Colorectal cancer (CRC) remains the third most commonly diagnosed cancer and the second leading cause of cancer death in the United States. In 2009, an estimated 146,970 new cases of CRC were diagnosed, and approximately 49,920 people died of the disease.¹ The average lifetime risk of developing CRC is 6%, with men and women almost equally affected. CRCs typically develop from adenomatous polyps which progress from small to large (>1 cm) size, and then to high-grade dysplasia and cancer. This progression from adenoma to carcinoma is believed to take at least 10 years.² The slow transition from polyps to CRC in most patients allows opportunities to prevent cancer by removing polyps, and to prevent cancer death by finding and removing early cancers. Several screening tests are available and well established, each with advantages and limitations. Although stool-based tests improve disease prognosis mainly by detecting early stage cancers, endoscopic and radiologic tests that visualize the bowel mucosa have the potential to also prevent cancer by detecting polyps that can be removed before malignant transformation. This article discusses the potential role of computed tomographic colonography (CTC) in a CRC screening program by first providing a brief review of current screening recommendations and traditional screening options, followed by a discussion of specific CTC test characteristics, economics and implementation issues that may affect the adoption and positioning of CTC within the overall framework of CRC screening.

CRC SCREENING: PREVALENCE AND BARRIERS

Despite considerable evidence supporting the effectiveness of CRC screening and the availability of various screening tests, half of the US population aged 50 years...
and older is still not undergoing CRC screening according to 2005 estimates from the National Health Interview Survey. This compares with more than 80% of eligible women participating in breast cancer screening programs. The prevalence rates for CRC screening are lower among people aged 50 to 64 years and especially low among individuals who are nonwhite, have fewer years of education, lack health insurance coverage, and are recent immigrants. These low rates cannot be attributed to any single factor (such as fear of undergoing colonoscopy) but are related to a variety of issues including lack of public knowledge about the importance of screening and testing options, lack of time, fear of being diagnosed with cancer, embarrassment, unpleasantness of the test, as well as concerns about costs. Health insurance barriers such as insurance status and coverage limitations are also significant factors. Although the addition of new and potentially less invasive screening tests such as CTC may overcome some of these barriers, they are unlikely to resolve all of them. Their effect on overall screening rates and the costs of screening can therefore not be easily predicted and need to be carefully studied and evaluated over time.

**CURRENT RECOMMENDATIONS FOR CRC SCREENING**

For more than 2 decades, CRC screening guidelines have been independently developed and updated by multiple organizations. Recently, 2 new sets of guidelines were published. One was developed by the American Cancer Society, the US Multisociety Task Force on Colorectal Cancer (a consortium representing the American College of Gastroenterology, the American Society of Gastrointestinal Endoscopy, the American Gastroenterological Association, and representation from the American College of Physicians), and the American College of Radiology (ACS-MSTF-ACR). The other guideline was developed by the US Preventive Services Task Force (USPSTF). The recommendations from these 2 guidelines are detailed in Table 1. Although their conclusions are similar, they differ in several specific recommendations, especially as they relate to CTC. To put these recommendations into the appropriate context, the traditional CRC screening tests are briefly reviewed.

**Fecal Occult Blood Tests**

Fecal occult blood testing (FOBT) is most commonly performed using a guaiac-based test that detects peroxidase activity of heme in small stool samples. These tests can be performed at home, are noninvasive, have a low initial cost, and require few specialized resources. Colonoscopy should be recommended if FOBT is positive, and testing should be done annually if the results are negative. One-time testing (3 samples) with a standard guaiac test has a sensitivity for advanced neoplasia of only 33% to 50%, whereas a more sensitive guaiac test (Hemoccult Sensa) has a sensitivity of 50% to 75%. The Minnesota Colorectal Cancer Control Trial showed that individuals who were screened with FOBT on an annual basis experienced a 33% reduction in CRC mortality with 38% of these individuals undergoing colonoscopy at some point during the 13-year study.

Immunochemical-based FOBT tests use antibodies against human hemoglobin or other blood components and are therefore more specific for human blood. Their sensitivity for detecting cancer ranges from 60% to 85% but the performance of different commercially available tests has varied considerably leaving many questions with regard to the optimal test and the required number of stool samples.

Stool DNA testing is based on the detection of specific mutations associated with CRC in DNA which is excreted in stool. Advantages include the potential for high
test accuracy, the theoretic ability to detect cancers proximal to the colon, and the relative noninvasiveness of the test. However, the lack of data from screening populations, and the high cost of the currently available versions of the test limit its usefulness at this time.10

### Barium Enema

Double contrast barium enema (DCBE) is no longer a recommended CRC screening modality according to the USPSTF guideline, and is only noted as a secondary modality in the ACS-MSTF-ACR guideline. DCBE identifies most late-stage cancers but cannot detect clinically important precursor lesions with any accuracy. It is rarely used as a screening tool in today’s practice.

### Sigmoidoscopy

Sigmoidoscopy allows for direct visualization of the bowel lumen and the ability to take a biopsy or remove lesions at the time of the procedure. Adenomas found during sigmoidoscopy often prompt full colonoscopy with subsequent detection of premalignant or malignant lesions in the portion of the colon not seen with the sigmoidoscope.

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<table>
<thead>
<tr>
<th>Table 1</th>
<th>US colorectal cancer screening guidelines 2008</th>
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<tbody>
<tr>
<td><strong>Screening Test</strong></td>
<td><strong>ACS-MSTF-ACR</strong></td>
</tr>
<tr>
<td>Sensitive guaiac fecal occult blood test</td>
<td>Recommended if &gt;50% sensitivity for CRC</td>
</tr>
<tr>
<td>Fecal immunochemical test</td>
<td>Recommended if &gt;50% sensitivity for CRC</td>
</tr>
<tr>
<td>Stool DNA test</td>
<td>Recommended if &gt;50% sensitivity for CRC</td>
</tr>
<tr>
<td>Flexible sigmoidoscopy</td>
<td>Recommended if sigmoidoscope is inserted to 40 cm of the colon or to the splenic flexure</td>
</tr>
<tr>
<td>Barium enema examination</td>
<td>Recommended, but only if other tests not available</td>
</tr>
<tr>
<td>Colonoscopy</td>
<td>Recommended, with referral for colonoscopy if polyps ≥ 6 mm in diameter detected</td>
</tr>
<tr>
<td>CTC</td>
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It is estimated that approximately half of all polyps and cancers are within reach of a flexible sigmoidoscope and that the prevalence of advanced proximal neoplasia in patients without distal adenomas is around 2% to 5%. An often-quoted case-control study found a 59% reduction in CRC mortality for cancers within the reach of the sigmoidoscope but no benefit of sigmoidoscopy with respect to mortality from cancers beyond the reach of the instrument. A large randomized controlled trial found no reduction in the incidence of colorectal cancer among individuals assigned to screening sigmoidoscopy, and in an intention-to-treat analysis, there was only a nonsignificant reduction in mortality at 6 years among these individuals compared with controls. Sigmoidoscopy requires a bowel preparation, an office visit, and it is not well reimbursed relative to the required resources. For many patients and physicians, colonoscopy has therefore become a more appealing option.

**Colonoscopy**

Colonoscopy is an attractive screening tool because it offers the ability to visualize the entire colon in most patients and to detect, take a biopsy, and/or remove mucosal lesions in 1 setting. Colonoscopy is also the final common pathway for the evaluation of other positive screening tests. The American College of Gastroenterology guidelines for CRC screening list colonoscopy as the preferred screening modality. The sensitivity and specificity of colonoscopy are difficult to measure because colonoscopy is often considered to be the gold standard. However, tandem colonoscopy studies have shown that 0% to 6% of large polyps (≥ 1 cm) are missed and up to 27% of smaller lesions are missed. Several large cohort studies have shown the feasibility and safety of colonoscopy as a primary screening test. These studies show that among patients at average risk who undergo screening colonoscopy, 0.5% to 1% have colon cancer and 5% to 10% have advanced neoplasia that can be removed. No randomized controlled trials have compared the outcomes of colonoscopy with those of other forms of screening. In case-control studies, colonoscopy is associated with reductions in the incidence of and mortality from CRC. The recommended 10-year interval for repeat examination is based on case-control studies.

**GUIDELINE RECOMMENDATIONS RELATED TO CTC**

Although the USPSTF and the ACS-MSTF-ACR reviewed the same evidence and similar decision models, these consensus groups reached different conclusions with regard to CTC (see Table 1). A commentary accompanying the USPSTF publication suggests that subtle differences in emphasis may underlie the differing conclusions. The USPSTF judged the evidence for CTC to be insufficient to evaluate its benefits and harms. This guideline put more emphasis on the unknown effects of radiation exposure and the potential for harm caused by the evaluation of extracolonic findings, taking a more longitudinal perspective. In contrast, the ACS-MSTF-ACR guidelines include CTC as a recommended screening option with a suggested interval of testing every 5 years. They focus on the capability of CTC to detect large polyps in a single screening visit and as such favor screening technologies with superior single screening detection characteristics over less sensitive tests, based in part on the presumption that the availability of additional methods of screening will improve compliance.

**FACTORS INFLUENCING THE ADOPTION OF CTC AS A SCREENING TOOL**

If CTC can be demonstrated to be effective, safe, and economically viable, and if it increases patients’ acceptance of CRC screening, its addition to the list of screening
options will be a positive development from a public health perspective. Whether CTC will be widely adopted as a screening tool is not entirely clear at the time of this writing and will depend, among other factors, on the demonstration of its accuracy outside of tertiary referral centers, the availability of testing facilities and trained readers, a proven safety record of the test itself and the follow-up studies it triggers, its associated costs, and coverage determinations by insurance carriers. Some of these issues are reviewed in the following sections.

**Accuracy of CTC**

The performance of CTC relative to colonoscopy is discussed in greater detail in other articles in this issue. Early studies of CTC typically involved smaller numbers of individuals at higher risk for colorectal disease and did not always control well for interpreter experience and technical factors. Initial, large, multicenter trials yielded variable results with regard to the sensitivity for polyp detection. CTC technology and techniques have since evolved at a rapid pace and it is not appropriate to simply combine results from those older studies with newer ones.

The largest study of a screening population, the American College of Radiology Imaging Network (ACRIN) trial, was recently published and showed favorable results. The primary aim of the trial was to evaluate the sensitivity of CTC compared with colonoscopy, for detecting individuals with a clinically significant lesion, defined as larger than 10 mm. The study found a 90% sensitivity and an 86% specificity of CTC for polyps 10 mm or larger. The positive and negative predictive values were 23% and 99%, respectively. Many of the current conclusions about the potential role of CTC as a screening tool rely on the generalizability of this trial to general screening populations and community radiologists. Important features of the trial included large number of enrolled individuals (>2500), multiple institutions (n = 15), minimum 16-slice CT scanner, stool tagging, and comparison of several commonly used bowel preparation regimens. It should be noted that the ACRIN trial featured a strict training and operator qualifying examination component. Each participating radiologist was required to submit confirmation of having interpreted at least 500 CTC examinations or having participated in a specialized 1.5-day CTC training session. In addition, all participating radiologists were required to complete a qualifying examination in which they achieved a detection rate of 90% or more for polyps measuring 10 mm or more in diameter in a reference image set. The importance of adequate training of CTC readers for the effectiveness of the technique has now been widely acknowledged, and it remains to be seen if similar high reading performance can be achieved in everyday clinical practice.

Translating this diagnostic sensitivity to an inference of effectiveness for preventing colon cancer mortality requires the same chain of logic that supports colonoscopy as an effective screening test. Thus, it can be assumed that a test that approaches the sensitivity of colonoscopy for the detection of clinically relevant polyps should logically approach the clinical effectiveness of colonoscopy as well. However, several other differences between colonoscopy and CTC regarding comfort, convenience, screening intervals, and other ancillary health outcomes are difficult to quantify. Although they may be viewed as minor, patients should be adequately informed of these differences, as these may influence the ultimate choice of the screening procedure.

**Patient Preference**

How CTC is perceived and tolerated will play an important role in its ultimate acceptance as a screening tool. Studies on patient preference for various colon imaging
procedures have yielded mixed results with some studies showing a preference for CTC and others concluding that colonoscopy is the preferred test. Current CTC techniques require meticulous bowel preparation analogous to that required for colonoscopy. Feasibility studies are being performed to evaluate if electronically subtractable fecal markers could be used to allow detection of polyps without a colon preparation. The elimination of the need for a purgative preparation would certainly further enhance the appeal of CTC, but these techniques are not currently ready for widespread use.

Although it requires a full bowel cleansing similar to that required for colonoscopy, CTC is usually done without sedation, may be faster to perform than colonoscopy and might therefore be more attractive to some patients. To what degree these differences will serve to enhance screening compliance remains to be determined. Presumably, the availability of same-day colonoscopy, if needed to remove polyps found on CTC, will be important to individuals who do not want to undergo a second colon preparation on a separate day. As outlined in the article by Cash in this issue, the number of cases requiring same-day colonoscopy can be anticipated to be small, but close coordination between radiology and gastroenterology units will be required. According to the ACRIN trial, 12% of patients would be referred for colonoscopy if the lesion threshold was 6 mm or larger (as recommended in the ACS-MSTF-ACR guideline), with approximately 4% of individuals exhibiting lesions of 10 mm or larger.

Safety

CTC is well tolerated. Colon insufflation has been associated with a small risk of perforation, but most of these complications occurred in symptomatic patients who underwent manual air insufflation as opposed to automated low-pressure carbon dioxide insufflation.30,31 The International Working Group on Virtual Colonoscopy reported no perforations in more than 11,000 screening CTC examinations and 1 perforation in 22,000 screening and diagnostic CTC examinations.

Another risk associated with CTC relates to radiation exposure, especially in patients who are obese and in those undergoing repeated examinations to follow up on small polyps left in situ. A routine CT scan of the abdomen administers a radiation dose of approximately 15 milliSievert (mSv). The dose of a CTC is less, but estimating the precise risk to the individual is difficult. In one model that used typical current scanner techniques, an approximately 0.14% increased lifetime cancer risk was calculated for a 50-year-old patient undergoing a single CTC. Imaging techniques using lower-dose radiation are currently being studied.34,35 Highly publicized studies on the potential hazards and uncertain risk-benefit ratios of ionizing radiation exposure during medical imaging may well contribute to the reluctance on the part of the public and some health professionals to consider screening modalities based on x-rays.

Effect of Extraluminal Findings

CTC can detect extracolonic lesions of varying importance (eg, calcifications, gallstones, hernias, bone lesions, abdominal aortic aneurysms, and benign and malignant tumors). The effect of these extraluminal findings has not fully been assessed, nor has its effect on cost-effectiveness. Although the opportunity to find and treat serious problems such as abdominal aortic aneurysms, renal cancers, and ovarian cancers in asymptomatic patients may be important, it is unclear if these discoveries change mortality (except for aortic aneurysms). Flicker and colleagues suggested that the incremental cost may be minimal if strict parameters are implemented for triggering additional evaluations, but further studies are needed to better understand the effect of these extracolonic findings as well as the benefits and costs of their work-up.
Cost-effectiveness

Cost-effectiveness assessments for screening tests are complex and need to include the costs associated with the original test, as well as the costs associated with the evaluation of positive test results, surveillance, complications, and the costs of cancers not avoided. Several cost-effectiveness models have been developed for screening CTC.41–45 Although some studies have found CTC to be a cost-effective screening strategy, others have suggested that it will not be as cost-effective as colonoscopy. These models are sensitive to CTC performance characteristics, presumed costs of various interventions, and the threshold for referring patients for colonoscopy. Many were based on older CTC studies and are now outdated. As screening CTC becomes more widely adopted, additional analyses using more up-to-date inputs will be needed to more accurately assess the cost-effectiveness of CTC.

Insurance Coverage

Reimbursement for CTC in general, and coverage of screening CTC in particular, remains highly variable but payor decisions are increasingly favorable. In May 2009, the Center for Medicare and Medicaid Services (CMS) issued a noncoverage decision stating that “the evidence is inadequate to conclude that CT colonography is an appropriate colorectal cancer screening.”46 This noncoverage decision by the largest US payor undoubtedly slowed the adoption of CTC as a screening test. The CMS decision notwithstanding, many health insurance plans are now covering CTC for screening and/or for a variety of other indications. To some degree, coverage by private payors is driven by state laws, now in place in 26 States and the District of Columbia,47 mandating coverage for CRC screening services.

The Blue Cross/Blue Shield Technology Evaluation Center (TEC), a group of research scientists and medical advisors who provide comprehensive evaluations of the clinical effectiveness and appropriateness of medical procedures, devices or drugs, recently revised its initial negative assessment and concluded that CTC for the purpose of colon cancer screening meets their TEC criteria.48 The California Technology Assessment Forum (CTAF), a public service forum spearheaded by the Blue Shield of California Foundation, which assesses new and emerging medical technologies, concluded in their March 2009 assessment of CTC that “…despite the exciting results of the ACRIN trial, several important questions remain before CTC can be recommended for widespread use. First, how well would it perform in a setting where the radiologists were not so highly trained. Second, what is the clinical impact of the possible harms of the procedure, including radiation risk (especially with CTC repeated periodically) and the high incidence of extracolonic findings? Thus, despite its diagnostic accuracy, because the impact of the potential harms is not currently known, CTC is not currently recommended for screening asymptomatic individuals for CRC.”49

The Current Procedural Terminology (CPT) Panel of the American Medical Association established category I CPT codes for CT colonography in January 2010. CPT 74263 now describes screening CTC, and CPT 74261 and CPT 74262 are to be used to describe diagnostic CTC without and with contrast, respectively. The existence of category I CPT codes does not immediately equate to insurance coverage and payment for these services, but their existence facilitates reporting of a service, indicates to third parties that a service has become more established, and as such often prompts carriers to reevaluate previous coverage decisions.
IMPLEMENTATION ISSUES

Before CTC can be implemented as a screening tool on a more widespread basis, several additional pragmatic and logistical issues have to be addressed. The first relates to the number of centers and qualified readers required to perform CTC on a widespread basis. With some 40 to 60 million Americans eligible for a colon cancer screening examination and in excess of 10 million colonoscopies performed each year, there is a high demand for screening services. It has been estimated that although the number of multidetector CT facilities in the United States may be adequate, there are currently no more than a few hundred highly trained readers; there will be a demand for several thousand readers if this screening volume is to be met.

Another issue has to do with whether and how to report polypoid lesions at the time of CTC. Should small lesions (<5–6 mm) be ignored and not reported as some have suggested? Although the rate of malignancy in such small lesions is likely very small, it is not zero, and leaving small polyps in place and following these patients with serial CTC examinations would represent a fundamental departure from current screening paradigms. The optimal surveillance protocol for this situation has not been established, and cumulative costs, procedural risks, and radiation exposure from serial CTC examinations would have to be considered. More research is needed in these areas, especially as it relates to flat lesions, right colonic hyperplastic polyps, and certain types of serrated adenomas where size alone may not be the key determinant of neoplastic risk. It remains unclear whether patients and providers would accept a practice in which patients are given a choice as to whether or not to remove certain lesions or leave them in place and follow them on a regular basis. Studies of this issue have yielded conflicting results.

The potential effects of CTC adoption on colonoscopy rates has been hotly debated. Is CTC attractive enough as a new screening modality to increase the proportion of those being screened, or will it simply divert those who are already being screened from one test to another? Will it lead to a decrease in the number of colonoscopies being performed or increase the number of therapeutic examinations being done for removal of polyps that were detected on CTC? To some degree, the answer to the latter question depends on the threshold set for triggering a colonoscopy; although a polyp size threshold of greater than 10 mm might lead to fewer follow-up colonoscopies, a reduced polyp size threshold, if coupled with an increased number of individuals recruited for CRC screening, would likely lead to a significant demand for follow-up colonoscopies.

As mentioned previously, any implementation of a CTC screening program will benefit from a close collaboration between radiologists and gastroenterologists with regard to triaging individuals to the various available screening methods, arrangements for same-day colonoscopy if required, patient education about test results, and follow-up arrangements.

SUMMARY

In summary, CTC has become well established as a new technology for large bowel imaging. Following favorable results in recent large-scale trials, CTC is gaining acceptance among patients, clinicians, professional societies, and third party payors as a viable option for CRC screening. It remains to be determined, however, whether CTC will ultimately become a preferred screening tool or play a secondary role within CRC screening programs. High test accuracies need to be replicated in community practice settings, and additional testing facilities and highly trained readers are required to meet demand. Various patient and provider concerns still need to be
addressed with regard to safety issues, and optimal management algorithms need to be determined for lesions found on CTC. Additional favorable coverage determinations and reimbursement decisions from third party payors will also further promote the widespread adoption of CTC as a screening tool.

REFERENCES


