The Present and Future of Colorectal Cancer Screening

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Abstract: There have been multiple recent updates for recommendations pertaining to colorectal cancer (CRC) screening. Among the most notable is the recommendation from several guideline-issuing bodies to initiate CRC screening examinations at 45 years of age for individuals at average risk for CRC. Current CRC screening methods include stool-based tests and colon visualization examinations. Currently recommended stool-based tests include fecal immunochemical testing, high-sensitivity guaiac-based fecal occult blood testing, and multitarget stool DNA testing. Visualization examinations include colonoscopy, computed tomography colonography, colon capsule endoscopy, and flexible sigmoidoscopy. Although these screening tests have shown encouraging results for CRC detection, there are important differences between these testing modalities for precursor lesion detection and management. In addition, emerging CRC screening methods are being developed and evaluated. However, additional large, multicenter clinical trials in diverse populations are needed to validate the diagnostic accuracy and generalizability of these new tests. This article reviews the recently updated CRC screening recommendations and current and emerging testing options.

Keywords
Colorectal cancer screening, colonoscopy, guidelines, computed tomography colonography, colon capsule endoscopy, stool DNA

Colorectal cancer (CRC) is the third most commonly diagnosed cancer in men and women in the United States, with 104,270 new cases of CRC diagnosed in 2021.[1] However, CRC diagnoses have diminished yearly since the late 1980s, likely owing to increasing use of various CRC screening methods and government-mandated third-party payer coverage of screening costs.[1] Highlighting the value of prevention, CRC care has the second highest cost of any cancer in the United States. One study found the average annual Medicare cancer-related health care spending for individual patients with newly diagnosed CRC to be $40,000 in 2010 and projected this cost to be $80,000 in 2020.[2] This article reviews the recently updated CRC screening recommendations and current and emerging testing options.

Colorectal Cancer Screening Guidelines

In the United States, there are 3 major CRC screening guideline–issuing groups whose recommendations have direct impact on legislatively

Table 1. Recommendations for CRC Screening Tests

	ACS[3]	USPSTF[4]	USMSTF[5]
hsFOBT	Annually	Annually	Not included in guidelines
FIT	Annually	Annually	Annually
mt-sDNA	Every 3 years	Every 1-3 years	Every 3 years
CTC	Every 5 years	Every 5 years	Every 5 years
CCE	Not included in guidelines	Not included in guidelines	Every 5 years
FS	Every 5 years	Every 5 years Every 10 years if combined with annual FIT	Every 5-10 years but favors every 10 years
Colonoscopy	Every 10 years	Every 10 years	Every 10 years
mSEPT9	Not included in guidelines	Not included in guidelines	Not recommended for CRC screening

ACS, American Cancer Society; CCE, colon capsule endoscopy; CRC, colorectal cancer; CTC, computed tomography colonography; FIT, fecal immunochemical testing; FS, flexible sigmoidoscopy; hsFOBT, high-sensitivity guaiac-based fecal occult blood testing; mSEPT9, methylated septin 9; mt-sDNA, multitarget stool DNA testing; USMSTF, US Multi-Society Task Force; USPSTF, US Preventive Services Task Force.

mandated coverage decisions: the American Cancer Society (ACS), US Preventive Services Task Force (USPSTF), and US Multi-Society Task Force (USMSTF) (Table 1). In its 2018 update, the ACS issued a qualified recommendation that individuals at average risk for CRC start screening at 45 years of age.[3] A qualified recommendation indicates clear evidence of the benefit of screening but less certainty about the balance of benefits and harms or about patients' values and preferences, which could lead to different decisions about screening. The ACS retained its strong recommendation for CRC screening in average-risk individuals to begin at 50 years of age. A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. The inclusion of the younger age for screening initiation in the ACS guidelines represented a major shift in CRC screening recommendations and was based on observational and modeling data demonstrating a shift of increasing CRC incidence in younger patients over the past 3 to 4 decades.

The ACS has recommended CRC screening for average-risk individuals consisting of select stool-based tests or visualization examinations of the colon and rectum.[3] The stool-based tests in the ACS guidelines include fecal immunochemical testing (FIT), high-sensitivity guaiac-based fecal occult blood testing (hsFOBT), or multitarget stool DNA testing (mt-sDNA). Colonic visualization examinations in these guidelines include colonoscopy, computed tomography colonography (CTC), or flexible sigmoidoscopy (FS). In addition, the ACS has recommended that the decision to undergo CRC screening in individuals ages 76 years through 85 years should be based on individual patient preferences, life expectancy, overall health, and prior CRC screening history. The ACS guidelines do not include specific guidelines for individuals at increased risk for CRC, such as those with a family history of CRC, personal history of inflammatory bowel disease, or known hereditary CRC syndromes such as familial adenomatous polyposis or Lynch syndrome. The ACS did recommend that CRC screening for individuals with a prior history of radiation to the abdomen or pelvis should begin 5 years after the radiation or at age 30 years, whichever is reached last. For patients with inflammatory bowel disease, colonoscopy is generally recommended 8 years after diagnosis and repeated every 1 to 3 years.

In 2021, the USPSTF updated its CRC screening recommendations to initiate CRC screening in average-risk adults between the ages of 45 and 49 years.[4] This recommendation, similar to the qualified recommendation of the ACS, was a grade B recommendation, indicating that there is high certainty of moderate net benefit of the practice or moderate certainty that the net benefit is moderate to substantial. Initiating screening at age 50 years retained a grade A recommendation in the USPSTF guidelines, indicating that there is high certainty that the net benefit of the practice is substantial. According to the USPSTF, selective and individualized screening should be offered to individuals aged 76 to 85 years.

The third set of widely cited guidelines comes from the USMSTF and represents a consensus opinion from CRC screening experts representing the American

Table 2. Noninvasive CRC Screening Options

	Test	Test Characteristics	Test Details
Stool-Based Tests	FIT	• Sensitivity for CRC: 79% • Specificity: 94%[23]	• No dietary or drug restrictions • Single stool sample • Sensitivity and specificity modifiable • Colonoscopy for positive test
	mt-sDNA	• Sensitivity for CRC: 92% • Specificity: 87%[30]	• Single stool sample • Colonoscopy for positive test
Imaging-Based Tests	CCE	• Sensitivity for polyps ≥6 mm: 88% • Specificity: 82%[37]	• Requires bowel preparation • May take up to 10 hours • Colonoscopy for positive test
	CTC	• Sensitivity for polyps ≥6 mm: 89% • Specificity: 80%[34]	• Requires bowel preparation • Low-dose radiation exposure • Colonoscopy for positive test
Blood-Based Test	mSEPT9	• Sensitivity for CRC: 48% • Specificity: 80%-91%[47]	• Not recommended by USMSTF • Colonoscopy for positive test

CCE, colon capsule endoscopy; CRC, colorectal cancer; CTC, computed tomography colonography; FIT, fecal immunochemical testing; mSEPT9, methylated septin 9; mt-sDNA, multitarget stool DNA testing; USMSTF, US Multi-Society Task Force.

College of Gastroenterology, the American Gastroenterological Association, and the American Society for Gastrointestinal Endoscopy. These guidelines were updated in 2022 and offer slightly more specific recommendations than those of the ACS and USPSTF, including a hierarchal classification of commonly used CRC screening tests. The USMSTF recommends Tier 1 tests such as colonoscopy every 10 years or annual FIT as the cornerstones of screening.[5] Tier 2 tests include CTC every 5 years, mt-sDNA every 3 years, and FS every 5 to 10 years. Colon capsule endoscopy (CCE) every 5 years is included as a Tier 3 test owing to limited evidence and current obstacles to reimbursement. The updated USMSTF guidelines also recommend CRC screening to begin at 45 years of age in average-risk individuals.[6] According to the USMSTF, CRC screening should be discontinued in individuals with prior negative screening upon reaching 75 years of age or who have less than 10 years of life expectancy. However, the USMSTF guidelines state that CRC screening should be considered up to age 85 years in individuals with no previous screening. The USMSTF also recommends that individuals with a first-degree relative with CRC or advanced adenoma diagnosed at age less than 60 years, or with 2 first-degree relatives with the above findings at any age, should undergo screening with colonoscopy every 5 years, beginning at 40 years of age or 10 years before the age of diagnosis of youngest affected relative, whichever is earlier.[5] Per the USMSTF, clinicians may consider expanding the colonoscopy interval for patients with a single first-degree relative with CRC in whom no significant colorectal neoplasia is found by 60 years of age. In individuals with a single first-degree relative diagnosed with CRC or advanced adenoma after age 60 years, CRC screening should begin at 40 years of age with the same test options and intervals as average-risk individuals.[5]

Current Colorectal Cancer Screening Tests

CRC screening tests can be broadly conceptualized into a variety of descriptive categories (Table 2). First, there are tests that can detect prevalent CRC. Tests in this category include all stool- and blood-based tests as well as nonendoscopic visualization tests such as CTC and CCE. Conversely, colonoscopy and FS can both detect and prevent the development of CRC through the resection of early cancers or precursor lesions. Another classification of CRC screening tests distinguishes between those that rely on secondary markers of neoplasia, such as blood- and/or neoplasia-associated DNA or protein products, from those that rely on visualization of neoplasia within the colonic lumen; stool- and blood-based tests are included in the former, whereas colonoscopy, FS, CCE, and CTC comprise the latter. Finally, CRC screening options can be divided into triage tests and preventive tests. The only currently available preventive CRC screening test is colonoscopy, which permits detection and removal of colonic neoplasia (cancerous and precancerous) throughout the entire colorectum. All other CRC screening tests can be considered triage tests, implying that a positive result from any noncolonoscopy CRC screening test should result in timely referral for colonoscopy to confirm the findings of

the positive triage test and permit definitive management of endoscopic findings.

CRC screening tests vary in cost from a few US dollars to more than $1000. Because a screening program is intended to be applied to a healthy population without signs or symptoms of disease, the cost-effectiveness of these screening modalities has been studied extensively. A 2011 review by Lansdorp-Vogelaar and colleagues showed that the cost per year of life saved with CRC screening with any of the currently recommended tests is within the generally accepted amount of less than $50,000 compared with no screening.[7] Another review has also demonstrated that performing CRC screening as described in existent guidelines is more cost-effective than no screening.[8]

Fecal Occult Blood Testing

Guaiac-based fecal occult blood testing (gFOBT) detects occult blood in the stool through a chemical reaction based on the pseudoperoxidase activity found in hemoglobin. When stool containing hemoglobin is spread onto guaiac paper and exposed to hydrogen peroxide, an oxidative reaction turns the paper blue. Current gFOBT utilizes hsFOBT.

Five pragmatic randomized controlled trials of gFOBT showed a reduction in CRC mortality,[9-13] and meta-analysis has demonstrated a reduction in CRC mortality with gFOBT compared with no screening.[14] However, these conclusions should be interpreted with caution owing to significant limitations such as the use of older, non-hsFOBT and methodologic differences among studies involving gFOBT processing, frequency of testing, study quality, and use of statistical adjustments in the analysis and reporting of individual trial data.

Although largely replaced by FIT in the United States, hsFOBT continues to be used in some countries as the primary average-risk population CRC screening test and has a sensitivity for CRC detection of approximately 70%.[10-13] hsFOBT is not sensitive for the detection of colorectal neoplasia such as advanced and nonadvanced adenomas, however. Thus, any CRC mortality benefit derived from a positive gFOBT (high sensitivity or not) likely derives from subsequent colonoscopy with polypectomy or localization of curable CRC and appropriate surgical or medical therapy. Underscoring the inability of gFOBT to prevent CRC, patients in the Nottingham FOBT trial followed for 20 years demonstrated a sustained reduction in CRC mortality but no significant reduction in CRC incidence.[12]

Fecal Immunochemical Testing

FIT detects human globin in the gastrointestinal tract and is superior to hsFOBT for CRC screening. FIT has largely replaced gFOBT and hsFOBT in the United States and many other countries. The effectiveness of FIT for reducing CRC mortality was evaluated in a Taiwanese prospective cohort study that found that 1 to 3 rounds of screening with biennial FIT conferred lower CRC mortality at 6 years' follow-up compared with no screening (adjusted relative risk, 0.90; 95% CI, 0.84-0.95).[14] Similar to hsFOBT, the positivity rate, subsequent demand for colonoscopy, detection rate, and positive predictive value of FIT for CRC decreased with multiple rounds of testing in other studies.[15-21] These studies also showed that participation rates tended to remain stable through multiple rounds of screening with FIT. A meta-analysis that reviewed 31 studies found that FIT is highly sensitive for CRC, although with a high false-positive rate.[22] However, FIT is less sensitive for detecting advanced adenomas owing to the natural history of these lesions, with annual transition rates to CRC of 3% to 6%, suggesting that there is an opportunity for detection of CRC with regularly scheduled repeat screening tests.

Other large national and multinational prospective studies have demonstrated that FIT is an acceptable and cost-effective CRC screening test.[23-27] FIT has higher sensitivity than hsFOBT for both advanced adenomas and CRC with comparable specificity. Importantly, FIT involves no drug or dietary restrictions and requires only 1 stool sampling, compared with 3 samples for hsFOBT.[26,27] The optimal interval for FIT remains unclear. A Dutch study showed that the detection of advanced neoplasia was not influenced by variable intervals of 1 to 3 years.[21] A cost-effectiveness analysis also showed that FIT performed annually yielded life-years gained similar to colonoscopy performed every 10 years.[28] Finally, compared with qualitative hsFOBT, the quantitative results obtained with FIT demonstrate better quality control with automated reading and the ability to adjust the cutoff concentrations to define a positive test.[29]

Multitarget Stool DNA Testing

mt-sDNA consists of 2 distinct test modalities, with the results processed through a proprietary algorithm producing a positive or negative result. In addition to a FIT assay, mt-sDNA detects multiple neoplastic DNA markers through the performance of quantitative molecular assays for *KRAS* mutations, aberrant *NDRG4* and *BMP3* methylation, and B-actin. In a pivotal study of nearly 10,000 average-risk individuals undergoing both mt-sDNA and FIT, mt-sDNA demonstrated significantly higher sensitivity for the detection of CRC and advanced polyps, including polyps with high-grade dysplasia and sessile serrated polyps of greater than 1 cm.[30] However, mt-sDNA demonstrated more false-positive results than FIT. Also, a non-US study showed that advanced adenomas with high risk of progression were not detected

with significantly higher sensitivity by either mt-sDNA or FIT.[31] Because certain races are associated with an increased risk of CRC, mt-sDNA has been evaluated in the context of racial demographics. In one study, the sensitivity and specificity of mt-sDNA were similar between White and Black patients,[32] and in another study, the sensitivity of mt-sDNA in native Alaskan patients, who have one of the highest global rates of CRC, was significantly higher than FIT alone.[33]

Computed Tomography Colonography

CTC consists of postacquisition processing of CT digital image data to accentuate tissue and gas CT density differences. CTC platforms can present images in a 2- or 3-dimensional format that depicts the intraluminal aspect of the colon and rectum to detect polyps or masses. In 2003, a large, multicenter US Department of Defense trial comparing CTC with colonoscopy showed that CTC had a sensitivity of 94% and specificity of 96% for large (>1 cm) adenomas.[34] Using a lower size threshold of 6 mm or larger, the sensitivity and specificity of CTC decreased to 89% and 80%, respectively. With numerous additional studies demonstrating acceptable sensitivity and specificity for CRC and polyp detection, CTC is included in the ACS and USMSTF guidelines as an acceptable CRC screening test for average-risk individuals. Although CTC is safe and does not require sedation, it does require a full cathartic bowel preparation and its sensitivity for diminutive and flat neoplasia has been questioned. The CTC Task Force of the American Gastroenterological Association developed training standards for interpreting and applying CTC and updated these recommendations in 2011.[35] Owing to the infrastructure required and coverage limitations, CTC is not routinely used for CRC screening in 2022, with some notable geographic exceptions, and has been relegated primarily to complete screening in patients in whom colonoscopy is not feasible.

Colon Capsule Endoscopy

CCE utilizes a disposable capsule that records color video images from both ends of the capsule while being propelled through the colon by peristalsis. The dual cameras included in the device allow 344-degree coverage of the colonic mucosa. There are 2 generations of CCE that are available, with the later showing improvement in polyp detection.[36] The operation time of the capsule is approximately 10 hours, and a reader is needed to interpret recorded images that are uploaded to a reading program, like with small bowel capsule endoscopy. A thorough bowel cleanse is required before CCE to ensure complete visualization. Most research using CCE has evaluated the technique in high-risk patients with symptoms suggesting CRC or with positive hsFOBT or FIT.[36] Results from the TOPAZ trial, the first study to evaluate CCE in an average-risk CRC screening population, were recently published.[37] This multicenter study compared CCE with CTC and demonstrated that CCE was significantly more sensitive than CTC for the detection of polyps 6 mm or larger and noninferior to CTC for polyps 10 mm or larger. In this study, CCE had comparable accuracy to colonoscopy for neoplasia detection. The American College of Gastroenterology screening guidelines mention CCE as an option for patients who are unable to undergo colonoscopy or FIT,[38] and the USMSTF guidelines include CCE as a Tier 3 CRC screening test based on the limited evidence supporting its use in an average-risk screening population. CCE is approved for examination of the colon in patients at high risk for colonoscopy-related complications but does not currently have US Food and Drug Administration clearance for routine CRC screening in average-risk individuals.

Flexible Sigmoidoscopy

FS allows direct visualization, tissue sampling, and polyp removal from the colonic mucosa but is limited to visualizing the left side of the colon. It is typically performed without sedation and with a limited bowel preparation with enemas rather than the full catharsis used for other visual screening tests. Four randomized controlled trials employing 1 to 2 screening examinations with FS at intervals of 3 to 5 years have demonstrated CRC mortality reductions.[39-42] FS has been shown to reduce CRC incidence by 20% and CRC mortality by 27% at 11 years' follow-up.[38,40] Despite evidence for the efficacy of FS as a CRC screening test, it has low utilization rates in the United States owing in part to colonoscopy studies showing superior performance and the nonsedated nature of the examination.

Colonoscopy

Colonoscopy has been used as the ground-truth comparator in numerous evaluations of hsFOBT, FIT, mt-sDNA, and other noncolonoscopic test modalities. Although invasive, colonoscopy allows visualization as well as sampling and resection of cancerous or precancerous lesions and permits longer intervals between screening, with colonoscopy recommended every 10 years after normal evaluation. Two large trials that evaluated the results of screening colonoscopy were instrumental in its adoption as the preferred CRC screening and prevention test. The first was the Veterans Affairs Cooperative Study Group 380 trial by Lieberman and colleagues, in which screening colonoscopies in asymptomatic individuals found that if examination was limited to the distal colon (junction between the descending and sigmoid colon), only 31.9%

of advanced neoplasia would have been detected.[43] The second was the CONCeRN trial by Schoenfeld and colleagues.[44] This trial mimicked the Veterans Affairs Cooperative Study Group 380 trial, but with a 100% female population. Similarly, the study found that if FS alone was performed, then 65% of advanced neoplasia would have been undetected.

Screening colonoscopy has been shown to reduce rates of CRC-related adverse outcomes. A retrospective cohort study showed there is 46% and 95% reduced risk of CRC and CRC-related deaths, respectively, up to 12 years after a negative colonoscopy.[45] Another observational cohort study demonstrated a hazard ratio (HR) for CRC mortality of 0.32 (95% CI, 0.24-0.45) with colonoscopy vs no colonoscopy over 24 years, with better results observed for distal cancers (HR, 0.18; 95% CI, 0.10-0.31) than for proximal cancers (HR, 0.47; 95% CI, 0.29-0.76).[46]

Methylated Septin 9

Methylated septin 9 (mSEPT9) is a US Food and Drug Administration–approved blood-based CRC screening test.[47] SEPT9 is part of a group of GTP-binding proteins, and methylation of SEPT9 is associated with tumorigenesis and is a biomarker for CRC. However, detection of CRC with mSEPT9 is skewed toward advanced-stage neoplasia, so its use as a screening test for asymptomatic average-risk individuals has been questioned, and the USMSTF guidelines recommend against the use of mSEPT9 for this indication. Studies show a sensitivity of 48% for the detection of CRC and 11% for the detection of advanced adenoma with mSEPT9.[38,47]

Emerging Colorectal Cancer Screening Tests

Early detection of CRC has been shown to decrease cancer-related mortality by 33% to 60%.[48] However, CRC screening compliance among eligible patients remains below the 80% goal for the population established more than a decade ago,[1] highlighting the need for additional accurate CRC screening test options that are acceptable to patients and scalable to population screening. Over the past decade, there have been numerous important and promising advances, including the emergence of new screening tests and refinement of existing technology to improve the identification of colonic neoplasia. Advances in proteomics, genomics, and metabolomics are also leading to promising developments that may impact CRC screening in the future. Multiple companies and investigators are evaluating noninvasive tests using serum biomarkers (liquid biopsies) for colorectal neoplasia. These novel CRC screening test platforms are based on neoplasia-derived components such as circulating tumor cells, circulating tumor DNA (ctDNA), or protein markers that are isolated and amplified from peripheral blood (Table 3). These novel methods have broad potential not only for CRC screening but also for long-term monitoring and surveillance, prognostication of outcomes, and determination of adjunctive therapies for patients diagnosed with CRC. Currently, there are multiple ongoing trials evaluating the performance characteristics of different platforms and assays to detect circulating biomarkers for CRC and advanced adenomas in average-risk individuals. PREEMPT CRC is a prospective, multicenter study evaluating the performance of Freenome's novel blood test and comparing it with mSEPT9.[49] Preliminary data from this trial show high sensitivity and specificity of the novel blood test for detecting early-stage CRC using a combination of tumor- and immune-derived markers. Similarly, the ongoing BLUE-C trial by Exact Sciences is evaluating a blood-based CRC screening test,[50] and Guardant Health is sponsoring the ECLIPSE study[51] to establish the performance characteristics of its liquid biopsy test.

Table 3. Emerging Noninvasive CRC Screening Tests

Blood Test Developer	Biomarker Target(s)	Clinical Study
Freenome	cfDNA + protein	PREEMPT CRC
Guardant Health	ctDNA	ECLIPSE
Exact Sciences	ctDNA	BLUE-C

cfDNA, cell-free DNA; CRC, colorectal cancer; ctDNA, circulating tumor DNA.

Another novel CRC screening approach involves using volatile organic compound (VOC) detection as noninvasive target biomarkers for CRC screening. VOCs are the final product of cell metabolism and are excreted in feces, urine, and saliva; exhaled in the breath; and secreted into the blood. The presence of colonic neoplasia has been associated with changes in the microbiome and cellular metabolism, which can alter VOC production. Increasing knowledge surrounding the detection and classification of VOCs may be useful in screening modalities in the future.[52] More studies of these emerging technologies as CRC screening tests in diverse populations are needed to ensure the reliability and reproducibility of their promising preliminary data.

Finally, advances in computer science techniques such as artificial intelligence (AI), modeling, and clinical decision support are propelling encouraging research with CRC screening implications. AI has already significantly impacted multiple medical fields, and AI-augmented radiography, endoscopy, and capsule endoscopy have all been shown to improve gastrointestinal neoplasia detection.

AI-assisted colonoscopy is now commercially available and is intended to enhance CRC screening by aiding in the detection and possibly the characterization of colorectal neoplasia.[53] AI is also being explored in the realm of noninvasive testing such as triaging patients based on demographics and laboratory values to determine their risk of CRC development.[54] As researchers strive to optimize the reach and performance of CRC screening tests, factors such as test generalizability, patient compliance, testing intervals, and cost-effectiveness of new modalities will require additional study, and personalized and patient-centered care will likely be further emphasized as CRC screening options increase.

Conclusion

The incidence and mortality associated with CRC has decreased over the past 4 decades, owing largely to increased CRC screening implementation. Improvements in testing options and improved and mandated financial coverage for CRC screening have also played a major role in these outcomes. In addition, rates of CRC are increasing in younger populations, and this observation has led to new guideline recommendations to initiate screening at 45 years of age. This recommendation will undoubtedly increase demand for CRC screening that may exceed readily available resources for definitive colorectal neoplasia detection and management. Currently available and recommended screening tests have been well studied, but additional advances of highly accurate, noninvasive, and acceptable CRC screening tests are needed to improve detection and prevention of this disease. Further, continued efforts to raise awareness and decrease barriers to screening by clinicians and policymakers remain critically important.

Disclosures

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