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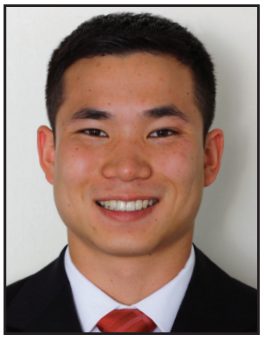
Current and Emerging Non-invasive Screening Tests for Colorectal Cancer

Pradeep Koripella



Lawrence J. Leung

Jeffrey K. Lee

Colorectal cancer (CRC) is the second leading cause of cancer-related death in the United States (US). Screening can help reduce CRC incidence and mortality but only 59% of adults are up to date to current screening recommendations. To achieve our national goal of screening 80% of the average-risk population, we must embrace non-invasive screening options for CRC. Our review aims to summarize the performance of currently available and emerging stool and blood-based CRC screening tests. Among the stool-based tests, fecal immunochemical testing (FIT) is the most widely used screening test. Multi target stool DNA is more sensitive than FIT for CRC, however, has a decreased specificity. Emerging stool-based tests include next generation multi-target stool DNA and multi-target stool RNA. Cell-free DNA blood-based screening tests are an appealing avenue to increase screening participation, but they will need better performance characteristics before they are widely adopted.

INTRODUCTION

Colorectal cancer (CRC) is the third most common cancer and second leading cause of cancer-related death in the United States (US).[1] In 2024, it is estimated that over 150,000 individuals will be diagnosed with CRC and over 50,000 will die from this disease.[1] Equally concerning is the rising incidence of CRC among adults less than 50 years of age, which currently accounts for 1 out of 10 CRCs diagnosed in the US.[2]

Randomized trials have shown that screening reduces CRC incidence and CRC-related mortality,[3] primarily through the early detection of cancer and removal of precancerous lesions. Current guidelines recommend several CRC screening modalities for average-risk adults ≥45 years of age including: 1) colonoscopy; 2) sigmoidoscopy; 3) computed tomography (CT) colonography; and 4) stool-based tests.[3] However, despite the availability of these screening options, only 59% of eligible adults are up to date with CRC screening[4] and rates are even

Pradeep Koripella MD[1] Lawrence J. Leung MD, MPH[2] Jeffrey K. Lee MD, MPH[2] [1]Kaiser Permanente San Francisco Medical Center, Department of Medicine [2]Kaiser Permanente San Francisco Medical Center, Department of Gastroenterology

lower among minority races and the underinsured.[5] The COVID-19 pandemic further exacerbated subpar screening rates as shelter-in-place orders led to fewer screening tests being performed, followed by a heightened demand that exceeded capacity as the pandemic waned.[6] However, even before the pandemic, CRC screening in the US fell short of the national goal of 80% up to date with screening.

In the US, colonoscopy is the most widely used screening modality because of its ability to detect and remove pre-cancerous lesions and accurately identify CRC. However, the test is invasive and inconvenient (e.g., requires taking a bowel preparation, obtaining help with transportation, taking time off from work, etc.).[7] Given these barriers to colonoscopy completion, there is a huge need for convenient non-invasive tests to improve screening uptake. In this review, we highlight current and emerging stool and blood-based CRC screening tests for average-risk adults.

Stool-Based Tests

High Sensitivity Guaiac-based Fecal Occult Blood Test (HS-gFOBT)

The high sensitivity guaiac-based fecal occult blood test (HS-gFOBT) detects colorectal neoplasia through a chemical oxidation reaction. When stool containing heme is spread onto guaiac paper, alpha-guaiaconic acid on the testing card is oxidized by the hydrogen peroxide reagent, which creates a blue color.[8] To perform the test, the patient uses an applicator stick to obtain a sample of stool on three separate occasions and then applies it to the Hemoccult slide.[9] Like all non-invasive stool or blood-based screening tests, a colonoscopy is required as a follow-up to a positive test.[3]

Multiple pragmatic randomized trials of screening with gFOBT have shown a reduction in CRC mortality when compared to no screening.[10–12] A 2021 systematic review by the United States Preventative Services Task Force (USPSTF) reported the following characteristics for the Hemoccult SENSA version of the test (**Table 1**): CRC sensitivity of 50.0%-75.0% (95% confidence interval [CI], 9.0-100) and specificity of 96.0%-98.0% (95% CI, 95.0-99.0); and advanced adenoma (AA) sensitivity of 6.0%-17.0% (95% CI 2.0-23.0) and specificity of 96.0%-99.0% (95% CI, 96.0-99.0).[13]

The benefits of HS-gFOBT-based screening

Table 1. Performance characteristics of stool- and blood-based screening tests for colorectal cancer

	Sensitivity CRC	Sensitivity AA	Specificity
Stool-Based Tests			
High sensitivity guaiac-based fecal occult blood test	50-75%	6-17%	96-98%
Fecal immunochemical test (FIT)	74-79%	23%	94%
Multitarget stool DNA (Cologuard)	92%	42%	87%
Next generation multitarget stool DNA	94%	43%	91%
Multitarget stool RNA (Colosense)	94%	46%	96%
Blood-Based Tests			
Septin 9, mSEPT9 (Epi Procolon, ColoVantage)	48%	11%	92%
Cell free DNA (Shield)	83%	13%	90%

CRC: colorectal cancer; AA: advanced adenoma

are that it is non-invasive, inexpensive, and can be performed at home. Limitations include the need for dietary restrictions (no red meat, raw beets, carrots, etc.) and medication restrictions (no NSAIDs, iron, blood thinners, etc.) for two days prior to testing as they can cause false positive results.[14] While the USPSTF currently recommends annual screening with this test, HS-gFOBT screening has largely been replaced by fecal immunochemical test (FIT) screening.

Fecal Immunochemical Test (FIT)

The fecal immunochemical test (FIT) uses an antibody against the globin moiety of heme to evaluate for the presence of occult blood in a stool sample.[15] FIT screening requires patients to test only one stool sample (as opposed to 3 samples with Hs-gFOBT) and the test does not require dietary or medication restrictions.

Most FITs are qualitative tests, meaning they visually indicate when hemoglobin is detected in stool above a predetermined threshold. However, there are also quantitative tests in which the amount of hemoglobin in stool is measured and reported as positive if greater than a prespecified threshold. The current FDA-approved threshold for a positive test is 20 micrograms of hemoglobin per gram of stool (20ug Hb/g feces) and the sensitivity and specificity for CRC and AA will vary if the threshold is changed.[16]

In a systematic review evaluating FIT screening at a threshold of 20ug Hb/g feces, the pooled sensitivity for detecting CRC was 75.0% (95% CI, 61.0-86.0) and the specificity was 95.0% (95% CI, 92.0-96.0).[17] For AA, the pooled sensitivity was 25.0% (95% CI, 20.0-31.0) and the specificity was 95.0% (95% CI, 93.0-96.0).[17] When the FIT threshold was lowered to 10ug/g feces, the pooled sensitivity for CRC increased to 91.0% (95% CI, 84.0-95.0) and the specificity decreased to 90% (95% CI, 86.0-93.0), and similarly for AA the sensitivity increased to 40.0% (95% CI, 33-47) with a decreased specificity of 90.0% (95% CI, 87.0-93.0).[17]

Multiple randomized trials have evaluated participation with FIT versus colonoscopy screening, either head-to-head or as a sequential choice. These studies have demonstrated that more people participate in FIT screening when offered compared to colonoscopy screening.[18–22]

FIT screening has demonstrated a higher sensitivity for CRC and AAs with similar specificity compared to HS-gFOBT screening. Although there is a lack of prospective randomized data, FIT's benefit is inferred from prior gFOBT data, given its superior performance characteristics.[13] One large prospective observational study in Taiwan (n=5,417,699) has evaluated the impact of FIT screening on CRC incidence and mortality.[23] This study found that 1 to 3 rounds of screening with biennial FIT was associated with a 34% reduction in advanced stage CRC and 40% reduction in death from CRC at 6 years.[23] There are currently three ongoing clinical trials evaluating the effectiveness of colonoscopy versus FIT for CRC incidence and mortality.[13]

Multi-Target Stool DNA Test (MT-sDNA)

The multi-target stool DNA test (MT-sDNA, commercially known as Cologuard, Exact Sciences) combines fecal hemoglobin detection via the FIT with additional biomarkers including mutant KRAS, aberrant NDRG4 and BMP3 methylation, and B-actin. In a prospective study involving 10,023 average-risk individuals, MT-sDNA-based screening demonstrated a superior sensitivity for CRC (92.3%; 95% CI, 83.0-97.5) and AA (42.4%; 95% CI, 32.6-52.8) but lower specificity for CRC or AA (86.6%; 95% CI, 85.9-87.2) compared to FIT [sensitivity of FIT for CRC: 73.8% (95% CI, 61.5-84.0), sensitivity of FIT for AA: 23.9% (95% CI, 20.8-27.0) specificity of FIT: 94.9% (95% CI, 94.4-95.3)].[24]

The MT-sDNA was approved for CRC screening by the FDA in 2014 and current guidelines recommend the test be performed every three years. However, despite the test's improved sensitivity for CRC and AA compared to FIT screening, there have been several barriers to widespread adoption of the test in the US and for its use in population-based screening. First, the MT-sDNA itself is much more costly than the FIT. Second, stool collection and sampling are more complex than for the FIT. In one prospective study, 6% of participants were unable to collect or send an adequate sample compared to 0.6% for the FIT.[18] Third, the test has a higher false positive rate compared to the FIT (due to a

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lower specificity for CRC) which results in more unnecessary colonoscopies. Fourth, a positive MT-sDNA followed by a negative colonoscopy raises the question of whether neoplasia was missed at colonoscopy given the test detects tumor DNA. This could potentially lead to over testing and anxiety among patients, although Cotter et al. reported that patients with a false-positive MT-sDNA result did not have a higher subsequent incidence of gastrointestinal and other cancers compared to those with negative test results.[25]

Recently, a next generation MT-sDNA was evaluated among 20,176 average-risk adults 40 years of age and older in a prospective study.[26] In this study, the next generation test showed higher sensitivity for CRC and advanced precancerous lesions (defined as advanced conventional adenomas and sessile serrated lesions) than FIT but lower specificity. The sensitivity of the test for CRC and advanced precancerous lesions was 93.9% (95% CI, 87.1-97.7) and 43.4% (95% CI, 41.3-45.6), respectively, while the specificity for advanced neoplasia (defined as CRC or advanced precancerous lesions) was 90.6% (95% CI, 90.1-91.0). In contrast, FIT sensitivity for CRC and advanced precancerous lesions was 67.3% (95% CI, 57.1-76.5) and 23.3% (95% CI, 21.5-25.2) respectively, while specificity for advanced neoplasia was 94.8% (95% CI, 94.4-95.1).[26] The main advantage of the next-generation MT-sDNA compared to the current generation test is its improved specificity for advanced neoplasia (i.e., 90.6%), which will decrease the false positive rate and thereby reduce unnecessary colonoscopies. The next generation MT-sDNA is currently awaiting FDA approval.

Multitarget Stool RNA Test (mt-sRNA)

The multitarget stool RNA test (mt-sRNA, commercially known as Colosense, Geneoscopy) is an emerging stool-based test which combines fecal hemoglobin detection via the FIT with additional RNA biomarkers. The performance of mt-sRNA versus FIT-based screening was recently evaluated in a prospective study (CRC-PREVENT) of 8,920 average-risk participants 45 years of age and older. The study showed that the mt-sRNA sensitivity for CRC and AA was 94.4% (95% CI, 81.0-99.0) and 45.9% (95% CI, 42.0-50.0), respectively, and was superior to the FIT. The specificity of the mt-sRNA for all other findings (medium risk adenomas, low risk adenomas, and no findings) was 85.5% (95% CI, 70.0-89.0) and lower compared to the FIT.[27] FIT sensitivity for CRC and AA was 77.8% (95% CI, 61-90) and 28.9% (95% CI, 25-33), respectively. Specificity for all other findings (medium risk adenomas, low risk adenomas, and no findings) was 95.7% (95% CI, 88-97). A unique aspect of the CRC-PREVENT study is its inclusion of 45-49 year-olds for which the USPSTF now recommends CRC screening. In this age group, mt-sRNA screening demonstrated 100% sensitivity for CRC and 44.7% sensitivity for AA (95% CI not available). The authors suggested that the high sensitivity and preserved specificity of the mt-sRNA in this younger age group (i.e., 45-49 year-olds) may be attributable to the inclusion of RNA biomarkers which are not subject to age-related methylation patterns that can impact test results across age groups.[27] Colosense was recently FDA approved this year.

Blood-Based Tests

In 2021, the Centers for Medicare and Medicaid Services (CMS) provided guidance on how blood-based CRC screening tests can gain approval for potential reimbursement. First, the guidance stated that blood-based tests need to have a 90.0% specificity and 74.0% sensitivity for CRC compared to an accepted standard. Second, blood-based tests must be approved by the Food and Drug Administration (FDA). Third, blood-based tests need to be endorsed by at least one professional society guideline.[28] We discuss some of the current and emerging blood-based screening tests below.

Septin 9 or mSEPT9 (Epi proColon, ColoVantage)

In 2016, a blood-based plasma methylated SEPT9 DNA assay (mSEPT9, marketed under the trade names Epi proColon and ColoVantage) was approved by the FDA for CRC screening. The SEPT9 gene plays an important role in the progression of CRC, as methylated SEPT9 DNA has been detected in most CRC tissues.[29] In a prospective study of 7,921 average-risk adults 50 years of age and older, mSEPT9 demonstrated

a 48.2% (95% CI, 32.4-63.6) sensitivity for CRC, 11.2% (95% CI, 7.2-15.7) sensitivity for AA, and 91.5% (95% CI, 89.7-93.1) specificity for CRC.[30] Although the test is FDA approved, neither the USPSTF nor the US Multi-Society Task Force (USMSTF) guidelines advocate for its use for CRC screening given its performance characteristics and lack of studies demonstrating its effectiveness in reducing CRC incidence or CRC-related mortality. However, two studies have demonstrated mSEPT9's potential role for CRC screening, particularly for individuals who prefer a blood-based screening option that is more convenient and does not require stool sampling. In a randomized trial of 413 average-risk adults who were due for CRC screening in two integrated US health systems, uptake of the mSEPT9 blood test was significantly higher compared to FIT screening; 99.5% of participants in the mSEPT9 arm completed the test within six weeks compared with 88.1% of participants in the FIT arm.[31] Additionally, mSEPT9 was shown to improve screening adherence by 7.5% among average-risk individuals who previously declined colonoscopy and FIT screening.[32]

cfDNA (Shield)

Recently, there has been growing interest in plasma cell free DNA (cfDNA), which is made of DNA molecules released from various tissues in the body, as a potential source for noninvasive diagnostic and cancer screening. Using this technology, Guardant Health developed a blood-based cfDNA test (Shield, Guardant Health) for colorectal screening. In a retrospective case-control study of 699 Korean individuals with stage I-III CRC and 297 colonoscopy negative control subjects, the sensitivity and specificity of the test for CRC was 96% and 94% respectively (95% CI not available).[33] It was later studied in a prospective study (ECLIPSE trial) of 7,861 average-risk adults 45 years of age and older, the cfDNA test detected CRC with a sensitivity of 83.1% (95% CI, 72.2-90.3), advanced neoplasia with a specificity of 89.6% (95% CI 88.8-90.3), and advanced precancerous lesions with a sensitivity of 13.2% (95% CI, 11.3-15.3).[34] Although cfDNA demonstrated an 83.1% sensitivity for CRC overall and 87.5% sensitivity for stage I-III CRC, which is comparable to most currently available stool-based tests, the relatively low sensitivity for detecting advanced precancerous lesions (13%) is a limitation. Also, the plasma cfDNA assay focuses on markers specific to CRC and it is possible that markers for AAs and sessile serrated lesions may be different, which would likely negatively impact the test's performance. Shield received FDA approval this year.

CONCLUSION

CRC is a common cancer worldwide and preventable through screening. Adherence to CRC screening in the US is below the 80% target, likely in part due to the fact that colonoscopy, the most commonly performed screening test, is both invasive and inconvenient. Non-invasive screening options offer the potential to increase CRC screening rates and address the rising incidence of CRC among adults under 50 years of age. Stool-based tests currently available include the HS-gFOBT, FIT, and MT-sDNA. Although the MT-sDNA has a higher sensitivity for detecting CRC compared with other stool-based tests, it is more costly and has a higher false positive rate. Emerging stool-based tests such as the next-generation MT-sDNA and the mt-sRNA have a slightly higher specificity compared to the current MT-sDNA, which may help reduce unnecessary colonoscopies. The FIT remains the preferred screening test for population-based screening due to its low cost, accuracy for detecting CRC, and ease for mailed outreach. The emergence of the blood-based cfDNA test is a promising avenue for non-invasive screening and may help improve screening participation, particularly among individuals who prefer a non-invasive screening test that does not require stool sampling. ■

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