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Advances in Colorectal Cancer Screening

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Colorectal cancer (CRC) screening has been shown to save lives. Screening can prevent CRC by detecting and removing precancerous adenomatous polyps, which are the precursors of most cancers.[1] Screening also can detect cancer at an early, asymptomatic stage while it is still localized and amenable to treatment; 5-year survival rates are 80% to 90% for patients with localized, early stage I/II CRC.[2] Based on the substantial evidence supporting the benefits of CRC screening, the US Preventive Services Task Force (USPSTF) currently recommends screening in asymptomatic adults, beginning at 50 years of age[3] using one of several screening options, which vary in efficacy, invasiveness, and cost: an annual high-sensitivity fecal occult blood test (FOBT), flexible sigmoidoscopy every 5 years, or colonoscopy every 10 years. The USPSTF is also in the process of updating its recommendations based on new evidence and will publish new guidelines soon. While the 2008 combined guidelines of the American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology also recommend double-contrast barium enema every 5 years,[4] its use for evaluation of the colon has been largely discontinued.

Despite these recommendations, only two-thirds of the eligible population 50 years of age and older get screened,[5] and CRC remains one of the leading causes of cancer-related death in the United States. Recent reports also indicate screening rates have plateaued after a decade of improvement.[6] This could widen the existing gap in screening and, given the aging population, negatively impact the Centers for Disease Control and Prevention's initiative to achieve an 80% CRC screening rate by 2018.[7]

Thus, there is still room for improvement in CRC screening. A key recent advance in noninvasive screening for CRC is the development of an assay that can detect in stool the presence of DNA biomarkers that are released from degenerating normal and neoplastic colonic epithelial cells. Here we review the most commonly used screening methods for CRC and discuss recent advances in noninvasive testing.

SCREENING TESTS FOR CRC

Colonoscopy

Screening colonoscopy is the reference method by which all other CRC screening tests are evaluated, and all other screening tests lead to a diagnostic colonoscopy for further evaluation of initial positive findings. Colonoscopy is a highly sensitive test that directly examines the lining of the entire colon and allows for diagnosis and, often, removal of suspicious lesions (polyps) in a single visit. Colonoscopy has the potential to prevent about 65% of CRC cases[8] and is the preferred screening method for patients at high risk for CRC. However, its acceptability and utility have limits for patients at average risk (ie, the majority of patients). Colonoscopy is invasive

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and involves cumbersome bowel preparation that when inadequate, can affect the quality of the exam.[9] The procedure is also time consuming, not only for the patient but also for friends or family members who may need to accompany the patient and take time off from work.[10]

Although the overall risk of complications with colonoscopy is very low, it requires moderate sedation, which may pose a higher risk of hypoxemia in the elderly and the obese.[11-13] Bleeding and perforations have been reported at a higher frequency in the elderly, those with chronic renal disease, and individuals taking anticoagulants.[14] Colonoscopy can miss some adenomas and cancers (particularly those in the proximal colon due to variations in polyp morphology, suboptimal bowel preparation, and patient anatomical differences)[15,16] and interval cancers, which occur between normally scheduled colonoscopies.[17-19] As a result, a risk for developing CRC remains even if guideline recommendations are regularly followed.

Screening colonoscopy is covered by Medicare at no cost every 2 years for those at high risk regardless of age, and every 10 years for those at average risk; however, if the test results in a biopsy or removal of a growth, participants may incur a cost. Additional costs may also occur if colonoscopies are performed at intervals shorter than the guideline recommendations; median times to follow-up of only 6.9 years (vs the current guidance of 10 years) have been reported among average-risk patients 50 to 65 years of age with no personal history of CRC and no prior findings on an initial colonoscopy.[20] This has contributed to a national effort by the American Board of Internal Medicine to encourage physicians to consider noninvasive screening alternatives for patients at average risk for CRC.[21]

Computed tomography colonography

Computed tomography (CT) colonography (or virtual colonoscopy) was developed as a less invasive alternative to colonoscopy that would be more acceptable to patients. It uses radiation to generate computerized 2- and 3-dimensional images of the entire colorectum, which are scanned for potential cancerous and precancerous lesions without using an endoscope.[22] The sensitivity of CT colonography for detection of large adenomas ≥10 mm is high (≥90%), but it drops to 78% for detecting smaller adenomas that are ≥6 mm.[23] CT colonography does not involve sedation, and patients find it to be more acceptable than colonoscopy.[24] However, some degree of bowel preparation is required; the colon is distended with gas insufflation or fluid infusion during the procedure, which may cause considerable discomfort to patients.[25]

The ionizing radiation used in the procedure can be potentially harmful to patients and may require access to specialized care and result in additional costs. Another drawback is the dependence on the operator's ability/expertise to detect lesions. Finally, CT colonography does not allow for removal of lesions at the time of detection, so patients with findings need to follow up with a colonoscopy. Although some US guidelines recommend CT colonography as one of several tests, the US Centers for Medicare and Medicaid Services denied coverage of this screening technique because no clear evidence suggests that it can reduce CRC incidence or mortality.[26]

Fecal occult blood test and fecal immunochemical test

The FOBT, which recognizes either the iron-bearing heme portion of the hemoglobin molecule (gFOBT) or the protein globin portion, is the most widely used noninvasive screening test for CRC.[27] The fecal immunochemical test (FIT), a variation of the FOBT, recognizes the protein (globin) portion of the hemoglobin molecule and was developed to address the concern of low sensitivity with gFOBT tests that recognize only the heme. Both tests detect blood in the stool, which may be a sign of cancer. The gFOBT generally requires collection of 2 to 3 stool samples from consecutive bowel movements, while FIT requires collection of only 1 to 2 stool samples.[28]

Evidence that gFOBT screening reduces CRC mortality was reported in a systematic review of 4 randomized controlled trials.[29] The relative risk of dying due to CRC was reduced by 16% in approximately 320,000 patients who were screened using gFOBT. A concern with gFOBT is the low sensitivity for detecting both CRC (25% to 38%) and precancerous (16% to 31%) lesions with one-time testing.[30] Limited data suggest that higher sensitivities are observed with FOBT for detection of CRC and large adenomas with 2 to 3 days of sample collection vs 1 day of sample collection.[30] FIT has a higher sensitivity for CRC (71% to 75%)[31,32] and precancerous lesions (27% to 29%)[32,33] compared with FOBT, but it is less specific (94% to 95% specificity for FIT[31,32] vs 98% to 99% for FOBT[30]).

A major disadvantage of gFOBT and FIT is that these tests assess only bleeding, which may be sporadic and could result from causes other than CRC. In addition, dietary and medication restrictions are necessary for FOBT since blood from certain foods (such as red meat),

interfering substances in some vegetables, and/or upper gastrointestinal bleeding due to medications (such as aspirin) could lead to false-positive results. Further, benign adenomatous polyps and even early CRC may not bleed unless large and ulcerated on the surface, hence, these lesions could go undetected.[34] Owing to other nonneoplastic causes of occult bleeding, there is a lack of clarity on the threshold levels of stool hemoglobin that should be used for referral to colonoscopy.[35] FIT is also limited by the stability of hemoglobin, which is rapidly degraded, and therefore more proximal lesions may not be adequately detected. Finally, even though these tests are noninvasive, patient compliance with annual testing is low. In a study that measured adherence to an annual FOBT in more than 1 million patients, less than half (42.1% of men, 42.9% of women) received a single initial test, and only 14.1% of men and 13.7% of women reported receiving at least 4 consecutive tests during the 5-year study period.[36]

Multitarget stool DNA testing

The progression from normal colonic mucosa to adenomatous polyps to CRC is characterized by a multistep accumulation of genetic and epigenetic changes, including DNA mutations and methylation.[37] While nearly a third of CRC cases cluster in families and a portion of these, particularly in younger patients, may be related to inherited genetic predispositions, most CRC cases are sporadic, and the genetic and epigenetic changes observed in CRC tissues are acquired (ie, not related to familial or inherited genetic changes).[38] A noninvasive screening test has been developed to detect asymptomatic CRC and adenomas by identifying the acquired DNA alterations of several selected genes associated with colorectal cancer. Altered DNA, even trace amounts, shed into the stool from the cells on the surface of CRC and, to a lesser extent, precancerous lesions, can be selectively amplified to identify patients with cancer before bleeding or other clinical signs and symptoms develop.

This multitarget stool DNA (sDNA) test (Cologuard; Exact Sciences, Madison, Wisconsin) was recently approved by the US Food and Drug Administration (FDA) to screen adults of either sex, 50 years of age or older, who are at average risk for CRC.[39] The test is designed to analyze stool samples to identify 7 DNA mutations in the *KRAS* gene and 2 aberrantly hypermethylated genes (*BMP3* and *NDRG4*) that are associated with CRC. The test also includes a normal human gene (β-actin) as an internal DNA control. In addition, the multitarget sDNA test includes an immunochemical assay to detect hemoglobin in stool.

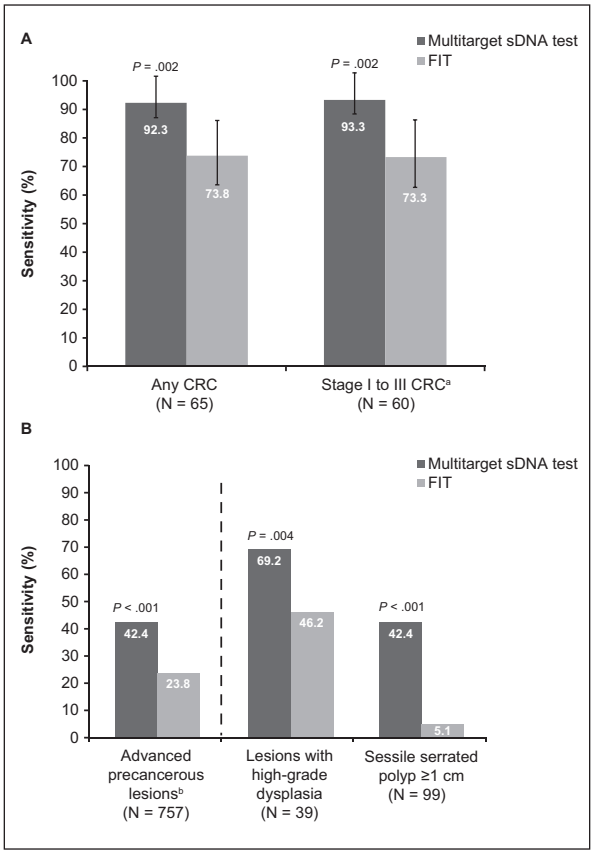
The test is easy to use, uses a single stool sample that can be collected at home, and does not require any bowel preparation or any changes in medication or diet. The stool sample is collected and stabilized with a buffer and shipped to a qualified laboratory to be homogenized and analyzed for abnormal DNA targets described above and hemoglobin. The results of the DNA and hemoglobin assays are combined in a diagnostic algorithm that provides a single composite positive or negative result. Patients with a positive test should undergo a diagnostic colonoscopy for full evaluation; those with a negative result can continue with their regular screening regimen. If the internal DNA control is of insufficient quantity, the test sample is considered inadequate and is not reported.

The ability of the multitarget sDNA test to detect CRC and precancerous lesions was evaluated in a prospective, multicenter, cross-sectional clinical study of more than 10,000 patients who were at average risk for CRC.[33] The study compared the performance of the multitarget sDNA test with both FIT (OC FIT-CHEK; Polymedco, Cortlandt Manor, New York) and colonoscopy, which was used as the reference standard for all other results.

Among the 9989 fully evaluable participants, colonoscopy identified 65 with CRC and 757 with advanced precancerous lesions. Multitarget sDNA testing showed significantly higher sensitivity than FIT for the detection of CRC (92.3% vs 73.8%; $P = .002$) and stage I to III CRC (93.3% vs 73.3%; $P = .002$) (**FIGURE 1A**).[33] Of the 65 cases of CRC detected with colonoscopy, multitarget sDNA testing missed only 5, whereas FIT missed 17, resulting in a miss rate that is more than 3 times greater than multitarget sDNA testing. The difference was more evident in early stage (I or II) CRC, where FIT missed 15 cancers but multitarget sDNA testing missed only 3 cancers. One of the cancers identified in the study could not be staged. The sensitivity of multitarget sDNA testing for detection of advanced precancerous lesions was also significantly higher than that of FIT (42.4% vs 23.8%; $P < .001$), including the detection of high-grade dysplasia (69.2% vs 46.2%; $P = .004$) and sessile serrated polyps that measured ≥1 cm (42.4% vs 5.1%; $P < .001$) (**FIGURE 1B**),[33] currently suspected of being the precancerous lesion leading to about 30% of CRC.[40]

Among the remaining 9167 study participants who had negative findings or nonadvanced adenomas (measuring <10 mm with no high-grade dysplasia or significant villous component) on colonoscopy, the specificity or true-negative rate for multitarget sDNA testing and FIT was 86.6% and 94.9%, respectively ($P < .001$).[33] In the subset of cases with completely negative findings on colonos-

FIGURE 1. Sensitivity of multitarget sDNA and fecal immunochemical tests for the detection of (A) colorectal cancer and (B) advanced precancerous lesions in participants with average risk for colorectal cancer[33]



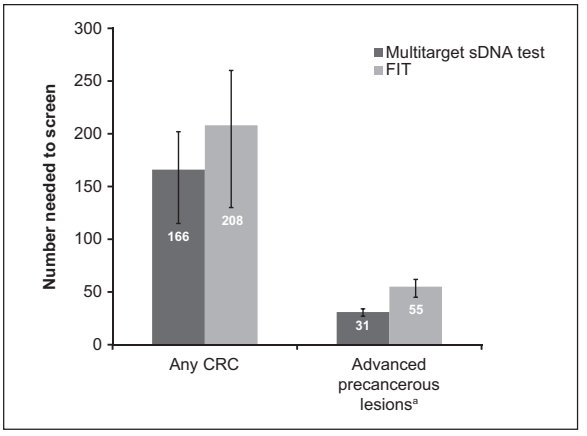
Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test.

Upper and lower limits on bars correspond to 95% confidence intervals.

[a]These stages of CRC, as defined by the system recommended by the American Joint Committee on Cancer, are associated with an increased rate of cure.

[b]Advanced precancerous lesions include advanced adenomas and sessile serrated polyps measuring 1 cm or more.

FIGURE 2. Number of participants needed to be screened to detect a cancer or an advanced precancerous lesion[33]



Abbreviations: CRC, colorectal cancer; FIT, fecal immunochemical test.

Upper and lower limits on bars correspond to 95% confidence intervals.

[a]Advanced precancerous lesions include advanced adenomas and sessile serrated polyps measuring 1 cm or more.

copy (n = 4457), the specificities were 89.8% and 96.4%, respectively ($P < .001$). Thus, the rate of false-positives was higher with multitarget sDNA testing than with FIT. Although recommended screening frequency differs, the increased rate of false-positive results with one-time use of multitarget sDNA testing compared to one-time use of FIT could increase costs related to noninvasive screening because of the follow-up colonoscopy. However, the cumulative rate of false positives is approximately equal, given annual use of FIT compared with a 3-year interval for multitarget sDNA testing. Longitudinal cost differences for these screening methods may differ from one-time use comparisons, though, due to frequency of FIT testing. It is worth noting that the isolated specificity for the hemoglobin component of the multitarget sDNA test was similar to that of FIT (94.8% vs 94.9%).

Following FDA approval, and based on the pivotal trial and cost-benefit modeling data, the US Centers for Medicare and Medicaid Services provided a National Coverage Determination for the multitarget sDNA test, covering it once every 3 years at no cost for Medicare Part B beneficiaries 50 to 85 years of age who are asymptomatic for CRC and do not have an increased risk of CRC.

There are several advantages to multitarget sDNA testing: It is a highly sensitive test and, unlike gFOBT/FIT, which are most sensitive in the distal colon, it has equal sensitivity for CRC in the proximal and distal colon and is more sensitive for precancerous lesions in the proximal colon than FOBT/FIT. The substantial efficiency of multitarget sDNA testing over FIT as a screening test for CRC is underscored by the number of individuals who would need to be screened to detect 1 malignancy (166 people with multitarget sDNA testing vs 208 with FIT) and 1 advanced precancerous lesion (31 with multitarget sDNA testing vs 55 with FIT) (**FIGURE 2**).[33] From a patient perspective, the benefits of multitarget sDNA testing include its ease of use with collection of only a single stool

sample in the privacy of one's home, no need for time off from work, no requirement for annual testing, no prior bowel preparation or dietary restrictions, and availability of resources/programs to improve compliance. A previous version of the sDNA test was preferred by most individuals who sought an alternative to colonoscopy.[41]

There are also a few drawbacks: It is unclear how the multitarget sDNA test compares with colonoscopy as a primary screening tool and how many participants with a positive multitarget sDNA test result will avoid recommended colonoscopy. Multitarget sDNA testing is currently not included in the USPSTF recommendations, but it is part of an ongoing evidence review that will form the basis for an updated recommendation statement. It is too early to determine the effect of the multitarget sDNA test on morbidity and mortality for CRC and quality-of-life outcomes; these data will become available with increased clinical use and modeling studies.

SUMMARY

The primary role of a screening test is to rule out diseases such as CRC in an asymptomatic population. Colonoscopy is effective for diagnosis and treatment, but its invasiveness, cost, and possible complications undermine its utility as a first-line screening tool for some patients. Multitarget sDNA testing is a highly sensitive, noninvasive screening tool that may be a viable alternative to colonoscopy in average-risk patients, 50 years of age or older, who avoid or choose not to have this procedure. Unlike other noninvasive tests such as gFOBT and FIT, multitarget sDNA testing has increased sensitivity for precancerous lesions and CRC in both the proximal and distal colon. The benefits of multitarget sDNA testing, including its ease of use and patient preferences, may lead to improved compliance and potentially increase overall CRC screening rates. ●

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