CME

A practical approach to selecting a colorectal cancer screening test

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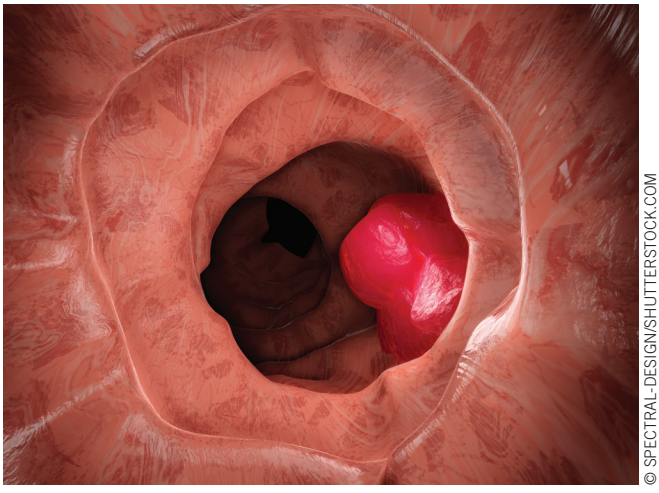
ABSTRACT

Colorectal cancer is the second leading cause of cancer-related deaths in the United States, but timely, effective, and adherent screening can reduce the number of cases. Screening tests continue to evolve, creating opportunities and challenges. Medical societies offer varying guidelines about optimal screening tests and when to begin screening. This article reviews available and emerging colorectal cancer screening tests and discusses how to educate patients, advise them in selecting an appropriate test, and promote increased participation in colorectal cancer screening.

Keywords: colorectal cancer screening, colonoscopy, sigmoidoscopy, CT colonography, FIT, FIT-DNA

Learning objectives

- Compare and contrast the advantages, limitations, test performance characteristics, costs, and screening intervals of various colorectal cancer screening tests.
- Integrate knowledge of the evolution of colorectal cancer into patient education and screening choice selection.
- Select a colorectal cancer screening test that benefits the health of the patient and aligns with patient preferences.



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Colorectal cancer is the second leading cause of cancer-related deaths in the United States after lung cancer, and is projected to cause 52,980 deaths in 2021.[1-6] Although the annual number of deaths attributable to colorectal cancer has declined over the past 2 decades, an opportunity for improvement remains.[7] The CDC notes an upward trend in the use of colorectal cancer screening tests, but millions of Americans still do not participate in screening.[8] From 2016 to 2018, colorectal cancer screening in adults ages 50 to 75 years increased by 1.4% to 68.8%, equating to an additional 4.2 million patients screened.[8] However, 21.7 million adults in this age group have never been screened.[8] Barriers to screening include patient unfamiliarity with test features, patient apprehension related to bleeding and perforation, inconvenience, cost, insurance coverage, and access issues.[9]

WHY SCREENING IS IMPORTANT

Most colorectal cancers arise from precancerous polyps such as tubular, tubulovillous, and villous adenomas.[4,5,10] The adenoma-to-carcinoma sequence takes about 10 years, with precancerous polyps often asymptomatic early on.[4] As such, colorectal cancer screening is aimed at early detection of cancer and prevention through the identification and removal of precancerous polyps. The 5-year relative survival for colorectal cancer for all races and both sexes in the United States is 63.8%, thus emphasizing the importance of timely and effective screening.[5,7,10,11]

EVOLUTION OF COLORECTAL CANCER

Colorectal cancer is primarily a cancer of older adults, with the mean age at diagnosis being 67 years.[12] However, the age of onset, histopathology, risk factors, and location associated with colorectal cancer continues to evolve.[1,12,13] Recent research demonstrating an increase in the incidence of colorectal cancer in patients under age 50 years

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Key points

- Screening is essential in the prevention of colorectal cancer, and patient adherence and compliance to testing are vital for effectiveness.
- Colonoscopy is the gold standard for colorectal cancer screening. Patients who defer a colonoscopy should consider alternative options with the caveat that an abnormal screening test mandates a *timely diagnostic colonoscopy* to further evaluate for colorectal cancer and adenomas.
- To increase patient participation in colorectal cancer screening, clinicians should support transparent dialogue and informed shared decision-making.

is concerning.[1,12,13] The US Preventive Services Task Force (USPSTF) states that the incidence of colorectal cancer in patients ages 40 to 49 years has increased 15% from 2000-2002 to 2014-2016.[1] The growing rate of colorectal cancer in younger patients is multifactorial, with research suggesting that the Western lifestyle, gut microbiome, and more aggressive tumor histology may be contributing.[12,13] More specifically, the obesity epidemic; diabetes; physical inactivity; consumption of processed, low-fiber foods; tobacco use; and the unhealthful use of alcohol are likely to play a role.[13] Additionally, studies suggest that disparities in healthcare contribute to higher rates of colorectal cancer in Black patients.[14]

In response to concern over the increase in early-onset colorectal cancer, in 2018 the American Cancer Society (ACS) changed its colorectal cancer screening guidelines to recommend that average-risk adults begin screening at age 45 years.[2] The American College of Gastroenterology (ACG) as well as the USPSTF changed their guidelines in 2021 to recommend that average-risk adults begin screening at age 45 years.[1,14] **Table 1** outlines medical societies' recommendations for the initiation and discontinuation of screening.

Additionally, although colorectal cancer commonly occurs in the left side of the colon, proximal and right-sided colon cancer has surfaced.[15] Traditional adenomatous polyps account for 70% of colorectal cancers; however, sessile serrated polyps represent an emerging and concerning type of precancerous polyp and account for 25% to 30% of colorectal cancer cases.[4,5,10,14,16] Sessile serrated polyps generally localize to the proximal and right side of the colon, are flat as opposed to pedunculated, and have no or few surface blood vessels, making them less likely to be identified on flexible sigmoidoscopy, CT colonography, or guaiac fecal occult blood test (gFOBT) and fecal immunochemical test (FIT) stool collections.[16] Clinicians should be mindful of these types of polyps when helping patients select a colorectal cancer screening modality.

SCREENING APPROACHES

Screening can be *programmatic*, relying on a population, systematic-based approach or *opportunistic*, stemming from a fee-for-service office visit between a healthcare provider and patient.[14,16] Opportunistic screening predominates in the United States.[14] In this setting, clinicians can use three broad strategies:

- *Sequential*, in which clinicians recommend their preferred test, and if the patient declines, the clinician discusses other options.[16]
- *Multiple options*, in which the patient and clinician have a detailed discussion of the benefits, risks, and costs of two or more tests and engage in informed shared decision-making.[16]
- *Risk-stratified approaches*, which weigh the patient's predicted risk for colon cancer based on specific factors (such as, sex, body mass index (BMI), smoking history, and dietary/lifestyle behaviors).[1,16] Although these risks are notable, patients remain within the category of average risk as opposed to high risk. *Average-risk* patients may choose from various screening modalities including direct visualization or stool-based tests beginning at age 45 to 50 years. *High-risk* patients are those with a family history of colorectal cancer or advanced adenoma, inherited cancer syndromes including familial adenomatous polyposis (FAP) or hereditary nonpolyposis colorectal cancer (HNPCC), or a personal history of inflammatory bowel disease (IBD).[12,13] *High-risk* patients are advised to undergo screening with a colonoscopy at an earlier age as dictated by their family or personal history.[16] Colorectal cancer screening guidelines for high-risk patients are beyond the scope of this article, but to determine when a patient should initiate and receive subsequent interval screening, clinicians should be familiar with the age at onset of the relative, degree of familial relation, and number of affected relatives.[14]

TABLE 1. Colorectal cancer screening guidelines[1,2,15,16]

Society	Initiate screening	Discontinue screening	Individualize
MSTF	Age 50 years (age 45 years in Black patients)	• Age 75 years if screening is up-to-date and previously negative • If life expectancy is less than 10 years	Age 76 to 85 years
USPSTF	Age 45 years	Age 75 years	Age 76 to 85 years
ACS	Age 45 years	Age 75 years	Age 76 to 85 years

SCREENING TESTS

Colonoscopy is the most commonly recommended and used colorectal cancer screening test in the United States.[10] It is considered the gold standard because it is diagnostic and therapeutic.[17] Colonoscopy provides direct optical visualization of the colonic mucosa and allows for removal of lesions in the areas examined.[2-4,9,16,18] Although the focus of this article is on the use of screening colonoscopy, an understanding of screening versus diagnostic versus surveillance colonoscopy is necessary to provide a framework for management. A *screening colonoscopy* is appropriate to screen for colorectal cancer in average-risk and high-risk patients. A *diagnostic colonoscopy* assesses for pathologic conditions in patients with symptoms, such as a change in bowel habits, hematochezia, iron-deficiency anemia, or unexplained weight loss. A diagnostic colonoscopy also is done as a follow-up to an abnormal or positive screening test. A *surveillance colonoscopy* is appropriate to closely monitor for recurrence in patients with a personal history of colorectal cancer or adenomas. Patients with adenomas require the interval use of a colonoscopy (for example, every 1, 3, or 5 years) depending on the number of polyps, size, and histopathologic features.

Although colonoscopy is the preferred test for colorectal cancer screening, patients may avoid the test if they fear the bowel preparation, sedation, or possibility of pain. Smaller-volume bowel preparations and split-dose regimens have increased patient tolerability and preprocedure bowel cleansing, minimizing the likelihood of a poor preparation and need for a repeat colonoscopy.[19] Propofol has widely supplanted the more traditional sedatives midazolam and fentanyl.[19] Anecdotally, endoscopists prefer propofol because it offers improved patient satisfaction with more reliable sedation and shorter postprocedural recovery times. Lastly, the use of water infusion rather than traditional air or carbon dioxide insufflation may help lessen patient discomfort, reduce angulations and facilitate endoscope advancement, improve visualization, and increase adenoma detection rates.[19]

Clinicians should be aware of these procedural advances and share them with patients to help boost screening participation. The colonoscopy; however, is not infallible and depends on operator skill and quality of the bowel preparation.[9,19] Endoscopists' adenoma detection rate, withdrawal time, and cecal intubation rate are benchmark measures to assess the quality of screening colonoscopy.[14] An acceptable screening colonoscopy interval for average-risk patients is every 10 years, provided the examination shows no precancerous polyps and is of good quality preparation.[2-4,16,18] Average-risk patients who cannot or prefer not to undergo colonoscopy can opt for a different type of visualization test or a stool-based test.[2-4,16,18]

Other visualization tests A flexible sigmoidoscopy provides direct optical visualization of the colonic mucosa to about 60 cm (the splenic flexure), and allows for biopsy and removal of lesions in the area examined.[2-4,16,18] Given that a sigmoidoscopy examines *only* the distal portion of the colon, a significant deficiency is protection against proximal lesions.[16] In the United States, the use of a flexible sigmoidoscopy for colorectal cancer screening has declined, due to deficiency in examining the entire colon.[14,16] An acceptable screening interval for a sigmoidoscopy is every 5 years, usually combined with a FIT.[2,16]

CT colonography, often referred to as a *virtual colonoscopy*, is a radiologic test that constructs two- and three-dimensional images of the colon, allowing for structural identification of colonic lesions.[2-4,16,18] Because CT colonography can miss flat or small (less than 6 to 10 mm) lesions, it may not be an optimal test for identifying precancerous polyps.[4,9] Patients should understand that a bowel preparation is still required and that the test exposes them to radiation. Extracolonic findings may require additional workup and may pose potential harms.[14] CT colonography generally is reserved for patients with comorbidities or anatomic variants (such as redundant tortuous colon, severe diverticulosis, or stricture) that may preclude the safe use of a colonoscope.[4] An acceptable screening interval for a CT colonography is every 5 years.[2-4,16,18] CT colonography has largely replaced a barium enema, which most major medical societies no longer recognize as an acceptable test for colorectal cancer screening.

Stool-based tests Most major medical societies also no longer recommend an office-based stool guaiac (or occult blood) test as a suitable colorectal cancer screening tool,

TABLE 2. Performance characteristics, costs, and screening intervals of colorectal cancer screening tests[6,7,9]

Test	Sensitivity for colorectal cancer	Sensitivity for advanced adenoma (>10 mm diameter)	Specificity	Cost	Screening interval
Colonoscopy	95%	95%	86%	$1,700	10 years
Flexible sigmoidoscopy	95% distal colon	95% distal colon	87%	$1,000	5 years
CT colonography	84%	84%	88%	$500	5 years
gFOBT SENSA	70%	23.9%	92.5%	$5	Annual
FIT	73.8%	23.8%	96.4%	$22	Annual
FIT-DNA	92.3%	42.4%	89.8%	$599	3 years

TABLE 3. Advantages and limitations of colorectal cancer screening tests[2-5,8,9,16,17]

Test	Advantages	Limitations
Colonoscopy	• Visualization of entire colon • Single session • Long screening intervals	• Invasive • Requires bowel preparation • Requires sedation and chaperone • Requires time off work • Accessibility • Risk of bowel perforation, bleeding, splenic injury, and cardiopulmonary complications of anesthesia • Operator skill influences adenoma detection rate • Poor bowel preparation may preclude adequate visualization
Flexible sigmoidoscopy	• Limited bowel preparation • Generally does not require sedation • Lower risk than colonoscopy	No visualization of proximal colon
CT colonography	• No sedation required • Semi-invasive • Lower risk than colonoscopy	• May miss flat or small polyps • Requires bowel preparation • Unable to remove polyps or perform a biopsy • Radiation exposure • Incidental extracolonic findings • Accessibility
gFOBT SENSA	• Noninvasive • No bowel preparation required • Accessible	• Requires three stool samples • Detects ingested hemoglobin; therefore, requires dietary modifications (avoidance of red meat and vitamin C) for 3 days before and during collection • Sensitivity for one-time screening is not ideal, requires adherence
FIT	• Noninvasive • No bowel preparation required • No dietary restrictions • Single stool sample	Sensitivity for one-time screening is not ideal, requires adherence
FIT-DNA	• Noninvasive • No bowel preparation required • No dietary or medication restrictions	• Requires full stool specimen collection • Sensitivity for one-time screening is not ideal, requires adherence

although the test is still available for evaluating iron-deficiency anemia and other gastrointestinal pathologies.[17] Acceptable stool-based tests for colorectal cancer screening include a high-sensitivity gFOBT SENSA, FIT, and the FIT-DNA test.[17] Both the high-sensitivity gFOBT and FIT detect hemoglobin in the stool. The gFOBT relies on a peroxidase reaction; the FIT occurs via an immunochemical reaction.[3,4,17] The gFOBT SENSA requires three stool samples and dietary modifications; the FIT test requires a single sample and no dietary restrictions. As such, FIT is more sensitive and specific than gFOBT.[9,10,17] Most major medical societies recommend annual interval screening for both the gFOBT and FIT collections.[2-4,17] However, the American College of Physicians recommends testing every other year.[5]

The multitarget stool DNA test combines FIT with testing for DNA mutations in the stool shed by colorectal cancer cells.[17] The FIT-DNA test was approved by the FDA in 2014.[17] Although the FIT-DNA stool test has a 92.3% sensitivity for the detection of colorectal cancer, it is only 42.4% sensitive in identifying advanced adenomas, hindering its optimal preventive role in colorectal cancer screening.[3,10,11,17] The test also has a higher false-positive rate than other stool-based tests.[16] A positive result warrants a timely diagnostic colonoscopy, which may contribute to undue anxiety and incur out-of-pocket expenses.[2] Further, in patients who have a positive FIT-DNA with a subsequent negative colonoscopy, uncertainty surrounds future screening management. The need for additional screening with an upper endoscopy, cross-sectional imaging, or repeat colonoscopy sooner than the recommended interval is unknown.[14] Cost also is a consideration, with the FIT-DNA averaging $600 for privately insured patients.[16] Most major medical societies recommend a screening interval of 3 years for a FIT-DNA.[2,16]

Stool-based tests are an option for colorectal cancer screening, although they have limitations. Unlike colorectal cancers that can ulcerate, become friable, and bleed, precancerous polyps may not bleed and thus can be missed by tests that assess for hemoglobin in the stool, limiting their optimal preventive role in colorectal cancer screening.[4,10,17] Additionally, false-positive results from dietary influences, a bleeding ulcer, and/or hemorrhoids can challenge the clinical picture. Further, one-time screening is not ideal; patient adherence to testing annually or every other year is vital for stool-based tests to be effective.[17] **Table 2** compares tests' performance characteristics, costs, and screening intervals, and **Table 3** summarizes the advantages and limitations of various tests.

EMERGING SCREENING TESTS

New screening tests for colorectal cancer include colon capsule endoscopy and a serum-based test, Septin 9. The colon capsule endoscopy is a visualization test that captures images of the colon using a wireless camera inside a pill-sized capsule that the patient ingests. This test is not FDA-approved for screening average-risk patients, but is approved for patients with a previous incomplete colonoscopy or those for whom colonoscopy is not appropriate.[16] For example, this test may be used in patients with lower gastrointestinal bleeding, for whom a colonoscopy is unsafe.[14] Reimbursement challenges also are an obstacle for the colon capsule endoscopy because it is not considered a primary screening test.

Septin 9, approved by the FDA in 2016, is a serologic test that detects methylated septin 9 DNA.[9] Although the test is convenient and is discussed in colorectal cancer screening guidelines, major medical societies do not endorse it as a primary screening strategy because of its inferior performance characteristics.[9,10,16] In a review of average-risk adults age 50 years and older who underwent screening colonoscopy, the Septin 9 test was 48% sensitive for colorectal cancer and 11% sensitive for advanced adenomas.[20] Specificity was higher at 92%.[20] This test may intrigue patients because it is noninvasive and requires no preparation compared with stool-based and visualization tests. Clinically, the colon capsule endoscopy and Septin 9 test are not widely available and should not be used for screening by primary care providers at this time.[14]

CHOOSING A SCREENING TEST

Clinicians often use opportunistic screening with the sequential and multiple options strategies in concert with a tiered approach. The Multi-Society Task Force (MSTF) ranks colorectal cancer screening tests in three tiers based on test features, performance characteristics, and costs.[16]

- Tier 1 tests, colonoscopy and FIT, are preferred.
- Tier 2 tests are FIT-DNA, CT colonography, and flexible sigmoidoscopy.
- Tier 3 test is the colon capsule endoscopy.[16]

This information can help guide clinicians and patients in selecting their screening choice. Below is a practical approach to selecting a screening test:

- *Average-risk, asymptomatic patients:* A screening colonoscopy is recommended first. This is the gold standard. If the patient declines, the clinician should offer multiple options including FIT, which is widely accepted and cost-effective, or FIT-DNA. CT colonography is an option, although it generally is reserved for patients with comorbidities or incomplete colonoscopy. Flexible sigmoidoscopy is an option, although it has fallen out of favor. Colon capsule endoscopy and Septin 9 are not widely available. Note that a positive (abnormal) screening test, other than by a colonoscopy, warrants a timely diagnostic colonoscopy to further evaluate for colorectal cancer and adenomas.
- *High-risk patients:* Offer age-appropriate screening with colonoscopy. Other recommendations are beyond the scope of this article.
- *Patients with a history of colorectal cancer or adenomas:* Enter a surveillance program with interval use of colonoscopy based on the number, size, and histologic features of the polyps. Other recommendations are beyond the scope of this article.

When reviewing screening test options with patients, clinicians should support informed shared decision-making and the selection of a test that balances the benefits with harms and is aligned with the patient's preference.[5] Remind patients that regular testing is vital for colorectal cancer screening to be effective.[16,17] Provide them with patient education handouts, phone calls, mailed letters, and brochures to help reinforce this information.

CONCLUSION

Colorectal cancer is a deadly yet preventable cancer. Early detection and removal of precancerous lesions is paramount.[5,10] Each of the various screening tests for average-risk patients has advantages and limitations. Clinicians and patients should discuss these test features and consider the evolution of colorectal cancer when selecting a screening test.[2-4,16,18] Advances in genetic testing and precision medicine may influence our approach to colorectal cancer screening in the future.[9] In the interim, enhanced knowledge, patient education, and a shared understanding of screening tests can help increase patient participation in colorectal cancer screening. **JAAPA**

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