Optimal Approach to Colorectal Cancer Screening

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Abstract: Rates of colorectal cancer (CRC) screening in the United States continue to fall short of guideline-recommended benchmarks. Challenges to increasing CRC screening include racial disparities, barriers at multiple levels of the health care system, and inadequate completion of 2-step screening. With new options for CRC screening and employment of programmatic strategies for screening by physicians, patients will have more opportunities to initiate and complete testing, which can ultimately improve CRC detection and prevention. This article highlights the current state of and optimal approach to CRC screening.

Keywords
Colorectal cancer, screening modalities, stool-based tests, colonoscopy

Colorectal cancer (CRC) remains the third most common cancer in both men and women and the second most deadly cancer.[1] In 2024, it was estimated that approximately 145,000 new cases of CRC would be diagnosed, and 45,000 patients would die from the cancer. Screening for CRC leads to early detection and prevention and is both efficacious and cost-effective.[2] This article focuses on current CRC screening modalities used in the United States for average-risk, screen-eligible individuals between ages 45 and 75 years, and the challenges and opportunities associated with increasing the population of screened individuals.

Current State of Colorectal Cancer Screening in the United States

Various national organizations have set benchmarks to increase the screened population to anywhere from 68% (US Department of Health and Human Services, Healthy People 2030) to 80% in every community (American Cancer Society National Colorectal Cancer Roundtable).[3,4] However, challenges with CRC screening remain nationally and include lower screening rates observed in minority and immigrant populations. According to National Health Interview Survey data, only 59% of the US population aged 45 years and older was up-to-date with CRC screening in 2021.[1]

Recent Epidemiologic Trends

Recent epidemiologic trends indicate declining rates of CRC for men and women over age 50 years.[1] This effect is largely attributed to increased uptake of CRC screening in the United States. However, for individuals younger than 50 years, there is a disturbing trend of rising incidence rates. This trend is described as a birth cohort effect, such that individuals born after 1970 carry a lifetime increased risk of CRC compared with birth cohorts born between 1940 and 1960.[5] In particular, individuals aged 45 to 49 years have CRC incidence rates of approximately 33 per 100,000, a threshold above which screening is largely deemed cost-effective. The reasons for these trends are not known, but the leading hypotheses include obesity, metabolic syndrome, early-life antibiotic exposure and dysbiosis, and ultraprocessed food intake.[6-9]

Recent Changes in Guidelines

Public health efforts have been focused on mitigating risk factors and extending screening efforts to earlier age groups. In 2018, the American Cancer Society gave a qualified recommendation to lower the screening age to 45 years,[10] followed by the American College of Gastroenterology, the US Preventive Services Task Force (USPSTF), the US Multi-Society Task Force, and the National Center for Health Promotion and Disease Prevention in the Veterans Health Administration.[2,11,12] The significance of these guideline recommendations is that the Centers for Medicare and Medicaid Services (CMS), all commercial payers, and the Veterans Health Administration now cover CRC screening tests starting at age 45 years. With the addition of the 45- to 49-year-old age group, another 19 million individuals have been added to the screening pool, which presents an opportunity and challenge for health care systems. For individuals who have a family history of 1 or more first-degree relatives with CRC or advanced colorectal polyps, the guidelines recommend initiation of screening at ages below 45 years, such as 40 years, or 10 years earlier than the youngest relative's age at diagnosis.[11]

Age Range for Screening

Most guidelines recommend screening until age 75 years and tailoring screening efforts for ages 76 to 85 years. For the latter age group, this entails weighing risks and benefits through shared decision-making by considering comorbidities, life expectancies, individual risk of CRC, and prior screening history.[2,11,12] At or above age 86 years, screening is not recommended as modeling studies suggest that the harms outweigh the benefits. Several decision guides are being developed that may assist with making benefit vs harm decisions based on individual risk factors rather than relying purely on chronologic age.

Colorectal Cancer Screening Modalities

Stool-based Tests

The USPSTF recommends CRC screening with: (1) a fecal immunochemical test (FIT) or high-sensitivity guaiac-based fecal occult blood test (FOBT) every year, or (2) a multitarget stool DNA (mt-sDNA) test every 3 years.[2] The FOBT utilizes a peroxidase reaction to evaluate for heme in the stool.[2,13] Deterrents to FOBT use include the need for dietary and medication restrictions prior to testing and for 3 consecutive stool samples. By contrast, FIT utilizes antibodies that are specific for hemoglobin and unaffected by diet or medications, and the test requires a single sample for collection, thus improving adherence.[2,13,14]

Randomized controlled trials (RCTs) have shown that when implemented yearly or biennially, FOBT decreases both CRC incidence (17%-20% reduction) and mortality (13%-32% reduction), with greater reductions shown with annual screening.[15-18] Observational studies demonstrate a decrease in CRC incidence (10%-33% reduction) and mortality (22%-47% reduction) with FIT; however, RCTs are lacking.[19-21] Compared with FOBT, FIT has superior sensitivity for detecting CRC and advanced adenomas while maintaining similar specificity.[22-24] A meta-analysis of 19 FIT studies demonstrated a pooled sensitivity and specificity for CRC of 79% (95% CI, 0.69-0.86) and 94% (95% CI, 0.92-0.95), respectively, with a one-time FIT.[25-27] After a single round, FIT sensitivity for advanced adenomas ranges from 6% to 56%, depending on the type of FIT and its threshold for positivity.[23] Although FIT positivity and sensitivity for CRC are highest in the initial round, FIT demonstrates continued effectiveness over multiple rounds of screening.[28]

The mt-sDNA test (Cologuard, Exact Sciences) detects hemoglobin in addition to DNA biomarkers associated with CRC.[13] A kit is mailed to the participant to collect a stool sample, obtain a scraping of the stool (for the FIT), and add a buffer, then label and ship the sample back to the manufacturer within 24 hours of collection, a process that can be technically challenging for some patients for which navigation assistance is available from the manufacturer. Furthermore, the cost of mt-sDNA without insurance can be prohibitive ($500-$600) in contrast to FIT ($25). In a study involving 9989 individuals who completed colonoscopies, mt-sDNA was shown to outperform FIT in the detection of both CRC and advanced preneoplastic lesions.[29] The sensitivity for CRC and advanced preneoplastic lesions was found to be 92% and 42%, respectively, with mt-sDNA, vs 74% and 24%, respectively, with FIT. The specificity for CRC and advanced preneoplastic lesions was lower with mt-sDNA (87% vs 95% with FIT), resulting in a higher false-positive

Table 1. Comparison of Current Screening Modalities for CRC in the United States

Modality	Sensitivity	Specificity	Considerations
FIT	79% for CRC 6%-56% for AA	94% for CRC	Typically requires a single sample No dietary or medication restrictions prior to collection Positive FIT must be evaluated with a colonoscopy (2-step screening) USPSTF recommends annual screening
mt-sDNA	92% for CRC 42% for advanced preneoplastic lesions	87% for CRC and advanced preneoplastic lesions	Sample collection is done at home and mailed back to the company Sample collection can be challenging High cost ($500-$600) without insurance Higher false-positive rate than FIT Positive mt-sDNA must be evaluated with a colonoscopy (2-step screening) USPSTF recommends screening every 3 years
Colonoscopy	95% for CRC	98% for CRC	Can detect and remove preneoplastic lesions Bowel preparation and dietary/medication modifications required preprocedure Need for sedation, time away from work, transportation, and an escort on the day of procedure Potential harms of procedure include bleeding and perforation USPSTF recommends screening every 10 years or shorter intervals if preneoplastic lesions are detected

AA, advanced adenoma; CRC, colorectal cancer; FIT, fecal immunochemical test; mt-sDNA, multitarget stool DNA; USPSTF, US Preventive Services Task Force.

rate. The impact of mt-sDNA on CRC outcomes remains unknown, and data to further tailor surveillance intervals are needed. Finally, it is imperative to note that noninvasive screening is a 2-step process, where an abnormal stool test result must be followed by a colonoscopy to examine for neoplastic lesions.[11]

Future Stool-based Tests

In a recent prospective study of 20,176 participants, a next-generation mt-sDNA test (Cologuard Plus, Exact Sciences) with improved biomarkers appeared to demonstrate improved specificity (90.6% for advanced neoplasia) without compromising sensitivity (ie, 93.9% for CRC and 43.4% for advanced neoplastic lesions), and the test was recently approved by the US Food and Drug Administration (FDA).[30] Results of a clinical validation study (CRC-PREVENT), which evaluated a multitarget stool RNA test (ColoSense, Geneoscopy) in 8920 individuals aged 45 years or older, were recently reported. The test demonstrated a sensitivity of 94% for CRC and 46% for advanced adenomas, and a specificity of 88%, with FDA approval obtained in 2024.[31] At this time, the performance characteristics for current and next-generation mt-sDNA and multitarget RNA stool tests are similar.

Colonoscopy

The USPSTF recommends colonoscopy every 10 years or at shorter surveillance intervals if preneoplastic lesions are detected.[2] Colonoscopy is the primary screening test for CRC utilized in the United States, in contrast to most countries which rely on a stool-based test (SBT) as the leading modality.[32,33] The advantages of colonoscopy include the ability to identify early-stage cancers, detect and remove precancerous lesions, and screen less frequently compared with SBTs. Considerations with colonoscopy include the need for bowel preparation, sedation, time away from work, and transportation, as well as potential harms associated with the procedure (eg, bleeding and perforation). Multiple cohort and case-control studies demonstrate lower CRC incidence (46%-91% reduction) and mortality (66%-88% reduction) among individuals who undergo screening colonoscopy.[34-40] In 2022, the first RCT (NordICC) examined the impact of an invitation to undergo screening colonoscopy, demonstrating an 18% reduction in CRC incidence and a nonsignificant reduction in CRC mortality after 10 years of follow-up.[41] It is important to note that screening uptake was low in the trial (only 42% of invited participants completed colonoscopy) and that higher participation rates are likely to confer larger reductions in incidence and mortality. Per-protocol analyses supported a reduction of 31% and 50%, respectively, in CRC incidence and mortality. Future release of 15-year follow-up is planned and will provide clarity as to whether the benefits of colonoscopy will be fully appreciated. A comparison of currently available screening modalities is described in Table 1.

Comparative Efficacy and Cost-Effectiveness

Large multisite RCTs to evaluate the efficacy of colonoscopy vs FIT are currently underway. CONFIRM

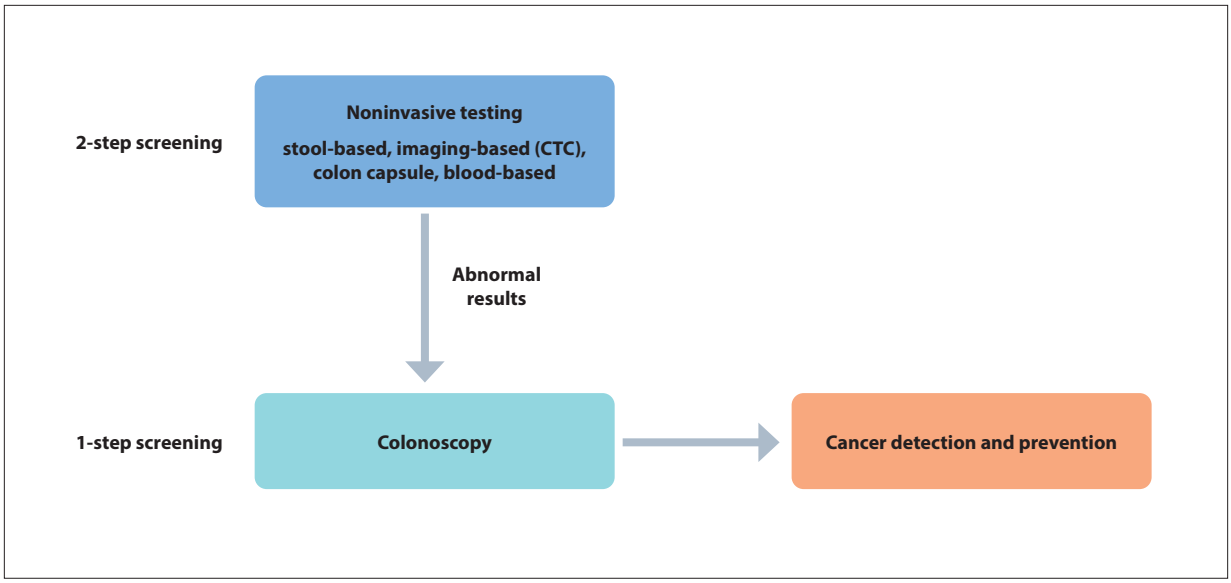

Figure. Colorectal cancer screening cascade.

CTC, computed tomography colonography.

(NCT01239082) is a multicenter trial that is examining screening colonoscopy vs annual FIT in a Veterans Affairs population of 50,000 average-risk participants aged 50 years and older.[42] The primary outcome is CRC mortality over 10 years, although CRC incidence, colonoscopy complications, and endoscopist characteristics are designated as secondary endpoints. The COLONPREV study (NCT00906997) based in Spain seeks to examine the efficacy of colonoscopy vs biennial FIT on CRC mortality at 10 years.[43] Finally, the SCREESCO study (NCT02078804) in Sweden is evaluating colonoscopy vs 2 rounds of FIT vs no screening; CRC incidence and mortality are primary endpoints.[44]

In modeling studies, CRC screening (particularly annual/biennial FIT/FOBT and colonoscopy every 10 years) is cost-effective compared with no screening.[45] Annual FIT or colonoscopy every 10 years is more effective and less costly when compared with triennial mt-sDNA.[46] For mt-sDNA to be cost-effective, adherence rates would need to increase 1.7 times (compared with FIT), or the cost of mt-sDNA would need to be reduced by 60%. A recent modeling study found that lowering the screening age from 50 to 45 years is highly cost-effective, with the lowest costs associated with FIT.[47] The model also found that reallocating colonoscopy resources from individuals younger than 50 years to focus on unscreened individuals aged 55 to 65 years would result in greater clinical benefits and cost savings, raising the broader question of how to prioritize colonoscopy capacity when faced with limitations.

Approach to Colorectal Cancer Screening

CRC screening should be viewed as 1-step or 2-step testing (Figure). Colonoscopy is the only 1-step screening test that can detect cancers and polyps of any neoplastic potential and allows for removal of these polyps at the same time. All other tests are 2-step screening tests that require an initial easy-to-complete noninvasive test and a colonoscopy if the initial test result is abnormal. The noninvasive test, by itself, does not reduce CRC incidence or deaths; rather, it is a risk stratification tool to bring individuals to colonoscopy, which can detect early cancers and remove any polyps, reducing long-term cancer risk (hence 2 steps). Awareness of this screening cascade is important to understand the effectiveness of programmatic screening. It is also important to strengthen all aspects of the cascade to ensure effectiveness. This means ensuring that the tests are completed and are of high quality and, in the case of stool testing, that the completion rate for colonoscopy following abnormal results should be high. Advocacy to reduce any financial costs associated with the screening cascade has been successful, such that patients should no longer incur a copay for a colonoscopy performed because of an abnormal stool test, and the colonoscopy is covered under a screening indication.[48]

Opportunistic vs Organized Screening

In the United States, screening is largely opportunistic, which means that the patient has to come in contact with the health care system, usually through a visit with their

Table 2. Challenges and Opportunities in Colorectal Cancer Screening

Challenges	Opportunities
Screening rates in the United States (59%) remain below national benchmarks (80% NCCRT, 68% HHS)	Establish partnerships with community organizations and stakeholders to understand health beliefs and barriers to screening
Disparities exist by age, race/ethnicity, immigration status, education, income, and insurance status	Develop multicomponent (eg, outreach, patient navigation) interventions to enhance screening efforts
Barriers to screening persist at the patient, provider, and health care system levels	Offer a choice in screening options, with the understanding that the most effective test is the test that gets done
Completion of 2-step screening remains inadequate, and adherence to multiple rounds of screening is difficult to maintain	Employ programmatic strategies to initiate screening, ensure completion of 2-step screening, and sustain adherence over multiple rounds

HHS, US Department of Health and Human Services; NCCRT, National Colorectal Cancer Roundtable.

primary care provider, to have the opportunity to discuss and receive screening recommendations and orders. Intuitively, this leaves out individuals who either do not have a health care provider owing to lack of insurance or access, or do not see a provider on a regular basis to benefit from the screening discussion. In the 2020 Behavioral Risk Factor Surveillance System survey by the Centers for Disease Control and Prevention, the 2 factors associated with low rates of screening were lack of health insurance and lack of a regular health care provider.[49]

A superior approach is organized screening where there is a systematic way to identify individuals eligible for screening across the health care system and to organize screening efforts through education, outreach, and navigation. Health care systems with the successful adoption of organized screening programs have reported high screening rates and improved outcomes. Kaiser Permanente of California was able to improve CRC screening rates from 38.9% to 82% over a 15-year period. An 80% adherence rate was achieved and exceeded by use of a mailed FIT and navigation to colonoscopy program for its members. The study also reported a decrease in annual CRC incidence and mortality of 25% and 52%, respectively, over the same period.[50]

Choice of Colorectal Cancer Screening Test

Several studies indicate that patients have different preferences for the screening test they are willing to undergo or complete. It is imperative to offer more than one screening test to patients to maximize adherence. Choice could be offered upfront in a sequential fashion or via other combinations, where offering a choice and flexibility improves adherence. Inadomi and colleagues reported higher screening uptake when patients were offered both FOBT and colonoscopy, as well as higher preference for FOBT among non-White groups.[51] One survey that asked 1000 unscreened Americans which test they were likely to undergo found there was a stronger preference for noninvasive tests, and this preference did not vary by age. Tailoring choice or the sequence of tests offered to the patient population is also an effective intervention for improving screening rates, as discussed in the next section.

Challenges and Opportunities in Colorectal Cancer Screening

As previously mentioned, only 59% of the US population is up-to-date with CRC screening, with rates varying across multiple sociodemographic factors (Table 2).[1] CRC is now the leading cause of cancer death in adults younger than 50 years, yet only 20% of adults aged 45 to 49 years are up-to-date with CRC screening in contrast to 70% to 80% of individuals 55 years and older.[1,52] By race/ethnicity, Asian, Hispanic, and American Indian/Alaskan Native individuals experience the lowest CRC screening rates.[1,53] This is especially alarming as Asian and Hispanic Americans remain the fastest-growing racial or ethnic groups in the United States.[54] By immigration status, 61% of US-born individuals, 53% of foreign-born residents (≥10 years US residence), and 29% of recent immigrants (<10 years US residence) are up-to-date.[1] This finding deserves further investigation as immigrants and their descendants are expected to contribute to 90% of US population growth over the next few decades.[55] Other factors associated with low screening uptake include less than a high school education, low household income, and lack of insurance.[1,53]

Multitiered barriers to CRC screening exist at the patient, provider, and system level, and these barriers will likely differ by intersectional group. Lack of knowledge, cancer fatalism, cultural health beliefs, perception of low CRC risk, fear, embarrassment, and financial burdens

Table 3. New Developments in CRC Screening

CRC screening modality	Sensitivity	Specificity
Blood-based tests		
Circulating tumor DNA	83.1% for CRC, 13.2% for APL	90%
FMBT-CRC	79.2% for CRC, 12.5% for AA	92.5%
Stool-based tests		
Next-generation mt-sDNA	93.9% for CRC, 43.4% for APL	90.6%
Multitarget stool RNA	94% for CRC, 46% for AA	88%

AA, advanced adenoma; APL, advanced preneoplastic lesion; CRC, colorectal cancer; FMBT-CRC, Freenome Multiomics Blood Test for CRC; mt-sDNA, multitarget stool DNA.

related to transportation or work absenteeism have been identified as patient-level obstacles.[56-58] Provider gender, culture, and language discordance as well as lack of physician recommendation and lack of time owing to competing medical priorities have been cited as provider-level barriers.[57,58] At the system level, lack of insurance, lack of primary care, and difficulty navigating the health care system are challenges to CRC screening completion.[56,58]

Noninvasive stool tests offer significant potential for bridging the CRC screening gap, particularly among medically underserved populations, and for addressing future screening disruptions. Delayed or incomplete colonoscopy following an abnormal stool test is associated with worse outcomes, such as increased CRC risk, late-stage disease, and mortality.[59,60] Unfortunately, completion of follow-up colonoscopy remains suboptimal across different health care settings (eg, 18%-52% for Federally Qualified Health Centers, 42%-50% in Veterans Affairs Medical Centers, and 56% in a national sample of 39 diverse health care organizations) and falls short of the National Colorectal Cancer Roundtable objective of 80%.[24,61-64] As the direction shifts toward noninvasive testing in both preference and development, ensuring timely follow-up colonoscopy should be a top priority for all health care systems.[65,66]

Finally, adherence to repeated rounds of screening remains a challenge to maintain. This is especially pertinent with noninvasive modalities (eg, FIT and mt-sDNA) given their frequency of testing. Unfortunately, prior studies have shown that adherence to SBTs can be difficult to sustain after multiple rounds, despite mailed outreach and telephone reminders (with 59% adhering in year 1 vs 28% in year 3) or when patient navigation is only offered in the first year (67% in year 1 vs 14% in year 3).[67-69] In a recent multisite RCT evaluating adherence to either colonoscopy or annual SBT, with patient navigation support offered throughout the trial, adherence to SBT in the first year was 73% but decreased to 38% after 4 years.[70]

Future Developments

Blood-based Tests

Recent developments in the identification of circulating tumor DNA (ctDNA) and cell-free DNA in the blood have signaled new possibilities for blood-based CRC screening. Blood-based tests have generated excitement among patients owing to their simplicity and minimally invasive nature.[71]

Emerging multicancer detection tests include Cancerguard (formerly CancerSEEK, Exact Sciences), which relies on machine-learning algorithms to identify specific proteins and mutations in ctDNA, and Galleri (Grail), which evaluates methylation patterns in ctDNA and is currently available in the United States ($949).[72,73] In a study of 1005 patients with 8 cancer types, CancerSEEK demonstrated a sensitivity of 43% for stage I cancers, 73% for stage II cancers, and 78% for stage III cancers.[74] The Circulating Cell-free Genome Atlas substudy was a prospective case-control study that evaluated the Galleri test in 4077 individuals with cancer. The study identified more than 50 cancers. The sensitivity for cancer was 51.5%, while the specificity was 99.5%. For CRC, the sensitivity was 82%; by stage, the sensitivity was 43.3% for stage I CRC, and improved to less than 85% for stage II to IV CRC.[75] The multicenter prospective cohort study PATHFINDER evaluated an earlier version of the Galleri test and enrolled 6621 asymptomatic participants aged 50 years and older who were followed for 12 months to ascertain cancer status.[76] The sensitivity and specificity were 29% and 99.1%, respectively; 2 CRCs were identified. Of the 92 positive tests, 57 were false-positives. False-positive blood tests bear important consideration given the potential for overdiagnosis, invasive or unnecessary procedures, and psychological harms. Furthermore, the approach to diagnostic workup in this setting remains unclear. Prospective validation studies for multicancer detection tests are ongoing at this time (eg, NCT04213326 and ISRCTN91431511).[77,78]

Blood-based tests focusing on the early detection of CRC have been developed by both Guardant Health and Freenome (Table 3). In 2024, results were released from the ECLIPSE study, a prospective multicenter study that evaluated a ctDNA test (Shield, Guardant Health) in 7861 average-risk individuals aged 45 years or older.[79] The sensitivity for CRC was 83.1%, while the specificity for advanced neoplasia was 90%. The sensitivity for stage I CRC was 65%, and reached 100% for stage II, III, and IV cancers. The sensitivity for advanced neoplastic lesions

was 13.2%. Preliminary findings from the PREEMPT CRC study, a prospective study of 27,010 average-risk individuals to evaluate a blood-based multiomics test for CRC screening (FMBT-CRC, Freenome), showed similar test performance characteristics.[80]

The CMS supports coverage of a blood test once every 3 years if it demonstrates 74% or higher sensitivity and 90% or higher specificity for the detection of CRC.[81] Current modeling studies have reported that a blood test that performs at CMS standards would improve CRC outcomes vs no screening but would not replace established methods (FIT, mt-sDNA test, colonoscopy) in terms of cost-effectiveness or clinical benefit.[82,83] Furthermore, for a blood test to be considered groundbreaking, it would need to demonstrate a sensitivity of 90% to 95% for CRC and 70% to 80% for advanced neoplastic lesions. The promise of a blood test lies in its potential to augment current screening efforts. Studies indicate that a blood test may improve adherence in unscreened individuals or serve as a viable option for individuals who are unwilling to undergo traditional modalities.[26,84,85] However, use of a blood test as a cancer prevention tool still requires significant enhancements, and its effectiveness remains to be determined.

Artificial Intelligence

In recent years, the field of artificial intelligence (AI) has grown exponentially, and its applications in endoscopy are expected to be wide-ranging. Most of the evidence to date examines the role of AI in colonoscopy using computer-aided polyp detection (CADe) and computer-aided diagnosis (CADx). Multiple randomized trials examining the use of CADe colonoscopy vs standard colonoscopy demonstrate a higher adenoma detection rate (8-15 percentage point increase) and an increase in adenomas per colonoscopy with CADe, without significant lengthening of withdrawal time.[86-89] In a prospective multicenter tandem study of 232 patients randomized to undergo CADe colonoscopy first vs standard colonoscopy first, individuals who first received CADe colonoscopy experienced a lower adenoma miss rate (20.1% vs 31.2%), lower sessile serrated lesion miss rate (7.1% vs 42.1%), and higher adenomas per colonoscopy on the initial assessment (1.2 vs 0.9).[90] CADx similarly demonstrates promise as a tool to aid in the optical evaluation of colorectal polyps. In a prospective single-arm study examining 1- to 5-mm rectosigmoid polyps, CADx diagnosis was attainable (98.6%) with high negative predictive value (97.6%), and a leave-in approach was feasible for 82% of lesions.[91] However, enthusiasm for real-world application has been tempered, as studies have shown no significant difference in adenoma detection rate or adenomas per colonoscopy with CADe.[92,93] These discrepancies highlight the importance of conducting a thorough baseline examination. Although promising, AI-assistive devices for CRC screening should be viewed as supplements rather than replacements of the endoscopist's tool kit. Moreover, future studies are needed to better characterize the AI-endoscopist interaction in order to enhance the efficacy of AI technologies in real-world clinical practice.

Conclusion

SBTs (FIT and mt-sDNA) and colonoscopy are preferred modalities for CRC screening, each with advantages and disadvantages that must be tailored to individual circumstances. Screening has been shown to reduce CRC incidence and mortality, yet CRC screening rates remain below national benchmarks. Variability in implementation (organized vs opportunistic) and adherence persists, exacerbated by obstacles at the patient, provider, and system level. Ongoing comparative effectiveness trials are expected to guide screening strategies. With emerging technologies poised to transform CRC prevention efforts like never before, the future of CRC screening is certainly bright.

Disclosures

Dr Wang has no relevant conflicts of interest to disclose. Dr Shaukat is a consultant for Iterative Health, Freenome, Universal Diagnostics, and Geneoscopy.

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