CME

Colorectal cancer screening: The role of MT-sDNA testing

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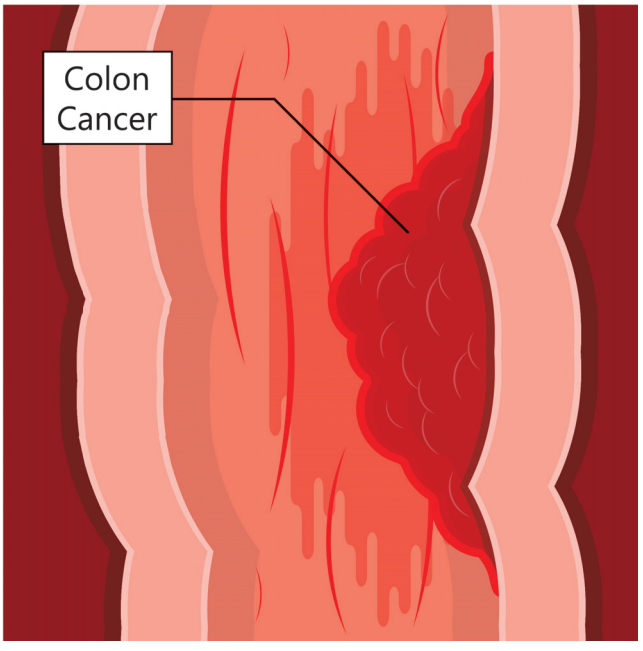
ABSTRACT

Because an estimated 10.5% of new colorectal cancer (CRC) cases occur in patients under age 50 years, the US Preventive Services Task Force in 2021 recommended CRC screening for adults ages 45 to 49 years. The prevalence of up-to-date CRC screening with any recommended test among patients age 45 years and older in the United States is only 59% in 2023, indicating that existing screening practices are ineffective. Screening options now include invasive and noninvasive measures. Multi-target stool DNA (MT-sDNA) testing is a simple, low-risk, noninvasive test that provides excellent sensitivity and specificity, is cost-effective, and may increase patient screening rates. CRC screening guideline recommendations and alternative screening methods may help improve patient outcomes and reduce morbidity and mortality. This article describes MT-sDNA testing, its effectiveness, recommended use, and potential expanding role as a screening option.

Keywords: colorectal cancer, screening, MT-sDNA, Cologuard, guidelines, sensitivity

Learning objectives

- Describe CRC pathophysiology.
- Describe how MT-sDNA screening works and its expected efficacy.
- Discuss the expanding evidence for MT-sDNA's role in new screening guidelines, different population subsets, and high-risk patients.
- Compare and contrast MT-sDNA cost-effectiveness with FIT and colonoscopy.



Colorectal cancer (CRC) is the third leading cause of cancer death in both men and women in the United States; an estimated 153,020 people will be diagnosed with CRC in 2023.[1] The American Cancer Society (ACS) found that the proportion of patients diagnosed with advanced-stage CRC increased from 52% in the mid-2000s to 60% in 2019.[1] CRC most frequently is diagnosed in patients ages 65 to 74 years, but recent data show that an estimated 10.5% of cases occur in patients under age 50 years.[2] This cancer progresses slowly, making it preventable and curable in up to 90% of patients if detected early.[3] Symptoms usually are only evident with advanced disease.[4] Therefore, early detection through patient screening can markedly reduce mortality.[4]

The gold standard diagnostic technique for CRC detection is colonoscopy. It offers diagnostic and preventive opportunities because precancerous polyps and more advanced lesions can be removed, further reducing mortality.[4] However, colonoscopy is an expensive and invasive technique, the bowel preparation is unpleasant, and the procedure carries risks.[4] Furthermore, procedural and operator errors may result in polyps being missed.[4]

More than 40% of the US population is not up-to-date with CRC screening, according to updated recommendations from the ACS.[1] Multi-target stool DNA (MT-sDNA)

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Key points

- CRC is the third leading cause of cancer-related death in men and women in the United States.
- New guidelines recommend regular screening in adults beginning at age 45 years—rather than 50 years, as previously recommended— because more than 10% of CRC cases occur in adults under age 50 years.
- MT-sDNA is sensitive, cost-effective, and patient-preferred.

testing (brand name Cologuard, manufactured by Exact Sciences) has gradually gained favor since its introduction in 2014.[3] This simple, low-risk, noninvasive test provides excellent sensitivity (92.3%) for CRC and is cost-effective.[5] It is preferred among patients and may increase screening uptake and adherence rates, improving clinical outcomes (**Table 1**).[6]

PATHOPHYSIOLOGY

An accumulation of genetic and epigenetic alterations, typically over decades, activates oncogenes, deactivates tumor suppressor genes, and creates genomic/epigenomic instability in the colon.[4] Aberrant crypt formation (clusters of abnormal tubelike glands) in the colonic mucosa slowly progresses to benign polyps, a potential precursor for early cancer, setting the stage for invasive and metastatic advanced neoplasms.[4] This pathogenesis makes CRC a slowly progressing cancer and, therefore, more preventable and curable with early detection.[4] However, detection is a concern because symptoms typically present only with advanced disease, placing significant emphasis on screening.[4]

Research on genome targeting reveals a highly complex landscape, with multiple alternative pathways leading to neoplasm.[7] This lends credence to the assumption that each case of CRC is unique. The sequence of morphologic events in CRC seems to follow a pattern, leading to associations with biomolecules that can serve as biomarkers and provide a basis for stool analysis to identify tumor-specific changes.[4] Because of molecular differences in polyps and the cancers that can come from them, a method for molecular classification of CRC has been proposed, although it is not yet recommended by National Comprehensive Cancer Network guidelines. However, using molecular classification in colon precursor lesions, correlating classification and gut microbiota, and predicting prognosis and/or response to the indicated treatment could lead to more precise medicine.[8] Ideal biomarkers fit three criteria: they are easily and inexpensively measured for identification, they identify the condition for improved patient outcomes, and they predict a patient's treatment response.[4] For a risk assessment model for CRC screening, see **Figure 1**.

MT-sDNA OVERVIEW

Previous stool-based testing primarily was performed by fecal immunochemical test (FIT) and fecal occult blood test (FOBT). The US Multi-Society Task Force (USMSTF) consensus statement summarizes the advantages of FIT over FOBT in detecting CRC in average-risk patients.[9] Most notably, the sensitivity of FIT comfortably exceeds that of FOBT, which is only about 35%.[9] A meta-analysis of 44 studies revealed pooled FIT sensitivities for all studies combined were 73% for stage I CRCs, 80% for stage II, 82% for stage III, and 79% for stage IV.[10] The author concludes this indicates a need for improvement upon this model for the early detection of CRC.[10] Novel testing with advanced methods has incorporated a stabilizing buffer and automation and also has increased discriminating markers and sensitive analytic methods. The results are determined via a logistic regression algorithm, resulting in higher sensitivity for detecting CRC and advanced precancerous lesions.[4,5]

MT-sDNA testing incorporates molecular assays for DNA mutation and methylated biomarkers associated with CRC (*KRAS* mutations and *NDRG4* and *BMP3* methylation) with a non-DNA immunochemical assay for human hemoglobin.[4,5] It also includes a reference gene (beta-actin) for estimating the total human DNA present in each sample.[4,5] The mutation, methylation, and hemoglobin assays are combined to produce a composite score, which is compared with a cutoff value to determine a positive or negative result.[4,5] Imperiale and colleagues found the test sensitivity of MT-sDNA to be 92.3% and 42.4% for CRC and advanced precancerous lesions, respectively, nearly 20 percentage points higher than FIT testing.[5] However, MT-sDNA specificity (86.6%) is inferior to FIT (94.9%) among

TABLE 1. Characteristics of selected CRC screening tests

Adapted with permission from Peterse EF, Meester RG, de Jonge L, et al. Comparing the cost-effectiveness of innovative colorectal cancer screening tests. *J Natl Cancer Inst.* 2021;113(2):154–161.

Test	Sensitivity, %*				Specificity, %
	Adenomas ≤5 mm	Adenomas 6-9 mm	Adenomas ≥10 mm	CRC	
Colonoscopy	75	85	95	95	100
FIT	7.6		23.8	73.8	96.4
MT-sDNA	17.2		42.4	92.3	89.8

*The sensitivity of colonoscopy was calculated per lesion; other sensitivities are per patient.

patients with nonadvanced or negative findings, which may lead to false-positive outcomes requiring unnecessary follow-up with colonoscopy.[5] As the comparative gold standard, colonoscopy has a sensitivity of 75% to 93% in detecting adenomas 6 mm or larger.[11] Sensitivity is considered the most critical characteristic for screening tests because the primary role of such testing is to rule out diseases such as cancer.[5]

MT-sDNA requires a single stool specimen without dietary restrictions. The kit is shipped directly to the patient's home with instructions for collection. An interactive website, phone and text reminders, and prepaid parcel drop-off or pick-up options may help alleviate collection challenges. FIT testing does not offer these additional benefits. The patient must return the MT-sDNA kit within 96 hours of sample collection. A positive result should be followed up with a full colonoscopy.[3]

Additionally, after a positive FIT, only 46.7% of patients underwent colonoscopy within 6 months, compared with 71.5% who had a positive mt-sDNA test; time to colonoscopy also was shorter for patients screened with mt-sDNA.[12]

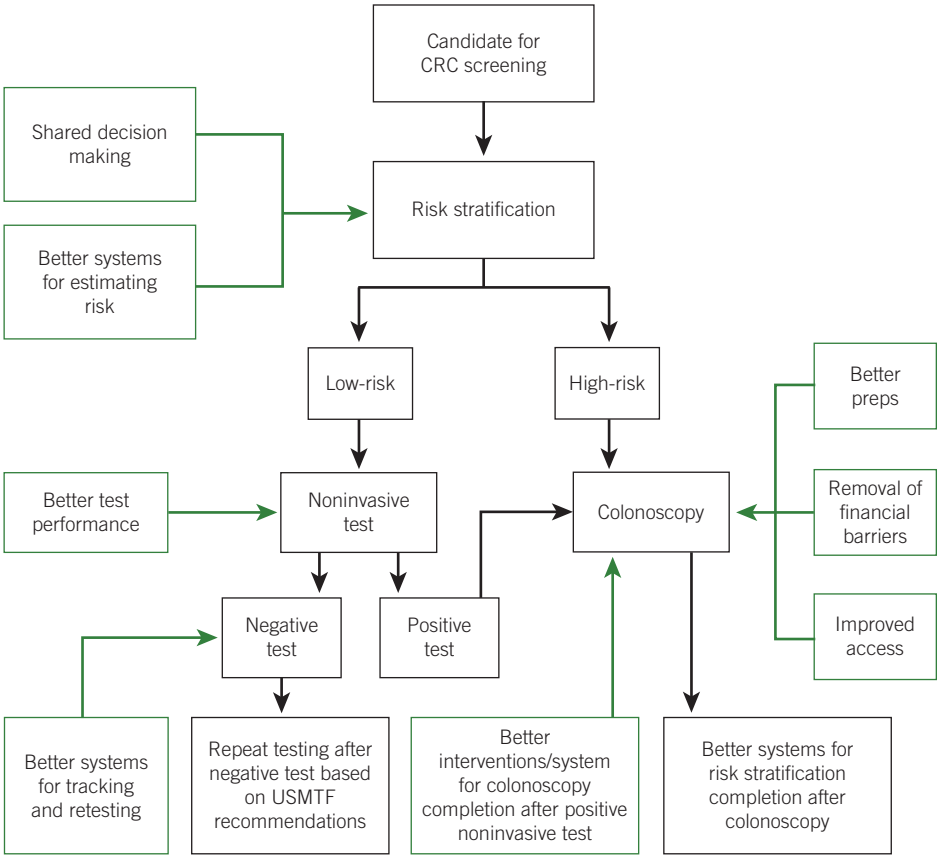

FIGURE 1. A risk assessment model with shared decision-making for CRC screening

Reprinted with permission from Melson JE, Imperiale TF, Itzkowitz SH, et al. AGA white paper: roadmap for the future of colorectal cancer screening in the United States. *Clin Gastroenterol Hepatol.* 2020;18(12):2667-2678.

SCREENING YOUNGER ADULTS

In May 2021, the US Preventive Services Task Force (USPSTF) added a grade B recommendation for CRC screening in adults ages 45 to 49 years, coinciding with evidence that one in seven cases of CRC is diagnosed before age 50 years.[3,13] Additionally, Cancer Intervention and Surveillance Modeling Network modeling suggests that starting screening at age 45 years can moderately increase life years gained and reduce CRC cases and deaths.[14] The USPSTF found that patients of older age, male sex, and/or Black ethnicity had the highest rates of CRC.[14] Therefore, offering screening at age 45 years to these population subgroups is particularly important.[14] FDA-approved MT-sDNA has USPSTF recommendation as a screening tool.[3,11,13] A study for this age group by Imperiale and colleagues revealed that MT-sDNA test specificity was 95.2% in participants with nonadvanced adenomas or negative findings, and this did not differ by sex or ethnicity.[15] The sensitivity for advanced precancerous lesions was 32.7%, with 83.7% measuring 10 to 19 mm and none having high-grade dysplasia.[15] The results indicate that with its high specificity, MT-sDNA has a role as a noninvasive option for CRC screening and may help reduce unnecessary diagnostic procedures.

POPULATION SUBSET EFFICACY

MT-sDNA efficacy studies have been performed in various populations, indicating the testing method's versatility for screening purposes. Alaskan Native peoples have one of the highest rates of CRC globally at 90.9 per 100,000.[16] Guaiac-based FOBT has a high false-positive rate due to endemically high rates of *H. pylori*-related bleeding among Alaska Natives, making it an unsatisfactory option.[16] Colonoscopy requires personnel, time, travel, and resources that may not be available in remote regions, necessitating alternative options.[16] A previous study by Redwood and colleagues showed that MT-sDNA had better sensitivity than FIT (100% versus 75% for CRC, 45% versus 28% for advanced adenomas), with respective specificities of 93% and 96% in the Alaskan Native population.[16,17] Furthermore, the model predicted (assuming imperfect adherence) a CRC reduction incidence of 40.7% for MT-sDNA, 15.5% for FIT, and 19.8% for colonoscopy.[16]

Similar mortality benefits were noted, with reductions of 41.8% for MT-sDNA, 17.7% for FIT, and 20% for colonoscopy.[16] Worst-case scenarios were 30.4%, 3.4%, and 9.8%, respectively.[16] In short, MT-sDNA showed superiority to FIT and colonoscopy in CRC incidence reduction with improved mortality benefits regardless of scenario.

The prospective study performed by Cooper and colleagues revealed similar efficacy outcomes for MT-sDNA testing in Black and White patients.[18] The prevalence of any adenoma (38.9% for Black patients and 33.9% for White patients) and that of advanced lesions (6.8% and 6.7%, respectively) were similar between groups.[18] The overall sensitivities of MT-sDNA for detecting advanced lesions and any adenoma were 43% and 19%, and the specificities were 91% and 93%, respectively.[18] These findings are significant because Black patients are less likely to have had colonoscopies, indicating the need for additional testing options.[18]

HIGH-RISK SCREENING

Patients with inflammatory bowel disease (IBD) have an increased risk of CRC (CRC-IBD).[19] Screening is strongly recommended for these patients. The gold standard of regular interval colonoscopies for patients with IBD has limitations because adherence is suboptimal, and up to 30% of CRC-IBD occurs between screenings.[19] The chronic inflammation associated with IBD predisposes patients to low-grade dysplasia with the potential for progression to high-grade dysplasia and, eventually, adenocarcinoma.[19]

Klepp and colleagues performed two independent prospective cohort studies that revealed that the MT-sDNA panel was positive in two out of two cases of CRC and five of 15 cases of low-grade dysplasia (less than 1 cm in diameter).[20] Sensitivities were 100% (95% CI 16%-100%) for CRC and 33% (95% CI 13%-61%) for low-grade dysplasia lesions less than 1 cm, with specificities of 87% (95% CI 81%-91%) and 93% (95% CI 88%-96%), respectively.[20] The estimated number of patients needed to screen to detect a single CRC was 96 (95% CI 93%-99%); to detect any colorectal neoplasia, the estimate was 28 (95% CI 22%-34%).[20]

Using tissue and stool studies in a prospective blinded study, Kisiel and colleagues tested the feasibility of using stool assay of exfoliated DNA markers to detect colorectal neoplasia associated with IBD.[21] Cases included 17 samples from patients with ulcerative colitis and two from patients with Crohn disease; nine samples had cancer, and 10 had dysplasia.[21] Controls had 25 samples with ulcerative colitis and 10 with Crohn disease. *BMP3,* vimentin, *EYA4,* and *NDRG4* markers individually showed high discrimination in stool for IBD and cancer.[21] At 89% specificity, the combination of *BMP3* and *mNDRG4* detected nine of nine cases (100%) of CRC and 80% of dysplasia—specifically, four of four cases (100%) of high-grade dysplasia and four of six cases (67%) of low-grade dysplasia.[21]

These findings indicate that MT-sDNA sensitivity for subcentimeter neoplasm in patients with IBD is similar to that of the general population.[20] MT-sDNA testing has shown the ability to detect CRC with high sensitivity and to detect small low-grade dysplasia lesions with modest sensitivity at an acceptable specificity.[20,21] This suggests that this test may be helpful in structured surveillance of patients with long-term IBD, and also may improve screening compliance and mitigate the need for potentially unnecessary procedures and associated risks.

The efficacy of these findings has prompted investigations into using methylated DNA markers in other high-risk patients, namely those with Lynch syndrome, the most common form of familial CRC. Lynch syndrome accounts for more than 3% of all new CRC cases and 10% to 20% of early-onset CRC cases.[22]

A study by Ballester and colleagues found that methylated DNA markers highly discriminate colorectal neoplasia in media such as stool or blood from patients with Lynch syndrome, raising the potential for screening or surveillance.[22] Although the markers in MT-sDNA (*BMP3* and *NDRG4*) showed less discrimination for Lynch syndrome than other methylated DNA markers tested, the results for noninvasive screening are nevertheless promising.[22] Current screening guidelines recommend colonoscopy every 1 to 2 years for patients with Lynch syndrome, which has proven effective in reducing CRC mortality.[22] However, CRC still occurs during surveillance programs because of accelerated carcinogenesis, operator-dependent variable detection rates, difficulty detecting proximal lesions, and colonoscopy adherence rates as low as 50%.[22] Given the high risk of interval CRC in screening in patients with Lynch syndrome, noninvasive complementary screening tools could improve early detection and reduce morbidity and mortality.[22]

Despite these findings, MT-sDNA testing is not indicated or approved for high-risk patients. Clinicians should continue to use colonoscopy for high-risk patients and reserve MT-sDNA and other noninvasive tests as options for average-risk patients.

COST CONSIDERATIONS

Initial studies called into question the cost-effectiveness of MT-sDNA compared with FOBT, FIT, and colonoscopy.[23,24] However, contemporary literature seems to show a shift in this narrative, particularly when considering real-world adherence compared with perfect adherence.

A study by Peterse and colleagues found cost-effectiveness ratios of annual MT-sDNA screening (about $214,974) and colonoscopy ($48,155) per quality-adjusted life years (QALY) gained.[25] A limitation of this study is that MT-sDNA screening is recommended every 3 years, not annually.[3]

The previously mentioned study of Alaskan Natives by Redwood compared MT-sDNA with FIT and colonoscopy while incorporating adherence rates.[16] The study used a Markov simulation economic model to evaluate the probabilistic cost-effectiveness of FIT, MT-sDNA, and colonoscopy over 40 years.[16] Under varied adherence scenarios, MT-sDNA

either dominated or was cost-effective using incremental cost-effectiveness ratio scores, compared with FIT and colonoscopy.[16,26] These findings suggest that in a wide range of scenarios, and accounting for patient adherence, MT-sDNA is more cost-effective than FIT and colonoscopy.[16]

Fisher and colleagues noted similar findings: that MT-sDNA was cost-effective compared with FIT and FOBT and also yielded improved clinical outcomes.[27]

Investigations of different populations using a similar methodology are needed to ascertain the generalizability of these data. Ideally, researchers would be able to compare prospective trials, head-to-head studies, and longitudinal surveillance as they become available, but such studies do not exist because of the recency of MT-sDNA testing.

Another study by Karlitz and colleagues compared 100% adherence rates with real-world simulations in an underserved Medicaid group via outreach.[28] The study used the Colorectal Cancer and Adenoma Incidence and Mortality Microsimulation (CRC-AIM) model to compare the cost-effectiveness of every-3-years MT-sDNA testing with annual FIT in 1 million Medicaid patients ages 50 to 64 years who had not been diagnosed with CRC.[28] MT-sDNA is more expensive than FIT and colonoscopy when assuming perfect adherence.[28] However, assuming real-world adherence rates with perfect colonoscopy follow-up, MT-sDNA resulted in the greatest reduction in incidence of and mortality from CRC (41.5% and 45.8%, respectively) compared with outreach with or without FIT.[28] MT-sDNA also was cost-effective compared with outreach with and without FIT ($32,150/QALY and $22,707/QALY, respectively).[28] MT-sDNA remained cost-effective versus FIT, with or without outreach, under real-world adherence rates for a follow-up colonoscopy.[28]

Another consideration is that commercial insurance covers a follow-up colonoscopy after a positive screening test with no cost-sharing (out-of-pocket costs for the patient). Medicare also will cover a screening colonoscopy after a positive stool-based study if the patient's healthcare provider accepts assignment; however, a 15% coinsurance cost may be incurred if a polyp or other tissue is removed.[29,30] In a simulation of Medicare beneficiaries, waiving coinsurance for follow-up colonoscopy after a positive stool-based test improved outcomes and was cost-effective when assumed to increase CRC screening and follow-up colonoscopy adherence modestly.[29] Concurrently, in sensitivity analyses, any increase in adherence after waiving coinsurance was cost-effective and increased QALY gained.[29]

In short, MT-sDNA shows the ability to improve quality of life cost-effectively compared with FIT and colonoscopy. This is particularly true in real-world simulations.

PATIENT PREFERENCE

For CRC screening, a common perspective is "the best test is the test that gets done."[28] CRC screening guidelines offer clinicians and patients various options for patients at average risk of CRC.[2] These options vary by invasiveness, frequency, cost, risk for harm, and precision; thus, clinician and patient shared decision-making is vital to individualizing the screening strategy. A cross-sectional online survey by Heidenreich and colleagues polled 1,249 average-risk patients ages 45 to 75 years and 200 physicians from primary care and gastroenterology.[6] The study found that physicians preferred colonoscopy (96.8%) over MT-sDNA (2.8%) and FIT (0.3%), valuing the precision of true-positive and true-negative rates with little concern for screening frequency.[6] Patients preferred MT-sDNA (38.8%) over colonoscopy (32.5%), and FIT (19.2%), still valuing precision but also driven by preferring screenings more frequently than every 10 years.[6] Although physicians overwhelmingly prefer colonoscopy, most patients, particularly hesitant, treatment-naive patients, prefer MT-sDNA.[6] These findings suggest that giving patients options about a preferred screening method could enhance adherence and improve screening rates.[6,31]

> Adherence to screening may reduce mortality from CRC by more than 50%.

CONCLUSION

CRC is the third leading cause of cancer-related death in the United States, with more than 150,000 cases expected in 2023.[1] Screening guidelines have been updated to address the fact that nearly 11% of cases are discovered in patients under age 50 years.[1] Because of its slow progression, CRC can be cured up to 90% of the time if detected early, and adherence to screening may reduce mortality from CRC by more than 50%.[3,32] However, traditional screening methods such as FIT and colonoscopy have not achieved the 80% target rate endorsed by the National Colorectal Cancer Round Table.[6] Colonoscopy, an effective diagnostic and therapeutic option, remains the gold standard, but screening rates have not reached target levels because of cost concerns, unpleasant preparation, risks inherent to an invasive procedure, and access issues.[4] Novel screening methods, including MT-sDNA, offer options to increase screening while potentially mitigating the inherent risks and high costs associated with colonoscopy. Studies have shown MT-sDNA to be efficacious and cost-effective in real-world applications.[25,28,29,33] It offers equal efficacy among patients of different ethnicities with increased specificity in patients ages 45 to 49 years.[13,16,18,34]

MT-sDNA testing is indicated only for average-risk patients. But it may have a role as a complementary surveillance tool in high-risk populations such as patients

with IBD or Lynch syndrome, because it shows acceptable sensitivity and specificity in these groups, and the increased risk of interval CRC between colonoscopies is as high as 30% in these patients.[19] Patient preference for MT-sDNA exceeds that for colonoscopy or FIT.[6] MT-sDNA is a valuable screening option that is not meant to replace colonoscopy but rather serve as an alternative to improve screening rates, especially among average-risk patients who encounter barriers to colonoscopy. By offering options to patients, clinicians may be able to improve CRC screening and detection rates and reduce the morbidity and mortality associated with CRC. **JAAPA**

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