ADVANCES IN ENDOSCOPY

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Stool-Based Tests Vs Screening Colonoscopy for the Detection of Colorectal Cancer

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G&H What tools are available to screen for colorectal cancer?

DA Several tools are available for colorectal cancer (CRC) screening, including the guaiac-based fecal occult blood test, the fecal immunochemical test (FIT), flexible sigmoidoscopy, colonoscopy, computed tomographic colonography, and the multitarget stool DNA test (MT-sDNA; Cologuard, Exact Sciences). Longitudinal screening trials have directly established the effectiveness of the guaiac-based fecal occult blood test and flexible sigmoidoscopy in reducing CRC incidence and mortality. Statistic modeling with input assumptions on performance has been used to estimate the effectiveness of the other screening modalities, which are now more widely used. The estimated effectiveness measures by these CRC tools are significantly better than those of the modalities used for screening other common cancers, such as breast cancer.

However, CRC remains the second-leading cause of cancer death in the United States despite clinicians' screening efforts. A gap exists between where we are and where we could be, and there is an opportunity to improve the effectiveness of screening. Effective screening is the product of 3 critical factors: sensitivity, compliance, and access. Currently, screening tools vary in their sensitivity or accuracy. For example, sensitivities for early-stage CRC are essentially equivalent between colonoscopy and MT-sDNA and are significantly higher than with FIT. Compliance rates are suboptimal; approximately 65% of Americans report being screened at least once on survey questionnaires, but the participation rates may be lower based on actual record reviews. Fewer still are compliant with the screening frequencies recommended in guidelines. Finally, access (geographic or otherwise) is a barrier to many patients.

G&H What are the current recommendations for CRC screening?

DA Multiple groups, including the US Preventive Services Task Force, the National Comprehensive Cancer Network, the American Cancer Society (ACS), and the US Multi-Society Task Force, have established CRC screening guidelines. Age ranges of target populations differ slightly between these groups. The ACS recently updated its recommendations to start screening at age 45 years for all individuals (not just African Americans) rather than age 50 years, and to continue until age 75 years. The ACS suggests that screening is acceptable for individuals ages 76 to 85 years based on good general health and estimated longevity. For average-risk population screening, the ACS and other groups recommend a test frequency of every 10 years for colonoscopy, every 3 years for MT-sDNA, and annually for FIT. The various groups advise that it is up to an appropriately informed patient to choose which screening modality to follow.

G&H How are FIT and MT-sDNA performed?

DA FIT uses antibodies to detect human blood in the stool. A single stool sample is probed several times with a sampling stick, placed into a tube containing buffer preservative, and sent to a laboratory where it is assayed with a countertop automated device that quantifies the amount of human hemoglobin within the buffer using an immunochemical method. MT-sDNA is used to detect both altered DNA and hemoglobin in the stool. A whole stool is deposited into a bucket mounted to a toilet seat, a FIT sample is obtained as previously described, and then buffer preservative is added to the bucket, which gets sealed and sent to a central laboratory by mail courier service. In the laboratory, multiple components (eg, 2 methylated DNA markers, mutant *KRAS*, total human DNA, FIT) are assayed in an automated fashion with high quality control. A logistic algorithm calculates a score that is reported, as required by the US Food and Drug Administration, to be positive or negative.

G&H What are the advantages of using FIT or MT-sDNA to screen for CRC?

DA Both of these stool-based screening modalities are simple and noninvasive. Neither require diet or medication restrictions or cathartic preparation, such as enema or laxative oral lavage. The tests can be performed at home without lost work time, and are fully covered by Medicare and nearly all private insurance, with no out-of-pocket expenses for patients. In contrast to older guaiac-based tests, which detect upper gastrointestinal bleeding, FIT is less affected by proximal gastrointestinal bleeding, reducing the false-positive rate and making it more colon specific.

MT-sDNA was designed to address each factor in the formula for effective screening (ie, sensitivity, compliance, and access). The sensitivity of the test for detecting CRC ranged from 92% to 100% in 2 reported population screening studies. These rates are similar to what has been reported for colonoscopy, although the frequency of every 3 years for MT-sDNA vs every 10 years for colonoscopy may translate into superior CRC detection within a program over time. The sensitivity of MT-sDNA for adenoma detection increases with polyp size (42%-50% for polyps ≥1 cm in size, 63%-67% for polyps >2 cm, and 70%-80% for polyps >3 cm), suggesting that this test is effective in preventing as well as detecting CRC. Additionally, the quality of the procedure is not operator dependent. In contrast to all other screening tests, MT-sDNA has a patient navigation system (with multiple languages) built into its cost. Compliance rates over the first couple million tests averaged nearly 70%. One study reported that compliance among Medicare patients who were unwilling to undergo colonoscopy screening was 88%, and the yield for both CRC and advanced adenoma in this older population was remarkably high. Finally, MT-sDNA can be delivered by mail to the patient, making access to the test virtually unlimited.

G&H What are the disadvantages of these stool-based tests?

DA Relative to MT-sDNA and colonoscopy, FIT has low sensitivity for detecting CRC (70%-75% using colonoscopy as the criterion standard). Sensitivity is also low for precursor lesions, approximately 20% to 25% for advanced adenomas and less than 5% for advanced sessile serrated polyps. The annual frequency of testing is viewed as a disadvantage by some patients, as the program logistics to maintain this level of intervention are more intense and costly, and patient compliance rates to annual testing over time are low (14% over 3 years in some studies). FIT performance can also vary by manufacturer, time and temperature of storage prior to testing, and age and sex of patients. Although stool collection may be offputting to some patients and affects both FIT and MT-sDNA compliance, most surveys have shown that patients prefer noninvasive over invasive tests. Furthermore, the high compliance rate with MT-sDNA and FIT (which have navigation systems in place) suggests that stool collection is a minimal barrier.

Low specificity is a common misperception concerning MT-sDNA. In a large, multicenter population screening study conducted by Dr Thomas Imperiale and colleagues, specificity with this method was reported at 87%. However, this was based on the inclusion of non-advanced adenomas in the control group. Using a clean, polyp-free colon as control, point specificity was 90%, and 93% in patients age 65 years and younger. Specificity was 93% in an Alaskan population screening study by Dr Diana G. Redwood and colleagues. What is critical over a screening lifetime is the cumulative false-positive rate. Because MT-sDNA is performed every 3 years, an annualized specificity of 96% to 98% can be estimated, which compares favorably to the 95% to 96% specificity by FIT, which is performed annually. In modeling by the US Preventive Services Task Force, MT-sDNA was associated with the fewest number of unnecessary colonoscopies and the highest benefit-to-harm ratio over a screening lifetime when compared to other screening modalities.

G&H What are the advantages and disadvantages of screening with colonoscopy?

DA Under ideal conditions, a colonoscopy inspects the entire colorectal surface. Lesions, if found, can typically be biopsied or removed during the same procedure. The sensitivity for CRC and polyp detection is exceptionally high when performed by expert endoscopists. However, although colonoscopy is often used as the reference standard, the quality differs depending on operator skill and attention. The adenoma detection rate across endoscopists varies from roughly 5% to 50% in clinical studies with a median adenoma detection rate of 25%, and the difference in detection rates for sessile serrated polyps may be even greater (nearly 20-fold across endoscopists). Large clinical studies have shown that screening colonoscopy is substantially less effective in reducing incidence and mortality from right-sided CRC vs left-sided CRC, and interval cancers are most common following colonoscopy by endoscopists who have low adenoma detection rates. Compliance rates vary, with one study observing rates between 38% and 42%. Additionally, colonoscopy requires up to 2 days of missed work, which may involve uncompensated wages, travel and lodging costs, and the need for a chaperone to accompany the patient. For individuals who live paycheck to paycheck, this can be a significant barrier.

G&H What adverse events are associated with each screening technique?

DA Each procedure may miss lesions or be associated with false positives, which can cause harm indirectly. However, only colonoscopy may cause harm directly. A meta-analysis demonstrated that the overall complication rate per 1000 procedures averaged 26, and gastrointestinal events (eg, bleeding, perforation), cardiopulmonary events, and mortality averaged 6.3, 19, and 1, respectively, per 1000 procedures. Complications also increased with age. Some studies have observed that 1% to 2% of all patients undergoing colonoscopy report to the hospital or emergency department within 7 days of the procedure. These are factors that should be discussed with patients when choosing an option.

G&H Have any cost-effectiveness studies evaluated the use of FIT, MT-sDNA, and colonoscopy to screen for CRC?

DA Modeling has shown that CRC screening with these 3 modalities is cost-effective, especially compared to the estimated cost of screening for other cancer types, such as breast cancer. Some cost-effective models have suggested that colonoscopy and FIT may be somewhat more cost-effective than MT-sDNA; however, input assumptions can be challenged. Of critical importance, cost-effectiveness modeling often assumes 100% compliance, which is not realistic, and is calculated from the perspective of the third-party payor, not the patient. Inclusion of patient costs of missed work, uncompensated wages, travel, and other inputs from a patient perspective would change cost-effectiveness outputs. Thus, there is a need to redo cost-effectiveness modeling with updated input assumptions on test performance and to consider models with patient-cost inputs.

G&H Are there any patients in whom these screening modalities are contraindicated?

DA All 3 tests are endorsed for average-risk, general population screening. Individuals who are at higher-than-average risk (eg, strong family history, genetic syndromes) should generally be surveilled by colonoscopy at intervals more frequent than every 10 years. Some providers have chosen to use stool testing off-label as an alternative option for higher-risk patients who do not want to undergo colonoscopy or who are at risk for complications from colonoscopy. Poor general health that compromises or shortens life expectancy is regarded as a relative contraindication, as screening may not meaningfully benefit such patients and may introduce harm. Finally, certain cardiovascular or pulmonary conditions or obligated medication usages (eg, anticoagulants) may represent contraindications to colonoscopy and should be considered on a case-by-case basis.

G&H What are the priorities of research in this field?

DA It is important to pursue approaches that address sensitivity, compliance, and access, the 3 factors contributing to screening effectiveness. Test sensitivity can be improved by reducing operator-dependent variables in colonoscopy performance and by refining characteristics of noninvasive tools to further increase sensitivity. Systems that can improve compliance and participation by reducing barriers need to be evaluated and implemented, and methods to maximize access and screening system capacity should be pursued.

Additionally, longitudinal prospective studies directly comparing short-term outcomes of patient preference and compliance; colorectal neoplasia yield; and complications of FIT, MT-sDNA, and colonoscopy would provide substantial value.

Finally, as technology continues to advance, there is always an opportunity to improve the tests themselves, whether through refinements of existing tests or by the development of new types of screening technologies that are not currently on the radar. CRC may be the most

screenable type of cancer based on its biology and accessibility. Screening success at the population level will require not only improvements in effective detection, but also the necessary collaborations between payors, providers, academia, professional societies, industry, and government. Concerted efforts at the community level have demonstrated that substantial improvements in CRC screening participation can be achieved.

Dr Ahlquist is a co-inventor of MT-sDNA and shares royalties from Exact Sciences with Mayo Clinic in accordance with institutional policy. He currently provides consultation to Exact Sciences and collaborators at Mayo Clinic on scientific strategy and research design for next-generation molecular screening tools.

Suggested Reading

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