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

ⁱThe term "polyp" refers to both polyp and nonpolypoid (flat) lesions.

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

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

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

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.¹ 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,² which led to the recommendation by some in 2005

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that CRC screening in African Americans begin earlier, at age 45 years.^{3,4} In addition, epidemiologic reports suggest that the incidence of CRC may be increasing in adults aged <50 years,^{5,6} supporting a rationale for CRC screening to possibly start before age 50 years.⁷ Based on statistical modeling incorporating these data which predicted potential increased benefit,^{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.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.^{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.¹ Current technology for CRC screening falls into 2 broad categories: stool/fecal-based tests and structural tests.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.^{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,^{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.^{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.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).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%.²¹ This reduction in CRC mortality using low-sensitivity

guaiac FOBTs has been confirmed by a systematic review and meta-analysis of multiple studies.^{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%.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.^{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.²⁸ Comparative studies have shown that FIT is more sensitive than guaiac FOBT.^{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%).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%).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.³⁴ Nonrandomized studies have also shown that FIT screening reduces CRC mortality.^{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).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

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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%; $P<.001$).³⁹ 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}

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Interestingly, in a Canadian case-control study that matched each of 10,292 individuals who died of CRC to 5 controls, colonoscopy was associated with lower mortality from distal CRC (adjusted conditional odds ratio [OR], 0.33; 95% CI, 0.28–0.39) but not proximal CRC (OR, 0.99; CI, 0.86–1.14).⁴⁸ Additional studies have also demonstrated a reduced effectiveness in the right versus left colon.^{49,50} A population-based, case-control study in Germany demonstrated that colonoscopy in the preceding 10 years was associated with an overall 77% decrease in risk for CRC.⁵⁰ However, although risk reduction was strongest for distal cancer, a 56% risk reduction was also seen for proximal disease. A case-control study using the SEER-Medicare database also found that colonoscopies are associated with a decrease in death from CRC, and the association was strongest for distal over proximal CRC.^{49,51} Some of these findings of a distal but not proximal risk reduction may be associated with variation in the quality of colonoscopy in alternative settings.

Flexible Sigmoidoscopy

Evidence from RCTs have also demonstrated that flexible sigmoidoscopy reduces the incidence of and mortality from CRC.^{47,52–58} 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.^{56–58} 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.⁵⁶ 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.⁵⁹ 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.⁵³ 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.⁵⁴ 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.⁵⁵ 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.⁵² 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).⁵² The benefit of one-time sigmoidoscopy demonstrating decreased CRC incidence and mortality was sustained after 17 years of follow-up.⁶⁰ 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.^{60,61}

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, and added a footnote highlighting alternative strategies, including flexible sigmoidoscopy every 10 years with annual FIT or longer-interval flexible sigmoidoscopy without FIT⁵⁹ (see CSCR-3, page 942).

CT Colonography

CT colonography (CTC), also known as virtual colonoscopy, is evolving as a promising alternative

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technique for CRC screening. CTC has the advantages of being noninvasive and not requiring sedation. However, extracolonic findings, which are present in up to 16% of patients, pose a dilemma because they have a potential for both benefit and harm.^{62,63} Data to determine the clinical impact of these incidental findings are currently insufficient, and further investigation is required.

The accuracy of CTC in detecting polyps or cancers measuring ≥ 10 mm has been assessed in several studies, with generally high sensitivity.^{64–66} In 2005, 2 meta-analyses reviewed the performance of CTC in the detection of colorectal polyps.^{67,68} In one of these studies, CTC 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.⁶⁷ In the other meta-analysis, the sensitivity of CTC, although heterogenous, improved as the polyp size increased (48% for polyps < 6 mm, 70% for 6–9 mm polyps, and 85% for polyps > 9 mm); specificity was 92% to 97% for the detection of all polyps.⁶⁸ Other studies have assessed growth rates of colorectal polyps (6–9 mm) using CTC surveillance,^{69,70} and determined that polyps 6 to 9 mm are unlikely to progress to advanced neoplasia within 3 years.⁷⁰ The current NCCN Guidelines for CRC Screening recommend rescreening with CTC in 3 years or colonoscopy if 1 to 2 polyps of 6 to 9 mm are detected. If ≥ 3 polyps are found or polyps are ≥ 10 mm, a subsequent colonoscopy is recommended. However, if the CTC screen is negative, the guidelines recommend rescreening with any modality in 5 years.

The radiation exposure risk of undergoing a single CTC screening procedure is unknown but likely very low, and no empirical data have shown increased risk at levels below an exposure of 100 mSv.⁷¹ Using the screening protocol for the ACRIN trial, an estimated effective dose of low-dose CTC was projected 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 years.⁷² The 2014 American College of Radiology practice guidelines for the performance of CTC in adults recommend the use of a low-dose, nonenhanced CT technique on a multidetector CT scanner to minimize radiation exposure to the patient.⁷³ Overall, available data indicate that

CTC is useful for the detection of larger polyps. Data on optimal frequency, polyp size leading to colonoscopy referral, and protocol for the evaluation of extracolonic lesions are evolving.

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

1. Siegel RL, Miller KD, Jemal A. Cancer statistics, 2018. *CA Cancer J Clin* 2018;68:7–30.
2. National Cancer Institute. SEER Cancer Statistics Review, 1975–2013. National Cancer Institute. 2016. Available at: https://seer.cancer.gov/archive/csr/1975_2013/. Accessed July 9, 2018.
3. Agrawal S, Bhupinderjit A, Bhutani MS, et al. Colorectal cancer in African Americans. *Am J Gastroenterol* 2005;100:515–523; discussion 514.
4. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Am J Gastroenterol* 2017;112:1016–1030.
5. Bailey CE, Hu CY, You YN, et al. Increasing disparities in the age-related incidences of colon and rectal cancers in the United States, 1975–2010. *JAMA Surg* 2015;150:17–22.
6. Siegel RL, Jemal A, Ward EM. Increase in incidence of colorectal cancer among young men and women in the United States. *Cancer Epidemiol Biomarkers Prev* 2009;18:1695–1698.
7. Siegel RL, Fedewa SA, Anderson WF, et al. Colorectal cancer incidence patterns in the United States, 1974–2013. *J Natl Cancer Inst* 2017;109:djw322.
8. Meester RG, Peterse EF, Knudsen AB, et al. Optimizing colorectal cancer screening by race and sex: microsimulation analysis II to inform the American Cancer Society colorectal cancer screening guideline. *Cancer* 2018;124:2974–2985.
9. Peterse EF, Meester RG, Siegel RL, et al. The impact of the rising colorectal cancer incidence in young adults on the optimal age to start screening: microsimulation analysis I to inform the American Cancer Society colorectal cancer screening guideline. *Cancer* 2018;124:2964–2973.
10. Wolf AM, Fontham ET, Church TR, et al. Colorectal cancer screening for average-risk adults: 2018 guideline update from the American Cancer Society [published online May 30, 2018]. *CA Cancer J Clin*, doi: 10.3322/caac.21457
11. US Preventive Services Task Force, Bibbins-Domingo K, Grossman DC, et al. Screening for colorectal cancer: US Preventive Services Task Force recommendation statement. *JAMA* 2016;315:2564–2575.
12. Rex DK, Boland CR, Dominitz JA, et al. Colorectal cancer screening: recommendations for physicians and patients from the U.S. Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2017;153:307–323.
13. Burt RW. Colorectal cancer screening. *Curr Opin Gastroenterol* 2010;26:466–470.
14. Hassan C, Giorgi Rossi P, Camilloni L, et al. Meta-analysis: adherence to colorectal cancer screening and the detection rate for advanced neoplasia, according to the type of screening test. *Aliment Pharmacol Ther* 2012;36:929–940.
15. Robertson DJ, Lee JK, Boland CR, et al. Recommendations on fecal immunochemical testing to screen for colorectal neoplasia: a consensus statement by the US Multi-Society Task Force on Colorectal Cancer. *Gastroenterology* 2017;152:1217–1237.e3.
16. Vart G, Banzi R, Minozzi S. Comparing participation rates between immunochemical and guaiac faecal occult blood tests: a systematic review and meta-analysis. *Prev Med* 2012;55:87–92.
17. Hardcastle JD, Chamberlain JO, Robinson MH, et al. Randomised controlled trial of faecal-occult-blood screening for colorectal cancer. *Lancet* 1996;348:1472–1477.
18. 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.
19. 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.
20. Shaikat A, Mongin SJ, Geisser MS, et al. Long-term mortality after screening for colorectal cancer. *N Engl J Med* 2013;369:1106–1114.
21. Scholefield JH, Moss SM, Mangham CM, et al. Nottingham trial of faecal occult blood testing for colorectal cancer: a 20-year follow-up. *Gut* 2012;61:1036–1040.
22. Hewitson P, Glasziou P, Watson E, et al. Cochrane systematic review of colorectal cancer screening using the fecal occult blood test (hemoccult): an update. *Am J Gastroenterol* 2008;103:1541–1549.
23. Holme O, Bretthauer M, Frøtheim A, et al. Flexible sigmoidoscopy versus faecal occult blood testing for colorectal cancer screening in asymptomatic individuals. *Cochrane Database Syst Rev* 2013;9:CD009259.
24. U.S. Preventive Services Task Force. Screening for colorectal cancer: U.S. Preventive Services Task Force recommendation statement. *Ann Intern Med* 2008;149:627–637.
25. 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.
26. Allison JE, Sakoda LC, Levin TR, et al. Screening for colorectal neoplasms with new fecal occult blood tests: update on performance characteristics. *J Natl Cancer Inst* 2007;99:1462–1470.
27. Allison JE, Tekawa IS, Ransom LJ, Adrain AL. A comparison of fecal occult-blood tests for colorectal-cancer screening. *N Engl J Med* 1996;334:155–159.
28. Lee JK, Liles EG, Bent S, et al. Accuracy of fecal immunochemical tests for colorectal cancer: systematic review and meta-analysis. *Ann Intern Med* 2014;160:171.
29. Faivre J, Dancourt V, Denis B, et al. Comparison between a guaiac and three immunochemical faecal occult blood tests in screening for colorectal cancer. *Eur J Cancer* 2012;48:2969–2976.
30. Hol L, van Leerdam ME, van Ballegoijen M, et al. Screening for colorectal cancer: randomised trial comparing guaiac-based and immunochemical faecal occult blood testing and flexible sigmoidoscopy. *Gut* 2010;59:62–68.
31. 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.
32. Parra-Blanco A, Gimeno-Garcia 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.
33. van Rossum LG, van Rijn AF, Laheij RJ, et al. Random comparison of guaiac and immunochemical fecal occult blood tests for colorectal cancer in a screening population. *Gastroenterology* 2008;135:82–90.
34. Rabeneck L, Rumble RB, Thompson F, et al. Fecal immunochemical tests compared with guaiac fecal occult blood tests for population-based colorectal cancer screening. *Can J Gastroenterol* 2012;26:131–147.
35. Chiu HM, Chen SL, Yen AM, et al. Effectiveness of fecal immunochemical testing in reducing colorectal cancer mortality from the One Million Taiwanese Screening Program. *Cancer* 2015;121:3221–3229.
36. Giorgi Rossi P, Vicentini M, Sacchetti C, et al. Impact of screening program on incidence of colorectal cancer: a cohort study in Italy. *Am J Gastroenterol* 2015;110:1359–1366.
37. Zauber AG, Lansdorf-Vogelaar I, Knudsen AB, et al. Evaluating test strategies for colorectal cancer screening: a decision analysis for the U.S. Preventive Services Task Force. *Ann Intern Med* 2008;149:659–669.
38. van Roon AH, Goede SL, van Ballegoijen M, et al. Random comparison of repeated faecal immunochemical testing at different intervals for population-based colorectal cancer screening. *Gut* 2013;62:409–415.

Colorectal Cancer Screening, Version 1.2018

39. Imperiale TF, Ransohoff DF, Itzkowitz SH, et al. Multitarget stool DNA testing for colorectal-cancer screening. *N Engl J Med* 2014;370:1287–1297.
40. 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.
41. Berger BM, Schroy PC III, Dinh TA. Screening for colorectal cancer using a multitarget stool DNA test: modeling the effect of the intertest interval on clinical effectiveness. *Clin Colorectal Cancer* 2016;15:e65–74.
42. Redwood DG, Asay ED, Blake ID, et al. Stool DNA testing for screening detection of colorectal neoplasia in Alaska Native people. *Mayo Clin Proc* 2016;91:61–70.
43. 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.
44. 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.
45. 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.e351.
46. 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.
47. 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.
48. Baxter NN, Goldwasser MA, Paszat LF, et al. Association of colonoscopy and death from colorectal cancer. *Ann Intern Med* 2009;150:1–8.
49. Baxter NN, Warren JL, Barrett MJ, et al. Association between colonoscopy and colorectal cancer mortality in a US cohort according to site of cancer and colonoscopist specialty. *J Clin Oncol* 2012;30:2664–2669.
50. 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.
51. Kahi CJ, Pohl H, Myers LJ, et al. Colonoscopy and colorectal cancer mortality in the Veterans Affairs health care system: a case-control study. *Ann Intern Med* 2018;168:481–488.
52. 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.
53. 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.
54. 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.
55. 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.
56. 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.
57. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the PLCO cancer screening trial: results from the baseline screening examination of a randomized trial. *J Natl Cancer Inst* 2005;97:989–997.
58. Weissfeld JL, Schoen RE, Pinsky PF, et al. Flexible sigmoidoscopy in the randomized Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer screening trial: added yield from a second screening examination. *J Natl Cancer Inst* 2012;104:280–289.
59. Knudsen AB, Zaubler AG, Rutter CM, et al. Estimation of benefits, burden, and harms of colorectal cancer screening strategies: modeling study for the US Preventive Services Task Force. *JAMA* 2016;315:2595–2609.
60. Atkin W, Wooldrage K, Parkin DM, et al. Long term effects of once-only flexible sigmoidoscopy screening after 17 years of follow-up: the UK Flexible Sigmoidoscopy Screening randomised controlled trial. *Lancet* 2017;389:1299–1311.
61. Holme O, Loberg M, Kalager M, et al. Long-term effectiveness of sigmoidoscopy screening on colorectal cancer incidence and mortality in women and men: a randomized trial. *Ann Intern Med* 2018;168:775–782.
62. Kim DH, Pickhardt PJ, Taylor AJ, Menias CO. Imaging evaluation of complications at optical colonoscopy. *Curr Probl Diagn Radiol* 2008;37:165–177.
63. 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.
64. 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.
65. Johnson CD, Toledano AY, Herman BA, et al. Computerized tomographic colonography: performance evaluation in a retrospective multicenter setting. *Gastroenterology* 2003;125:688–695.
66. Pickhardt PJ, Choi JR, Hwang I, et al. Computed tomographic virtual colonoscopy to screen for colorectal neoplasia in asymptomatic adults. *N Engl J Med* 2003;349:2191–2200.
67. 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.
68. Mulhall BP, Veerappan GR, Jackson JL. Meta-analysis: computed tomographic colonography. *Ann Intern Med* 2005;142:635–650.
69. Pickhardt PJ, Kim DH, Pooler BD, et al. Assessment of volumetric growth rates of small colorectal polyps with CT colonography: a longitudinal study of natural history. *Lancet Oncol* 2013;14:711–720.
70. Tutein Nolthenius CJ, Boellaard TN, de Haan MC, et al. Evolution of screen-detected small (6–9 mm) polyps after a 3-year surveillance interval: assessment of growth with CT colonography compared with histopathology. *Am J Gastroenterol* 2015;110:1682–1690.
71. Health Physics Society. Radiation risk in perspective: position statement of the Health Physics Society. Available at: http://hps.org/documents/risk_ps010-3.pdf. Accessed July 12, 2018.
72. Berrington de Gonzalez A, Kim KP, Yee J. CT colonography: perforation rates and potential radiation risks. *Gastrointest Endosc Clin N Am* 2010;20:279–291.
73. ACR-SAR-SCBT-MR Practice Parameter for the Performance of Computed Tomography (CT) Colonography in Adults. Available at: <https://www.acr.org/-/media/ACR/Files/Practice-Parameters/ct-colonog.pdf>. Accessed September 1, 2016.
74. Ahmed D, Danielsen SA, Aagesen TH, et al. A tissue-based comparative effectiveness analysis of biomarkers for early detection of colorectal tumors. *Clin Transl Gastroenterol* 2012;3:e27.
75. deVos T, Tetzner R, Model F, et al. Circulating methylated SEPT9 DNA in plasma is a biomarker for colorectal cancer. *Clin Chem* 2009;55:1337–1346.
76. Lofton-Day C, Model F, Devos T, et al. DNA methylation biomarkers for blood-based colorectal cancer screening. *Clin Chem* 2008;54:414–423.
77. Wasserkort R, Kalmar A, Valcz G, et al. Aberrant septin 9 DNA methylation in colorectal cancer is restricted to a single CpG island. *BMC Cancer* 2013;13:398.
78. Johnson DA, Barclay RL, Mergener K, et al. Plasma Septin9 versus fecal immunochemical testing for colorectal cancer screening: a prospective multicenter study. *PLoS One* 2014;9:e98238.
79. Church TR, Wandell M, Lofton-Day C, et al. Prospective evaluation of methylated SEPT9 in plasma for detection of asymptomatic colorectal cancer. *Gut* 2014;63:317–325.
80. Potter NT, Hurban P, White MN, et al. Validation of a real-time PCR-based qualitative assay for the detection of methylated SEPT9 DNA in human plasma. *Clin Chem* 2014;60:1183–1191.
81. Orntoft MB, Nielsen HJ, Orntoft TF, et al. Performance of the colorectal cancer screening marker Sept9 is influenced by age, diabetes and arthritis: a nested case-control study. *BMC Cancer* 2015;15:819.

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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.