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ARTICLE

Colorectal cancer screening: An update to the American Cancer Society guideline, 2026

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ABSTRACT

Colorectal cancer (CRC) is a leading cause of cancer incidence and mortality in the United States, with rates recently increasing among adults younger than 65 years. In 2018, the American Cancer Society (ACS) lowered the recommended age to initiate screening for average-risk adults to age 45 years. Since then, new molecular-based screening tests—a multitarget stool RNA test (mt-sRNA), a next-generation

mt-sDNA test, and a blood-based cell-free DNA assay—have received regulatory approval for CRC screening. For this update, the ACS Guideline Development Group commissioned a targeted, systematic evidence review evaluating diagnostic performance and published modeling studies to judge the potential impact of these tests on CRC incidence and mortality. The ACS reaffirms the recommendation that average-risk adults should initiate CRC screening at age 45 years and continue through age 75 years for those with a life expectancy greater than 10 years. Consistent with prior guidelines, the ACS emphasizes that offering multiple, recommended screening options supports informed patient choice and may improve participation, because the most effective screening test is the one that the patient completes. The next-generation mt-sDNA test, which is an updated version of an already recommended mt-sDNA test, and the mt-sRNA test demonstrated high sensitivity for CRC and moderate sensitivity for advanced precancerous lesions and are recommended, along with annual high-sensitivity fecal immunochemical and high-sensitivity guaiac-based fecal occult blood tests, as preferred stool-based screening options at 3-year intervals. Compared with established stool-based tests, blood-based tests demonstrated lower sensitivity for both advanced precancerous lesions and stage I cancers, with modeling studies predicting less effectiveness in reducing CRC incidence and mortality. At this time, blood-based tests should be recommended only to individuals who decline or do not complete preferred screening tests. Ongoing evaluation of adherence, real-world implementation, and clinical outcomes will inform future updates for these new tests. For screening to be effective, a positive result on any noncolonoscopy screening test requires timely follow-up with colonoscopy, preferably within 6 months, to complete the screening process.

KEYWORDS
blood-based screening tests, colorectal cancer, epidemiology, multitarget stool RNA (mt-sRNA), public health, screening and early detection

INTRODUCTION

Colorectal cancer (CRC) is a major public health burden; it is the third most frequently diagnosed cancer among adults in the United States and the second leading cause of cancer death.[1] In 2026, CRC is estimated to account for 158,850 new cancer diagnoses and approximately 55,000 deaths.[1] The American Cancer Society (ACS) has a long-standing history of championing screening to reduce CRC incidence and mortality. The ACS first issued formal guidelines for CRC screening in 1980,[2] initially emphasizing digital rectal examination, guaiac-based fecal occult blood testing (gFOBT), and sigmoidoscopy. The ACS subsequently expanded recommendations to include additional screening options: colonoscopy, computed tomography colonography, and newer stool-based tests. Over time, ACS screening guidelines have evolved to reflect advances in screening technology, growing evidence on test performance and utilization in clinical practice, and an increasing emphasis on patient-centered decision-making around screening options.[3–8] This evolution has been guided by the tenet that offering multiple, high-quality screening options can improve screening uptake because the most effective screening test is the one that the patient completes.[9,10]

CRC incidence and mortality rates have steadily declined in the United States over the past several decades, largely attributable to improvements in screening, early detection, and treatment. However, overall declines in incidence mask increasing rates from 2013 to 2022 in those under younger than 50 years (3% increase per year) and aged 50–64 years (0.4% increase per year), largely because of increasing numbers of distal colon and rectal tumors.[11] After decades of decline, rectal cancer incidence increased by 1% per year from 2018 to 2022, now accounting for nearly one third of all CRC cases. Epidemiologic analyses indicate a birth-cohort effect underlying the rising incidence of CRC in younger adults, with successive generations born since 1950 demonstrating higher risk at earlier ages than preceding cohorts.[12] The birth-cohort effect appears to be multifactorial in origin; perinatal and early life exposures, diet, exercise, tobacco and alcohol use, antibiotic exposures, and metabolic syndrome have all been hypothesized to cause carcinogenic changes in the gut microbiome.[13] Consequently, among US adults younger than

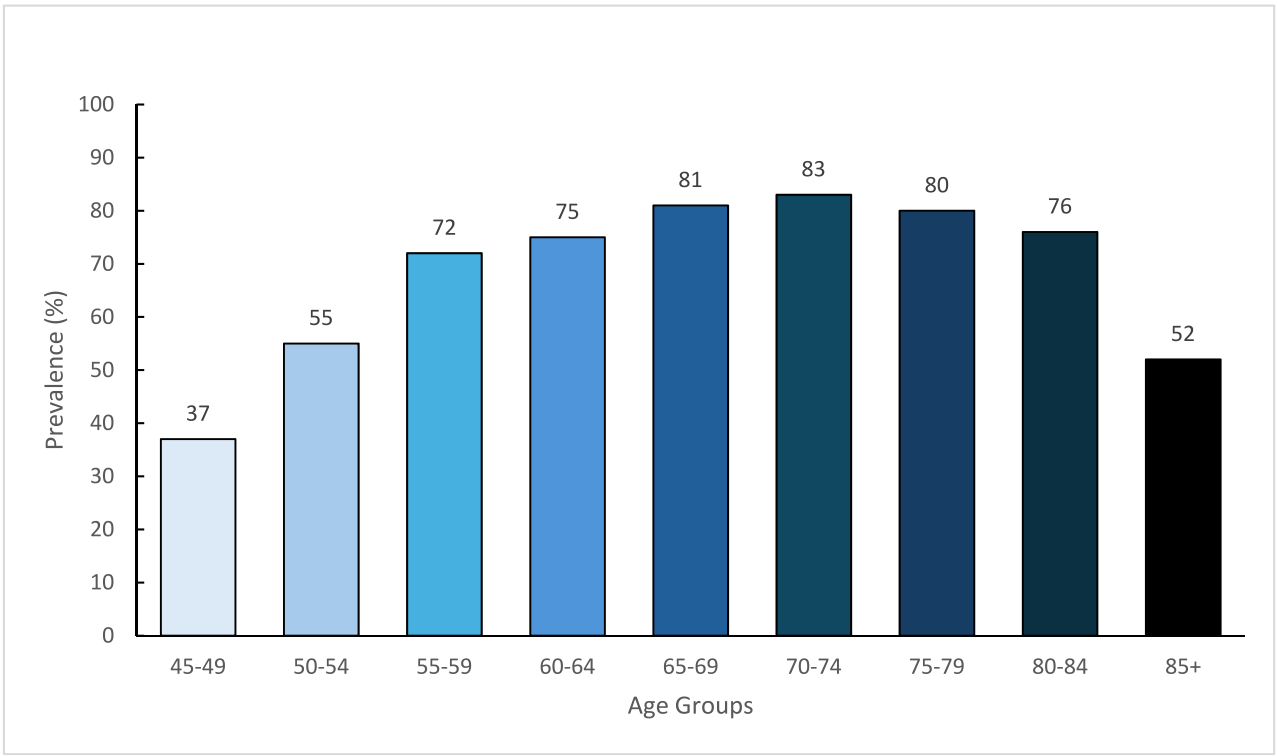

FIGURE 1 Colorectal cancer screening (%). Adults 45 years and older, by age, United States, 2023 estimates stratified by age are presented crude. Up-to-date colorectal cancer screening is defined as a fecal occult blood test/fecal immunochemical test, sigmoidoscopy, colonoscopy, computed tomography colonography, or mt-sDNA test in the past 1, 5, 10, 5, and 3 years, respectively. *Source*: National Health Interview Survey, 2023.

50 years, CRC is now the leading cause of cancer death among men and the second leading cause among women.[14]

US data also show substantial racial and ethnic disparities in CRC incidence and mortality. Age-adjusted CRC incidence rates are estimated to be 11% higher among Black individuals, and their mortality rates are about 40% higher compared with White individuals. American Indian and Alaska Native populations have the highest burden, with incidence rates 48% higher and mortality rates about 44% higher than Whites. Alaska Native people, in particular, have the highest incidence and mortality rates: more than double the rates observed among White populations in the United States.[11]

These epidemiologic trends underscore the importance of both initiating screening before age 50 years and having acceptable, accessible, and effective screening options. Recent data show that the prevalence of adults aged 50 years and older who self-reported being up to date with recommended CRC screening increased substantially from approximately 38% in 2000 to 72% in 2023.[15] The prevalence of up-to-date screening was comparable between White (67%) and Black (66%) individuals but was lower among Hispanic (56%), Asian (58%), and American Indian or Alaska Native (59%) individuals. Lack of insurance and lower socioeconomic status are also associated with a lower screening prevalence.[15] Importantly, given the birth-cohort effect, participation remains much lower among younger eligible adults. In 2023, only 37% of those aged 45–49 years and 55% of those aged 50–54 years reported being up to date with ACS recommended CRC screening (Figure 1). However, self-reported data on screening uptake are misleading because of overreporting of recent screening, lack of regular adherence to screening over time, and noncompletion of follow-up colonoscopy among respondents with a positive noncolonoscopy screening test.[16]

The principal goals of CRC screening are to reduce population-level CRC incidence and mortality through detecting and removing advanced precancerous lesions (APLs) and through detecting early stage cancers. Progress in achieving these goals has not been uniform across the US population, particularly given the worrisome trends for younger adults and racial and ethnic disparities. The most recent, comprehensive update of the ACS CRC screening guideline, published in 2018, represented a pivotal shift in national screening policy.[8] In response to rising CRC incidence among younger adults, the guideline lowered the recommended age to initiate screening for average-risk individuals from 50 years to 45 years.[17] The 2018 guideline reaffirmed the previously recommended screening strategies, including stool-based tests with a high sensitivity for detecting CRC (high-sensitivity gFOBT, high-sensitivity fecal immunochemical test [FIT], and multitarget stool DNA [mt-sDNA]) as well as visual examinations (colonoscopy, computed tomography colonography [CTC], and flexible sigmoidoscopy). The guideline emphasized that there is no single preferred test for all individuals, instead

recommending that individuals be offered the choice between a stool-based test or a direct visual examination. This underscores the expectation that screening uptake can be maximized when individuals can select a recommended option that aligns with their values, preferences, and care access.[8]

The landscape of CRC screening has changed since the last ACS guideline publication. The most notable developments have been advances in molecular biology, genomics, and biomarker discovery, leading to the emergence of a multi-target stool RNA (mt-sRNA) test and blood-based screening assays for CRC.[18–20] The mt-sRNA test (ColoSense; Genoscopy, Inc.) test uses an algorithm based on a combination of RNA transcripts, participant-reported smoking status, and a commercially available FIT to identify persons at higher risk for colonic neoplasia. This provides average-risk individuals with an additional option for multitarget stool-based testing.[18] The mt-sRNA test has been evaluated in a large prospective validation study and received US Food and Drug Administration (FDA) regulatory approval in 2024 for screening average-risk individuals.[21] In parallel, two blood-based tests, including the Guardant Shield circulating cell-free DNA methylation assay (Guardant Health) and the Freenome multiomics blood test (SimpleScreen; Freenome Holdings, Inc.), have been evaluated in large, prospective, diagnostic validation studies. The Guardant Shield test has received both FDA regulatory approval and a Centers for Medicare & Medicaid Services (CMS) coverage determination in 2024 for screening average-risk individuals.[22–25] At the time of this writing (May 2026), the Freenome SimpleScreen test had only recently been submitted to the FDA for review. These tests represent a broader shift in cancer screening toward minimally invasive approaches that may improve acceptability and adherence, particularly for individuals who decline or do not complete established stool-based testing or direct visual examinations.[26–28]

The introduction of new screening modalities raises critical issues for population-level screening guidelines. Blood-based and stool-based molecular tests differ in their sensitivity for early stage cancer and APL, in their specificity for nonadvanced lesions, and in the availability of real-world data on optimal screening intervals, clinical utilization, and outcomes. Importantly, whereas increasing screening participation is a crucial step for a successful screening program, screening tests must be evaluated not only on their acceptability but also on their ability to meaningfully reduce CRC incidence and mortality through prevention and timely detection of early stage disease.

The purpose of this guideline update is to review current evidence for the newly available mt-sRNA test (ColoSense) and two blood-based CRC screening tests (Guardant Shield and Freenome SimpleScreen) and to define their role in relationship to the stool-based and visual examinations previously recommended by the ACS CRC screening guideline. This update also presents an overview of the evidence for an updated version (next-generation mt-sDNA [ng-mt-sDNA]; Cologuard Plus; Exact Sciences Corporation [now Abbott Cancer Diagnostics]) of the currently recommended mt-sDNA test.

As with previous ACS guidelines updates, decisions regarding the inclusion of new tests are grounded in a comprehensive assessment of disease burden, test performance, the balance of benefits and harms, certainty of evidence, feasibility of implementation, follow-up requirements, patient-centered care, and the potential impact on screening participation and equity. The overarching aim is to inform whether, and under what circumstances, the new mt-sRNA test and the blood-based tests may appropriately be added to or complement established modalities.

Below, we present the ACS Guideline Development Group's (GDG) evaluation of the evidence and provide recommendations for using the new tests. These recommendations apply to average-risk, asymptomatic individuals aged 45 years and older who are initiating CRC screening or have had consistently normal screening results in the past. The ACS screening recommendations do not apply to individuals at increased risk for developing CRC, including individuals with a personal history of CRC, adenomatous or sessile serrated polyps, or inflammatory bowel disease; a family history of first-degree relatives with CRC or advanced adenomas, particularly diagnosed before age 60 years; a confirmed or suspected hereditary CRC syndrome; or a history of abdominal or pelvic radiation for a previous cancer.

MATERIALS AND METHODS

The ACS cancer screening guidelines are developed and updated by the GDG, a multidisciplinary volunteer panel of clinicians, methodologists, public health experts, and patient representatives. The development process for the ACS cancer screening guidelines and the operation of the GDG are described in detail elsewhere.[8,29] Briefly, the update included a targeted, systematic evidence review relevant to the new CRC screening tests; a review of published microsimulation models; deliberation by the GDG; and a transparent process for disclosure and management of potential conflicts of interest.

In response to FDA approval of the Guardant Shield blood-based test and the ColoSense mt-sRNA, the GDG requested a systematic review by the ACS Cancer-related Evidence Synthesis Team (CrEST) to evaluate the benefits, harms, and diagnostic accuracy of the blood-based and mt-sRNA screening tests. The GDG and ACS Guideline Development staff worked with the CrEST investigators to develop specific key questions relevant to the scope of the update and to define the populations, interventions, comparators, outcomes, timing, and settings for each question. The scope of the review was limited to interventions and outcomes relevant to average-risk CRC screening populations. The systematic evidence review was conducted independently by the CrEST, and the methods and results of the evidence review are reported in a separate publication.[30]

The GDG is responsible for evaluating and interpreting the evidence, formulating and voting on recommendations and their strength, and authoring the guideline. To promote efficient and effective use of volunteer time, GDG members participate in

guideline-specific workgroups consisting of a minimum of five members. The GDG CRC workgroup had primary responsibility for reviewing and deliberating upon the evidence on the new screening technologies, drafting recommendations for updating the guideline, and presenting to the entire GDG for review, discussion, voting, and final approval of the updated guideline. The GDG explicitly considered the relationship between screening test performance, downstream diagnostic evaluation, and health outcomes.

Findings from the evidence review were presented to the CRC workgroup, whose deliberative process considered the new tests in the context of established CRC screening modalities and the overarching ACS approach of offering multiple high-quality options to increase screening participation and reduce the burden of CRC. The GDG CRC workgroup members served as the writing committee and worked in collaboration with the ACS Guideline Development staff, who served as guideline methodologists, provided administrative support to the GDG, contributed expertise in cancer screening, CRC, and evidence evaluation, and participated in preparing the article. However, ACS staff did not formulate recommendations nor vote on approval of the final guideline update.

The draft guideline update was presented to the full GDG for review, discussion, and voting on the proposed amendments to the CRC screening recommendations. After obtaining GDG approval, the draft underwent external review by four expert advisors to the GDG. The recommendations and rationale statements were shared with 10 relevant outside organizations, representing both professional and patient-oriented stakeholders. The CRC GDG workgroup documented and reviewed responses from both groups and determined whether modifications in the recommendations or narrative were warranted. The GDG subsequently reviewed and approved the revised narrative of the guideline update before submission for publication.

The recommendations were reviewed by the ACS Chief Scientific Officer and the ACS Science and Technology Committee for feedback and were subsequently presented to the ACS Board before publication. Guideline development is supported by ACS general operating funds.

ACS guidelines and conflicts of interest

All participants in the guideline development process, including GDG members and external advisors, are required to disclose all financial and nonfinancial (including personal, intellectual, and practice-related) relationships and activities that could be perceived as potential conflicts of interest in developing cancer screening and related guidelines (see Supporting Materials).[29] Disclosures, including those from ACS staff and GDG members, are made available to all committee members for review. The chairperson of the ACS GDG and the CRC screening workgroup was responsible for ensuring that balanced perspectives were considered during discussions and decision-making. GDG members with relevant conflicts of interest were recused from voting on approval of the recommendations.

RECOMMENDATIONS AND RATIONALE

The ACS reaffirms the CRC screening recommendations established in the 2018 guideline (Table 1). *The ACS recommends that adults aged 45 years and older with an average risk of developing CRC undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability.* For screening to be effective, a positive result on any noncolonoscopy screening test requires a timely follow-up colonoscopy to complete the screening process, preferably within 6 months of the initial test.[31–33] The 2026 update adds a new preferred test to the choice of stool-based testing (mt-sRNA) and presents guidance on offering blood-based CRC screening tests. *Blood-based screening tests are not preferred screening options at this time; they should be recommended only to individuals who decline or have not completed a preferred CRC screening test.* Blood-based screening tests are not preferred primarily because of lower sensitivity for APL and stage I CRC (although confidence intervals [CIs] for the latter estimate are wide) and uncertainty regarding optimal screening intervals for long-term effectiveness (see Table 2). Patients should be informed that, if a blood-based screening test is positive, they will need to undergo a timely follow-up colonoscopy to complete the screening process.

Multitarget stool RNA test

The primary evidence for the effectiveness of mt-sRNA is derived from CRC-PREVENT, a large, prospective, cross-sectional study examining the test's accuracy in detecting CRC and advanced adenoma (AA) compared with a FIT test (OC-Auto FIT; Polymedco; ClinicalTrials.gov identifier NT04739722).[18] The mt-sRNA test uses an algorithm to combine results from eight RNA biomarkers and a commercially available FIT test (OC-Auto) along with smoking status to determine a positive or negative result.

Barnell and colleagues evaluated an mt-sRNA test for CRC screening in adults undergoing screening colonoscopy as the reference standard. Of 14,263 enrolled participants, 8920 comprised the validation cohort; 6.5% reported a first-degree family history of CRC. In the validation cohort, sensitivity for CRC was 94.4% for mt-sRNA compared with 77.8% for the FIT component alone, including 100% sensitivity for stage I disease versus 71.4%, respectively. Sensitivity for AA (defined as high-grade dysplasia, adenomas ≥10 mm, tubular or traditional sessile serrated adenomas ≥10 mm, and any adenomas with villous histology) was 45.9% for mt-sRNA versus 28.9% for the FIT component. Overall specificity among individuals without advanced colorectal neoplasia (CRC or APLs) was 85.5% for mt-sRNA versus 95% for the FIT component.[18]

A distinguishing feature of the mt-sRNA test is incorporating self-reported smoking status into the diagnostic algorithm. The investigators included smoking status to improve calibration of the model and optimize specificity, but it had only a small effect on overall accuracy. Because there is a known association between smoking and colorectal neoplasia,[32] including smoking status as a

covariate may enhance test performance in those with a history of tobacco use. Because mt-sRNA is the first cancer screening test to incorporate a patient-reported risk factor into the screening assay itself, postmarketing evaluation will be needed to determine whether this affects test performance in real-world settings (e.g., smoking status not reported or reported inaccurately).

In direct comparison with its FIT component, mt-sRNA demonstrated greater test sensitivity for CRC and AA but lower specificity.[18] However, these comparisons can be misleading because they do not account for differences in the recommended screening intervals—annual for FIT and triennial for mt-sRNA. Repeated FIT testing over multiple screening rounds will increase the cumulative advanced colorectal neoplasia detection rate compared with a single round of FIT testing.[33] In the absence of direct comparative studies with mt-sDNA, available evidence suggests that mt-sRNA has comparable sensitivity for detecting CRC and AA. However, its specificity

TABLE 1 American Cancer Society guideline for colorectal cancer screening, 2026 update.

Recommendations[a]

The American Cancer Society (ACS) recommends that adults aged 45 years and older with an average risk[b] of developing colorectal cancer undergo regular screening with either a high-sensitivity stool-based test or a structural (visual) examination, depending on patient preference and test availability. Blood-based screening tests are recommended only for individuals who decline or have not completed a high-sensitivity stool-based test or a structural (visual) exam.

Patients should be informed that a positive result on a noncolonoscopy screening test requires timely follow-up with a colonoscopy to complete the screening process.

The recommendation to begin screening at age 45 years is a *qualified recommendation*.

The recommendation for regular screening in adults aged 50 years and older is a *strong recommendation*.

The ACS recommends that average-risk adults in good health with a life expectancy of greater than 10 years continue colorectal cancer screening through the age of 75 years (*qualified recommendation*).

The ACS recommends that clinicians individualize colorectal cancer screening decisions for individuals aged 76 through 85 years, based on patient preferences, life expectancy, health status, and prior screening history (*qualified recommendation*).

The ACS recommends that clinicians discourage individuals older than 85 years from continuing colorectal cancer screening (*qualified recommendation*).

Preferred screening options

Stool-based tests:

- High-sensitivity fecal immunochemical test every year
- High-sensitivity guaiac-based fecal occult blood test every year
- Multitarget stool DNA test (original or next-generation) every 3 years
- Multitarget stool RNA test every 3 years

Direct visual examinations:

- Colonoscopy every 10 years
- Computed tomography colonography every 5 years
- Flexible sigmoidoscopy every 5 years

Recommendation for blood-based colorectal cancer screening

Blood-based screening tests are not preferred screening options at this time; they should be recommended only to individuals who decline or have not completed one of the preferred colorectal cancer screening tests.

- Blood-based tests should not be ordered without prior discussion with the patient.
- Patients who choose a blood-based test should be informed that:
  - Blood-based tests have lower sensitivity than high-sensitivity stool-based tests and direct visual examinations in detecting advanced precancerous lesions and stage I colorectal cancers, limiting their effectiveness for reducing colorectal cancer incidence and mortality relative to the preferred options (see Table 2).
  - If their blood-based test is positive, patients will need to undergo a follow-up colonoscopy to complete the screening process.
  - Manufacturers have not specified a recommended testing interval; however, the Centers for Medicare and Medicaid Services specifies a 3-year interval for Medicare beneficiaries.

[a]A strong recommendation conveys the consensus that the benefits of adherence to that intervention outweigh the undesirable effects that may result from screening. Qualified recommendations indicate there is clear evidence of benefit (or harm) of screening but less certainty about the balance of benefits and harms or about patients' values and preferences that could lead to different decisions about screening.

[b]These recommendations represent guidance from the ACS for persons without a history of adenomatous polyps or colorectal cancer and those who are not at increased risk for colorectal cancer because of a strong family history of colorectal cancer, a confirmed or suspected hereditary colorectal cancer syndrome (such as familial adenomatous polyposis or Lynch syndrome), or a personal history of inflammatory bowel disease or of receiving radiation to the abdomen (belly) or pelvic area to treat a prior cancer.

TABLE 2 Considerations in choosing a colorectal cancer screening test.[a]

Screening test	Recommended screening interval	Evidence of effectiveness and test performance	Limitations	Patient considerations	Cost and reimbursement
Stool-based screening tests					
FIT with high sensitivity for cancer	Annual	• Indirect evidence of CRC incidence and mortality reductions from RCTs of gFOBT • Equivalent or better performance compared with high-sensitivity gFOBT • FIT sensitivity varies substantially by assay and hemoglobin detection threshold.	• Low adherence to repeat annual testing in absence of reminder systems • One-time testing is less effective than mt-sDNA for detecting APL. • Few available FIT tests have published peer-reviewed performance data.	• Done at home. • Most brands require only a single sample. • No diet or medication restrictions • Positive test requires follow-up colonoscopy.	• Inexpensive compared with visual examinations, mt-sDNA, mt-sRNA, and blood tests
gFOBT with high sensitivity for cancer	Annual	• RCT evidence for CRC incidence and mortality reductions with lower sensitivity gFOBT • Low-sensitivity gFOBT versions are not recommended because of poor performance.	• Low adherence to annual testing in absence of reminder systems • One-time testing is less effective than mt-sDNA for detecting APL. • Difficulty in ascertaining diagnostic test performance among the FDA-cleared tests	• Done at home. • Requires multiple samples • Requires dietary and medication restrictions • Positive test requires follow-up colonoscopy.	• Inexpensive compared with visual examinations, mt-sDNA, mt-sRNA, and blood tests
mt-sDNA (original and next-generation)	Every 3 years (according to manufacturer)	• Indirect evidence of CRC incidence and mortality reductions from RCTs of gFOBT • Higher sensitivity for cancer and APLs compared with FIT • Lower specificity for ACN compared with FIT		• Done at home. • Higher likelihood of needing follow-up colonoscopy than with FIT because of lower specificity • Positive test requires follow-up colonoscopy.	• More expensive than FIT and gFOBT
mt-sRNA	Every 3 years	• Indirect evidence of CRC mortality and incidence reductions from RCTs of gFOBT	• New test with limited data on screening outcomes; performance needs to be monitored over time • Self-reported smoking history required for prediction model	• Done at home. • Higher likelihood of needing follow-up colonoscopy than with FIT	• More expensive than FIT and gFOBT • CMS coverage determination

(Continues)

TABLE 2 (Continued)

Screening test	Recommended screening interval	Evidence of effectiveness and test performance	Limitations	Patient considerations	Cost and reimbursement
		• Higher sensitivity for cancer and APLs compared with FIT • Lower specificity for ACN compared with FIT		because of lower specificity • Positive test requires follow-up colonoscopy.	pending at time of publication
Structural (visual) examinations for screening					
Colonoscopy	Every 10 years	• There is only observational evidence of CRC mortality reduction. • Extrapolation from RCTs of sigmoidoscopy demonstrating mortality and incidence reductions • Offers both early CRC detection and prevention (through polypectomy)	• Risk of bowel perforation/bleeding and cardiopulmonary complications of anesthesia. • Performance quality depends on adequacy of bowel preparation and endoscopist factors, including cecal intubation rate, withdrawal time, and adenoma detection rate. • Limited performance quality data available in many settings • Surveillance colonoscopy has marginal clinical benefit for patients with low-risk polyps.	• Requires full bowel cleansing • Requires time off work and a chaperone (sedation is used)	• Expensive test but currently reimbursable for those with insurance coverage • Polypectomy and anesthesia may incur out-of-pocket costs.
Computed tomographic colonography	Every 5 years	• Extrapolation from RCTs of sigmoidoscopy demonstrating CRC mortality and incidence reductions • Sensitivity and specificity for ACN comparable to colonoscopy	• Incidental extracolonic findings may require work-up, with unclear benefit-burden balance. • Exposure to low-dose radiation	• Requires full bowel cleansing • Positive test requires follow-up colonoscopy. • Positive test requires two separate bowel cleansings if diagnostic colonoscopy not immediately available.	• Relatively expensive and may not be covered by insurance (not routinely covered by Medicare at this time)

TABLE 2 (Continued)

Screening test	Recommended screening interval	Evidence of effectiveness and test performance	Limitations	Patient considerations	Cost and reimbursement
				• Not widely performed	
Flexible sigmoidoscopy	Every 5 years	• RCT evidence for CRC mortality and incidence reductions	• Does not examine the proximal colon • Concerns about lack of quality standards, limited availability, failure to achieve a complete examination	• Pain and discomfort • Requires enema before procedure • Positive test requires follow-up colonoscopy. • Not widely performed	
Blood-based tests					
Cell-free DNA blood tests[b]	Every 3 years (CMS coverage for Guardant Shield)	• Prospective cross-sectional validation with colonoscopy reference standard • Good sensitivity for CRC detection, lower than for mt-sDNA test • Fair to good specificity for ACN, lower than for stool-based tests	• Very low sensitivity for APLs • Lower sensitivity for stage I cancers than for later stage cancers • Optimal testing interval not established • Real-world adherence to repeat testing and diagnostic follow-up unknown • Reduction in overall CRC mortality expected to be substantially lower than for colonoscopy or stool-based screening tests • Specificity for ACN declines with age, which may lead to more colonoscopies in older adults.	• Simple blood draw in clinic or laboratory • May be preferred by individuals unwilling to complete stool tests or structural tests • Positive test requires follow-up colonoscopy.	• Guardant Shield covered by CMS; coverage status pending for Freenome SimpleScreen • More expensive than stool-based tests

Abbreviations: ACN, advanced colorectal neoplasia; APLs, advanced precancerous lesions; CMS, Centers for Medicare & Medicaid Services; CRC, colorectal cancer; FDA, US Food and Drug Administration; FIT, fecal immunochemical test; gFOBT, guaiac fecal occult blood test; mt-sDNA, multitarget stool DNA; ng-mt-sDNA, next-generation multitarget stool DNA; RCT, randomized controlled trial.

[a]The American Cancer Society considers these options as acceptable choices for CRC screening in average-risk adults. Individuals should be given information on the characteristics related to prevention potential, effectiveness, accuracy, costs, and potential harms of available and accessible tests to make an informed decision about which test to choose for CRC screening. All positive noncolonoscopy screening tests should be followed with timely colonoscopy as a part of the screening process. Follow-up with a noncolonoscopy test is not acceptable.

[b]Shield by Guardant Health (approved by the FDA); SimpleScreen by Freenome Holdings, Inc. (pending FDA approval).

for the absence of advanced colorectal neoplasia is lower than that of ng-mt-sDNA (85.5% vs. 90.6%, respectively).[34]

Several microsimulation modeling studies have examined the effectiveness and benefit–burden trade-offs of screening strategies that incorporate mt-sRNA testing. By using the CRC-AIM (Colorectal Cancer and Adenoma Incidence and Mortality) microsimulation model, Ebner and colleagues simulated a cohort of one million average-risk individuals followed over a lifetime of CRC screening between ages 45 and 75 years.[35] Benefits were quantified as life-years gained and quality-adjusted life-years (QALYs) gained, whereas surrogate measures of burden included the number of colonoscopies performed, total patient time required, and the number of stool-based or blood-based screening tests administered for each strategy. QALY calculations weighed life-years gained by health utility losses of various health states throughout an individual's lifespan, including utility losses (harms) associated with initial screening; colonoscopy complications, such as perforation, bleeding, and cardiovascular complications of anesthesia; and cancer stage and treatment by phase of care. Meester and colleagues used the COSMOS-CRC (the Comprehensive Cancer Simulation Model of Screening for Colorectal Cancer) to model a cohort of 1000 average-risk individuals who start screening at age 45 years and stop at age 75 years.[36] Benefits were lifetime CRC cases and deaths averted, as well as life-years gained; burdens included the total number of required screening tests and harms related to colonoscopy complications. In these modeling studies, triennial mt-sRNA screening was projected to reduce CRC incidence and mortality to a degree comparable to that of other stool-based strategies under assumptions of similar adherence. However, mt-sRNA strategies were not as consistently effective as other screening options relative to the number of colonoscopies required, meaning that they provided fewer life-years gained for an equal or greater number of lifetime colonoscopies. This was largely because of increased colonoscopy burden associated with the roughly 5-percentage-point lower specificity.

The GDG concluded that the mt-sRNA test demonstrated high sensitivity for CRC and moderate sensitivity for APL. The GDG acknowledged that, once randomized controlled trials confirmed the efficacy of gFOBT-based CRC screening to reduce both incidence and mortality from CRC,[37] stool-test developers have pragmatically relied on cross-sectional diagnostic performance studies to evaluate new screening tests. These studies typically assess the ability of the tests to detect APL and CRC in screening populations, with colonoscopy used as the confirmatory reference standard. Thus, the GDG relied on evidence-based, inferential reasoning informed by the gFOBT randomized controlled trial data to evaluate the mt-sRNA test given the programmatic similarities among stool-based screening tests that require colonoscopy follow-up after abnormal results.[37]

One important uncertainty regarding mt-sRNA testing is the optimal screening interval; new tests lack real-world and clinical study data evaluating test performance, adherence, and clinical outcomes across repeated screening rounds. The microsimulation modeling studies reviewed for this update indicated that a 3-year screening interval for mt-sRNA achieved reductions in CRC incidence and mortality that were comparable to those observed with the ng-mt-sDNA test.[35,36] These modeling assumptions are consistent with the conclusions from the CRC-PREVENT study, which support a 3-year interval, mirroring the interval recommended for the original and ng-mt-sDNA tests.[18] However, at the time of this guideline update (May 2026), CMS has not issued a coverage determination for mt-sRNA testing.

In its deliberations about mt-sRNA, the GDG considered both the clinical diagnostic performance data and the modeling data. The systematic evidence review rated the overall strength of evidence as low, reflecting limitations related to enrollment, study design characteristics of the primary validation study, and the inability to determine consistency of results (currently, there is only one published study).[30] The GDG acknowledged that the specificity of mt-sRNA testing is lower than that of ng-mt-sDNA testing but comparable to that reported for the original mt-sDNA assay.[38] Lower specificity translates to more colonoscopies done in the follow-up of positive results. The GDG determined that the totality of evidence indicates that mt-sRNA testing has the potential to achieve the key outcomes of reducing CRC incidence and mortality when used within a screening program that includes appropriate diagnostic follow-up. Based on this assessment, the GDG concluded that the anticipated benefits of mt-sRNA testing outweigh its limitations and thus recommends it as a preferred triennial, stool-based option for CRC screening.

Next-generation multitarget stool DNA test

In 2024, the FDA approved an ng-mt-sDNA test (Cologuard Plus) developed by the same manufacturer (Exact Sciences Corporation; now Abbott Cancer Diagnostics) as the original mt-sDNA assay recommended in the 2018 ACS guideline. The ng-mt-sDNA test replaces the original assay's DNA methylation markers with a revised marker set designed to improve specificity while preserving high sensitivity for CRC detection. Both assays incorporate FIT as one component of the multitarget platform. Because ng-mt-sDNA testing represents an iteration of an established screening test, it was not included in the systematic evidence review conducted by the ACS CrEST. However, the GDG determined that it was important to include evidence about the ng-mt-sDNA test in the updated guideline.

The primary evidence supporting the ng-mt-sDNA test derives from the BLUE-C study, a prospective, cross-sectional cohort study conducted from 2019 to 2023 at 186 US sites (ClinicalTrials.gov identifier NCT04144738).[34] The study evaluated test accuracy for the ng-mt-sDNA test compared with FIT (OC-Auto FIT) among individuals aged 40 years and older undergoing screening colonoscopy, including average-risk individuals and those with a family history of CRC in one first-degree relative. Of the 26,758 participants enrolled, 20,176 comprised the validation cohort; 5.2% reported a family history of CRC. In the validation cohort, sensitivity for CRC was 93.9%

for ng-mt-sDNA compared with 67.3% for FIT, and sensitivity for APL was 43.4% versus 23.3%, respectively. APLs were defined as tubular adenomas or sessile serrated lesions ≥10 mm, lesions with villous histology, or high-grade dysplasia. Overall specificity for no advanced colorectal neoplasia was 90.6%, compared with 94.8% for FIT.[34] Sensitivity did not vary meaningfully by age, whereas specificity declined with advancing age, a pattern also observed with first-generation mt-sDNA testing and attributed to age-related background methylation.[39–41]

Available evidence suggests that the next-generation assay achieves improved specificity while maintaining comparable sensitivity for CRC and APL, although no studies directly comparing both versions of the test were conducted. In the DeeP-C study, which provided the primary evidence base for the original mt-sDNA test, sensitivity was 92.3% for CRC and 42.4% for APL, which are similar to estimates reported for the ng-mt-sDNA test (ClinicalTrials.gov identifier NCT01397747).[38] Specificity for nonadvanced or negative findings was 86.6% for the original assay compared with 90.6% for the new test. Because these performance measures were derived from separate study populations, there is some uncertainty regarding the comparability of the estimated specificities.

The microsimulation modeling studies discussed above also evaluated the ng-mt-sDNA test and concluded that screening average-risk populations every 3 years from ages 45 to 75 years does achieves favorable life-years gained relative to the number of lifetime colonoscopies required.[35,36] A separate modeling study similarly suggested that ng-mt-sDNA testing produces reductions in CRC incidence and mortality comparable to those achieved with FIT and mt-sRNA testing when applied at recommended intervals.[34] As with mt-sRNA testing, no studies have directly evaluated the optimal screening interval for mt-sDNA assays, although a longitudinal screening outcomes study is ongoing.[42] The manufacturer recommends a 3-year screening interval, a strategy that is supported by modeling evidence and CMS coverage determination.

In discussing the diagnostic performance of the ng-mt-sDNA test, the GDG noted that it was at least as accurate as the original mt-sDNA assay included in the 2018 ACS guideline; therefore, an mt-sDNA test (either original or next-generation) remains a preferred stool-based option for triennial CRC screening.

Blood-based testing

Cell-free DNA–based blood tests (hereafter referred to as *blood-based tests*) use an emerging, noninvasive technology for detecting DNA fragment patterns, aberrant methylation, and genomic alterations associated with colorectal neoplasia.[20] Algorithms constructed with artificial intelligence and machine learning then classify assay results as positive (abnormal signal is detected) or negative (no abnormal signal is detected). The performance data from blood-based tests for detecting advanced colorectal neoplasia have been reported in two large, prospective, cross-sectional studies of average-risk adults who were undergoing screening colonoscopies.[19,24] The ECLIPSE study,[19] funded by Guardant Health, evaluated nearly 8000 participants (ClinicalTrials.gov identifier NCT04136002), whereas the PREEMPT CRC study, funded by Freenome Holdings, Inc., evaluated over 27,000 participants (ClinicalTrials.gov identifier NCT04369053). Both studies were conducted at more than 200 sites across the United States. The mean ± standard deviation participant age in the ECLIPSE study was 60.3 ± 9.1 years, and 0.7% were older than 80 years. The mean ± standard deviation participant age in the PREEMPT CRC study was 57.0 ± 8.2 years, and 3.0% were older than 75 years. Women comprised 53.7% of ECLIPSE participants and 55.8% of PREEMPT CRC participants. The racial and ethnic distribution of participants in both studies were representative of national demographics. All participants completed blood-based tests before undergoing colonoscopy. Overall, 3.7% of ECLIPSE tests and 2.9% of the PREEMPT CRC tests did not produce valid results.

Cancer sensitivity was slightly higher in the ECLIPSE study (83.1%; 95% CI, 72.2%–90.3%) than in the PREEMPT CRC study (79.2%; 95% CI, 68.4%–86.9%). Sensitivity for stage I cancers was relatively lower in both studies compared with sensitivity for more advanced-stage cancers, although it was higher in the ECLIPSE study (64.7%; 95% CI, 41%–83%) compared with the PREEMPT CRC study (57.1%; 95% CI, 39.1%–73.5%). Overall sensitivity for stage II–IV CRC was 100% in the ECLIPSE study and 93% in the PREEMPT CRC study. Sensitivity did not differ by demographic characteristics, tumor location, or histologic grade for either study, although sensitivity was higher for larger lesions (≥3 cm) in the PREEMPT CRC study. Sensitivity for detecting APL was low in both studies at 13.2% (95% CI, 11.3%–15.3%) in ECLIPSE and 12.5% (95% CI, 11.3%–13.8%) in PREEMPT CRC.

Test specificity, based on accurately identifying persons without any advanced colorectal neoplasia found on colonoscopy (including nonadvanced polyps, nonneoplastic findings, or no findings), was 89.6% (95% CI, 88.8%–90.3%) in ECLIPSE and 91.5% (95% CI, 91.2%–91.9%) in PREEMPT CRC. Specificity decreased with increasing age in both studies, from >90% among participants younger than 55 years to about 80% in those 70 years and older.

The GDG reviewed recent modeling studies evaluating the comparative benefits and burdens of established and emerging CRC screening tests.[35,36] These studies modeled reductions in CRC incidence and mortality and gains in life-years and QALYs against the number of lifetime colonoscopies. Triennial blood-based screening strategies (the screening interval for which the test is approved for coverage by CMS) were consistently less effective in reducing CRC burdens for an equal or greater number of lifetime colonoscopies than strategies based on colonoscopy, FIT, and mt-sDNA (and, in some analyses, mt-sRNA). Models suggested that blood-based tests would need a sensitivity for APL of at least 30%–50% or to be performed more frequently than triennially to be comparable to FIT or colonoscopy in reducing CRC mortality.[43,44]

In its deliberations about blood-based tests, the GDG considered both clinical diagnostic performance and modeling data. They also noted the benefits of blood-based tests described in the evidence review, particularly the potential for widespread uptake and

adherence, given the relative ease of blood testing compared with stool-based and structural tests. Although the evidence review reported moderate-strength evidence to support the performance characteristics of blood-based tests,[30] the GDG considered several important test limitations. First, the low sensitivity of blood-based tests for APL and their reduced sensitivity for stage I CRC versus sensitivity for stage II–IV CRC predict less effectiveness in reducing CRC incidence and mortality compared with currently recommended CRC screening tests. This concern is corroborated by a modeling study estimating that 80% of long-term CRC mortality benefit comes from detecting and removing precancerous lesions.[45] Second, the declining specificity of blood-based tests with advancing age would increase the rate of false positives at older ages, when colonoscopy-associated risks are the greatest.[46,47] Third, there is a paucity of data, apart from modeling studies, to support the 3-year screening interval approved by CMS, and only minimal data are available on uptake, completion of diagnostic testing, and adherence with repeat testing.

However, the GDG acknowledged the substantial number of individuals who have never been screened for CRC or have not been adherent with recommended screening tests. Comparative modeling estimates of screening effectiveness generally assume 100% adherence across strategies; therefore, they do not fully reflect the real-world impact of tests that increase participation among previously unscreened individuals. For these individuals, a blood-based test could contribute to increasing screening uptake and reducing the burden of CRC. Weighing these factors, the GDG determined that blood-based tests could not be recommended as a preferred option for CRC screening at this time and should be offered only to individuals who decline or do not complete preferred screening tests. Providers who offer blood-based tests for CRC screening should counsel patients on their limitations, stress the advantages of the preferred tests, and, importantly, emphasize that a positive test requires a follow-up colonoscopy to complete the screening process.

DISCUSSION

Screening uptake, adherence, and patient choice

Adherence to regular screening with any of the recommended options is critical to achieving meaningful reductions in CRC incidence and mortality. Nonadherence with regular FIT screening is an enduring challenge in the United States. A recent systematic review of 24 cohort studies and clinical trials indicated that 47.1% of participants were consistent screeners, 30.3% were intermittent screeners, and 30.3% were never screened through four rounds of screening.[48] FIT-based screening programs achieving high adherence with repeat testing, such as occurs in the Kaiser Permanente program, have demonstrated substantial reductions in CRC incidence and mortality and have eliminated previous persistent disparities.[49] The few industry-sponsored studies examining multiround adherence with mt-sDNA reported overall rates in the 80% range or higher but were limited to insured populations.[50–52] To date, there are limited data on adherence to the new screening tests reviewed for this guideline update.

Expanding screening options for CRC may increase participation and adherence, particularly among individuals who decline or face barriers to completing stool-based testing and direct visual examinations. Moreover, screening uptake can be improved by providing patients with multiple screening options and allowing them to choose their preferred test.[9,53,54] Accordingly, providing the choice of a new CRC screening modality—blood-based testing—has the potential to expand the reach of CRC screening to individuals who might otherwise remain unscreened. Survey data after FDA approval of blood-based CRC screening suggest limited baseline awareness but high willingness to use them if covered by insurance, with many respondents expressing preference for triennial blood testing (53%) over annual stool-based testing (32%) or colonoscopy every 10 years (16%).[27]

Studies evaluating the effect of offering blood-based tests on screening utilization have produced mixed results. In one randomized trial conducted in a US integrated health system, offering blood-based tests to individuals who had not completed FIT increased short-term screening completion compared with usual care (30.5% vs. 13.0%). However, fewer participants who had a positive blood test completed a follow-up colonoscopy within 6 months of the result compared with those who had a positive FIT test (50% vs. 70%), although the difference was not statistically significant.[26] A randomized, population-based Australian trial found no overall improvement in screening participation when blood-based testing was offered either as a rescue strategy (for those not completing a FIT test) or as an initial choice test, with 6.5% and 1.5%, respectively, completing screening.[55] In a follow-up analysis, the investigators found that longitudinal adherence across subsequent screening rounds did not differ significantly between groups (66% for FIT and 61% for the blood test).[28] These findings suggest that blood-based tests may facilitate initial participation but may not improve rates of diagnostic testing or adherence with repeat screening. Thus, additional investigations are needed.

Although blood-based testing may increase initial uptake, its lower sensitivity for APL and stage I CRC compared with the currently recommended tests may limit reductions in CRC incidence and mortality. Modeling analyses suggest that substitution effects may have a negative impact on the broad goals of reducing the burden of CRC; for blood-based testing uptake to reduce CRC mortality, it must preferentially engage individuals who would otherwise remain unscreened rather than individuals who replace more effective modalities with blood-based testing.[56]

Thus, supporting patient choice must be coupled with clear communication about the benefits and limitations of available screening options to ensure that decisions are informed and aligned with patients' values and preferences. If an individual prioritizes preventing CRC by detecting and removing APLs, blood-based screening tests, although convenient, do not align with those

preferences. In contrast, stool-based molecular tests, with higher sensitivity for APLs and stage I cancers, better meet the goals of individuals who seek to minimize the burden from CRC but prefer a noninvasive procedure.

Real-world adherence to the new screening options is also likely to be influenced by insurance coverage, cost-sharing requirements, and clinician endorsement. The ng-mt-sDNA test is FDA-approved, and CMS covers triennial screening. The mt-sRNA test is FDA-approved, but CMS coverage determination is pending. The Guardant Shield blood test is FDA-approved, and CMS has approved reimbursement for triennial testing.[57] As of May 2026, the Freenome SimpleScreen blood test is under review at the FDA and has not yet been brought to market. Because the most recent CRC screening recommendations (2021) from the US Preventive Services Task Force (USPSTF) did not include blood-based and mt-sRNA tests (these tests had not yet been submitted to the FDA for approval), they do not qualify for waived cost-sharing under the Affordable Care Act requirement that private insurers provide first-dollar coverage for US Preventive Services Task Force grade A or B preventive services. Like with all screening modalities, other factors such as variations in clinician familiarity, practice patterns and policy, and quality metrics will further influence uptake and utilization of the new screening options.[58]

Equity considerations

The inclusion of additional screening modalities aligns with the ACS's commitment to access, equity, and patient-centered care.[59] Newer, noninvasive options could help address systemic barriers, resource inequities, perceived invasiveness, and, in the case of blood-based tests, aversion to undergoing preferred options, thereby providing an opportunity to increase screening rates and reduce the burden of CRC. However, unless steps are taken to ensure equitable access and coverage, the anticipated high cost of blood-based tests, mt-sRNA, and ng-mt-sDNA will represent a significant barrier to adoption in uninsured and underinsured populations. High-sensitivity FIT and gFOBT tests remain as low-cost options among the recommended CRC screening tests.

Clinical and implementation considerations

Table 2 provides key attributes of the CRC screening options for clinicians and their patients to consider in selecting the best test for the individual patient. Of the tests reviewed in this guideline update, mt-sRNA and the newest version of the mt-sDNA are among the preferred options that should be recommended to average-risk patients. Clinicians now have the opportunity to offer blood-based screening to individuals who have declined preferred options, because screening with a blood-based test is preferable to no screening. However, clinicians should discuss the greater preventive potential of established, stool-based and direct visual examinations compared with a blood-based test. Patients should have a clear understanding that, if their test is positive, the screening process is not complete without a follow-up colonoscopy. Furthermore, just as stool testing in the office after a digital rectal examination is not recommended, neither should a positive stool-based test or blood-based test be repeated before referring to diagnostic colonoscopy.

Clinicians should communicate to patients that age-related considerations apply equally to all CRC screening modalities, meaning that decisions should incorporate overall health status, life expectancy, and weigh the balance of potential benefits and harms.[60] The ACS recommends that clinicians discourage screening in individuals older than 85 years and in those of any age with a life expectancy less than 10 years or substantial comorbidity because the potential benefits of screening are unlikely to outweigh the potential harms. In addition, the specificity of some molecular screening tests, including blood-based tests and mt-sDNA, declines with advancing age. Declining specificity leads to higher false-positive rates and an increased likelihood of follow-up colonoscopy among older adults, in whom it has been demonstrated that colonoscopy-related risks are greater.[46,47] Clinicians should consider these factors when counseling older patients about screening options.

The new screening tests will likely face implementation challenges, including being integrated into electronic health record systems, coverage variability, workflow considerations, and patient education. Optimizing CRC screening ultimately requires multilevel interventions that address the barriers to screening and follow-up testing (e.g., costs, availability, insurance coverage, ease of test completion, education on benefits vs. harms of tests, etc.) at the individual, clinician, organizational, and policy levels[58] (for considerations in choosing a test, see Table 2).

CONCLUSION

This guideline update reflects the continued evolution of CRC screening related to technological advances, emerging evidence, and persistent gaps in participation. Adding mt-sRNA and ng-mt-sDNA tests to the list of preferred stool-based options is supported by performance data and modeling studies indicating potential to reduce CRC incidence and mortality when used with appropriate follow-up. Blood-based CRC screening tests are not recommended as preferred options at this time given their lower predicted effectiveness for reducing the burden of CRC. They should be offered only to individuals who decline or do not complete preferred screening tests, where they have the potential to increase the detection of CRC in those who would not otherwise undergo screening. These individuals should be informed about the need to undergo timely follow-up colonoscopy after a positive result.

Persistent disparities in CRC screening uptake and outcomes underscore the need for state and national commitments to

population-based strategies that expand access to screening, thereby reducing the burden of CRC. Incorporating evidence from ongoing clinical studies, real-world implementation data, and modeling analyses will be critical to refining screening strategies and informing future guideline updates. The ACS remains committed to periodically reassessing its recommendations to reflect the best available evidence and to advancing CRC screening practices that support informed patient choice, maximize benefit, minimize harm, and promote reductions in CRC incidence and mortality for all populations.

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CONFLICT OF INTEREST STATEMENT

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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