

# CT Colonography (“Virtual Colonoscopy”) for Colon Cancer Screening



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## Executive Summary

### Background

Computed tomographic (CT) colonography, also known as “virtual colonoscopy,” is an imaging technique of the colon involving helical computed tomography and computer software to generate high-resolution 2-dimensional and 3-dimensional images of the inner surface of the colon. These images are then interpreted by a radiologist to determine the presence of several types of abnormalities of the colon. CT colonography has been investigated as a technique for colon cancer screening. Although it requires a full bowel cleansing similar to that required for conventional colonoscopy, the procedure requires no sedation or analgesia, and is faster to perform than conventional colonoscopy.

### Objective

To determine whether there is adequate evidence to demonstrate that CT colonography screening is effective in reducing mortality from colon cancer. A companion Special Report will provide a critical appraisal of cost-effectiveness analyses of CT colonography.

### Search Strategy

Studies that examine the diagnostic sensitivity and specificity of CT colonography for the detection of polyps.

### Selection Criteria

For the main evidence review, adequately designed studies that assess the diagnostic sensitivity and specificity of CT colonography. Studies were included if they had the following characteristics:

1. Prospective enrollment of subjects undergoing both CT colonography and optical colonoscopy
2. Valid reference standard (usually colonoscopy, sometimes “unblinded colonoscopy”)
3. Valid per-patient analysis of CT colonography allowing calculation of both sensitivity and specificity at a specific polyp size threshold, and adequate data to calculate prevalence rates of polyps and referral rates (test-positive rates)
4. Minimum sample size of 50 patients

### Main Results

Diagnostic performance of CT colonography is highly dependent on the technology and techniques used. Thus, many of the older studies reviewed may no longer represent currently possible diagnostic performance of the test. A large study published in 2003 showed diagnostic test performance of CT colonography for polyps to be equivalent to that of optical colonoscopy. Other studies published previously and after that study showed variable performance, with 2 large studies showing much lower sensitivity than optical colonoscopy. Results from the largest study of a screening population, the ACRIN trial, were recently published. This study used 16–64 row detector CT scanners, stool tagging

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techniques, and minimum training standards for interpreters of the test. The results of this study showed 90% sensitivity of CT colonography for polyps 10 mm or larger and 86% specificity; positive and negative predictive values were 23% and 99%, respectively.

Translating this diagnostic sensitivity to an inference of effectiveness for preventing colon cancer mortality requires the same chain of logic that supports optical colonoscopy as an effective screening test. Thus, a test that approaches the sensitivity of optical colonoscopy for the detection of clinically relevant polyps should logically approach the clinical effectiveness of optical colonoscopy, as optical colonoscopy is considered to be the most effective technique for cancer screening and prevention.

Several other differences between optical colonoscopy and CT colonography regarding comfort, convenience, screening intervals, other ancillary health outcomes are difficult to quantify, but are probably small in magnitude in terms of ultimate health outcomes. However, patients should probably be adequately informed of these differences, as these may very well determine which type of screening test the patient chooses to have.

### **Authors' Comments and Conclusions**

The conclusions of this Assessment rely on the generalizability of the ACRIN trial to general screening populations and community radiologists. This trial constitutes the most important and substantively new evidence available since the prior TEC Assessment, which was published in July 2004. The prior TEC Assessment concluded that CT colonography did not meet the TEC criteria. Overall, sensitivity reported in the literature was quite variable among studies. Interpreter experience and technical factors were suggested to be likely explanations for the observed variability in performance. The 2004 Assessment also noted that clear criteria needed to be established for polyp size threshold for removal and for frequency of screening in order to estimate the effectiveness of CT colonography.

The ACRIN trial addressed many of the gaps identified in the prior Assessment. Important features of the trial include a large population (n=2,600), multiple institutions (n=15), minimum 16-slice CT scanner, stool tagging, and comparison of 3 commonly used bowel preparation regimens. As described in the trial protocol (ClinicalTrials.gov Identifier NCT00084929), the primary aim of the trial was to evaluate the sensitivity of CT colonography, compared to optical colonoscopy, for detecting individuals with a clinically significant large lesion, defined as larger than 10 mm. Secondary aims were sensitivity for detecting polyps from 5–10 mm and for detecting signal characteristics (i.e., high-grade dysplasia, invasive carcinoma, and/or villous features) of polyps 5 mm or larger. Of practical importance, the trial evaluated interobserver variability in accuracy of CT colonography examination interpretation. Additional descriptive data that will contribute to assessing effectiveness of CT colonography include patient acceptance, prevalence and distribution of flat lesions, prevalence and clinical significance of extracolonic findings, and differences in interpretation techniques.

The ACRIN trial featured a training and operator qualifying examination component. The news item summarizing the preliminary ACRIN results also included comments from the principal investigator of the trial citing the importance of adequate training and credentialing of CT colonography readers for the effectiveness of the technique. This suggests the need to credential providers who perform this procedure, at least in the initial phase of dissemination. The 2008 guideline on colon cancer screening, a joint guideline of the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (ACR) notes that, following the publication of the results of the ACRIN trial, the 2006 *ACR Practice Guidelines for Performance of Computed Tomography (CT) Colonography in Adults* will be updated. The ACR Guidelines address “the techniques, quality control, clinical uses, training, and communication of results for [CT colonography].” The joint guideline also notes that the ACR is piloting quality metrics for CT colonography, has begun construction of an interactive training facility, and is evaluating “a process for individual certification and proficiency.” Standards for training of gastroenterologists performing CT colonography were published by the American Gastroenterological Association in 2007.

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether CT colonography for colon cancer screening meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

**1. The technology must have final approval from the appropriate governmental regulatory bodies.**

CT colonography may be performed using any CT scanner capable of producing helical (spiral) thin-section images ( $\leq 5$  mm). More recent studies have been conducted using commercially available multidetector-row (multislice) helical CT scanners that facilitate faster image acquisition and thinner sections. The 2-dimensional cross-sectional CT images may be interpreted directly and software algorithms using 3-dimensional reformatting techniques may also be used to facilitate interpretation. Three-dimensional reformatting software may be cleared through the U.S. Food and Drug Administration (FDA) for this specific application. For example, the Viatronix V3D-Colon<sup>®</sup> virtual colonoscopy system (Viatronix, Inc., Stonybrook, NY) was cleared for marketing by the FDA via the 510(k) process on April 19, 2004, for use as a screening tool in detecting colon cancer.

**2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

No direct evidence is available on health outcomes. An inference of effectiveness must be made based on a chain of logic that starts with the diagnostic sensitivity and specificity of CT colonography. The ACRIN study, a large trial of a screening population, using the latest scanners and techniques for bowel preparation and image interpretation, showed a 90% sensitivity of CT colonography for detection of polyps 10 mm or larger and a specificity of 86%; positive and negative predictive values were 23% and 99%, respectively.

**3. The technology must improve the net health outcome; and**

**4. The technology must be as beneficial as any established alternatives.**

Given the chain of logic and other underlying evidence that support the practice of accepted colon cancer screening techniques such as optical colonoscopy, a 90% sensitivity of CT colonography for detection of polyps 10 mm or larger is consistent with an improvement in health outcomes due to detection and removal of precancerous lesions. The 86% specificity of CT colonography would result in some false-positive tests, which, in turn, would result in some unnecessary follow-up colonoscopies. However, compared with optical colonoscopy, there are several other types of health outcomes that may differ in terms of convenience, cost, detection of unrelated health problems, and radiation exposure. These are difficult to quantify, and are probably small in magnitude compared to the health benefit of identifying and removing cancer precursors.

**5. The improvement must be attainable outside the investigational settings.**

The results of the ACRIN trial were dependent on the technical standards required for performance of the test and the training and skill of the interpreters of the test. Each participating radiologist was required to submit confirmation of having interpreted at least 500 CT colonographic examinations or having participated in a specialized 1.5-day CT colonography 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. If these practices can be replicated in the community, then it is likely that improved health outcomes can be achieved outside investigational settings. Standards of performance and interpretation of CT colonography consistent with those reported in the ACRIN trial will be necessary for CT colonography to be an effective screening test.

Based on the above, CT colonography for the purpose of colon cancer screening meets the TEC criteria.

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## Assessment Objective

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Computed tomographic (CT) colonography, also known as “virtual colonoscopy,” is an imaging technique of the colon involving helical computed tomography and computer software to generate high-resolution 2-dimensional and 3-dimensional images of the inner surface of the colon. These images are then interpreted by a radiologist to determine the presence of several types of abnormalities of the colon. CT colonography has been investigated as a technique for colon cancer screening. Although it requires a full bowel cleansing similar to that required for conventional colonoscopy, the procedure requires no sedation or analgesia, and is faster to perform than conventional colonoscopy. However, since it is only an imaging procedure, patients with positive findings require conventional “optical” colonoscopy afterwards. Thus, its use is more rational for the screening situation, where there is a low probability of positive findings requiring referral for optical colonoscopy.

CT colonography can detect overt cancers, but these are rare in asymptomatic patients. The major benefit from CT colonography and other colon cancer screening techniques results from identification and removal of cancer precursors called adenomatous polyps. This clinical Assessment reviews evidence on the effectiveness of CT colonography for the purpose of colon cancer screening. A companion Special Report will provide a critical appraisal of cost-effectiveness analyses of CT colonography.

## Background

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### Colorectal Cancer

Estimates for both colorectal cancer incidence and mortality in the U.S. in 2003 ranked third among all cancers in men and women (American Cancer Society 2003). The primary risk factor is age; more than 90% of cases are diagnosed in adults over age 50. It is estimated that at age 50, a person has about a 5% remaining lifetime risk of being diagnosed with colorectal cancer. About 20% of cases occur in persons with specific risk factors (e.g., inflammatory bowel disease), and about 6% arise from persons with uncommon genetic syndromes such as familial adenomatous polyposis (U.S. Preventive Services Task Force 2002). The incidence also is increased in individuals

with a personal or family history of colorectal cancer or polyps.

Most colorectal cancers arise from lesions in the colon called adenomatous polyps. These develop slowly over the course of many years, and may eventually develop into cancer. The probability of developing into cancer is a function of the size of the polyp. Polyps smaller than 1 cm are thought to have a low probability of developing into cancer, whereas 10% of adenomatous polyps larger than 1 cm become malignant within 10 years. The prevalence of polyps is high in the general population, and ranges from 20% to 25% at age 50 to 50% by age 75–80 years (U.S. Preventive Services Task Force 2002).

Polyps and early stage colorectal cancers are often asymptomatic, but may bleed. This bleeding may be detected with simple tests of the stool. At more advanced states, patients have symptoms of anemia, rectal bleeding, change in bowel habits, and abdominal symptoms. The curability of colorectal cancer is related to the stage at which it is detected. If the tumor is entirely localized to the bowel, 10-year survival rates are 80–90%. If the tumor has spread beyond the bowel, survival rates are much lower.

### Colon Cancer Screening Effectiveness and Screening Options

Screening for colon cancer and colon cancer precursors has been studied intensively and there are a number of commonly used screening tests. The evidence supporting the various methods varies. In the 2002 recommendations of the U.S. Preventive Services Task Force, colon cancer screening is recommended, but without endorsement of specific techniques. The evidence for fecal blood testing was characterized as “good,” evidence for sigmoidoscopy was considered “fair,” and evidence for colonoscopy was considered “indirect” but supported by several lines of evidence. Barium enema was simply described as less sensitive than colonoscopy, but appears to have been endorsed. CT colonography was dismissed at that time as having insufficient evidence. In the most recent clinical guideline statement of the U.S. Preventive Services Task Force (2008), the evidence for CT colonography was still judged to be insufficient to evaluate the benefits and harms. This guideline was based on concerns about potential harms of

radiation exposure and potential for harm due to evaluation of extracolonic findings.

The 2008 edition of cancer screening guidelines released by the American Cancer Society (ACS; Levin et al. 2008) in conjunction with the U.S. Multi-Society Task Force on Colorectal Cancer and the American College of Radiology, recognizes two types of screening tests: colon cancer prevention and cancer detection. Colon cancer prevention tests detect both early cancer and adenomatous polyps. The cancer prevention options recommended were flexible sigmoidoscopy every 5 years, colonoscopy every 10 years, double-contrast barium enema every 5 years, or CT colonography every 5 years. For cancer detection, 3 types of fecal screening tests were supported; annual guaiac-based tests, annual fecal immunochemical tests, and stool DNA tests. The ACS endorses colon cancer prevention as the “primary goal of [colorectal cancer] screening” where resources and patient acceptance permit (Levin et al. 2008).

Of note, the evidence supporting various screening options is, for the most part, indirect. Fecal occult blood testing has been the only screening modality that has demonstrated effectiveness in randomized clinical trials. In 3 trials, risk of death from colorectal cancer was reduced by 15% to 33% (U.S. Preventive Services Task Force 2002). In a relatively small randomized trial of sigmoidoscopy in Norway, the incidence of colorectal cancer was reduced, but there was no statistically significant difference in colorectal cancer mortality or overall mortality (Thiis-Evensen et al. 1999).

Instead, the effectiveness of sigmoidoscopy, and by extension, colonoscopy, has been inferred from well-designed case-control studies. Selby et al. (1992) showed a 59% mortality reduction due to distal colon cancers associated with a prior rigid sigmoidoscopy screening examination. There was no association for deaths due to proximal colon cancers that would be out of reach of the sigmoidoscope, thus seeming to minimize any confounding effects associated with the likelihood of receiving a sigmoidoscopy examination.

The potential effectiveness of colonoscopy is inferred from studies such as that by Selby et al. (1992), as well as many studies examining the capability of colonoscopy to detect cancer precursors of various sizes, the prevalence of cancer in adenomas of various sizes, and an

understanding of the malignant potential and growth rate of various cancer precursors. Thus, the effectiveness of colonoscopy is inferred from a combination of observational empirical data and theoretical considerations. These kinds of data have been combined in decision models in order to estimate the net health benefit of screening colonoscopy. One decision model by Frazier et al. (2000) as estimated that screening colonoscopy every 10 years would reduce colon cancer incidence by 58% and colon cancer mortality by 61%.

There is little direct evidence comparing the different screening methods to each other. However, differences in effectiveness between different methods have been modeled in several cost-effectiveness studies. Pignone et al. (2002) compared the methods and results of several such cost-effectiveness studies. In general, all methods of screening were effective compared to no screening, and average cost-effectiveness ratios of most methods compared to no screening would all be considered reasonable. Across all studies, the most effective methods regardless of cost tended to be 1) annual fecal occult blood combined with every-5-year flexible sigmoidoscopy or 2) colonoscopy every 10 years. Fecal blood testing alone and flexible sigmoidoscopy alone tended to be less effective.

Aside from effectiveness in preventing colon cancer mortality, the different screening tests differ widely in testing frequency, inconvenience, and discomfort, costs, adverse effects and availability, and other health issues.

Given that much of the evidence supporting colorectal cancer screening is indirect, it is not so surprising that consensus groups reviewing the same evidence might come to different conclusions, as have the USPSTF and the ACS regarding CT colonography. Although both groups reviewed the same evidence and similar decision models to reach their conclusions, Pignone and Sox (2008) suggest that subtle differences in emphasis may underlie the differing conclusions. The USPSTF appears to put more emphasis on the potential unknown effects of radiation exposure and workups for extracolonic findings, taking a more longitudinal perspective. The ACS report concentrates on the capability of CT colonography to detect large polyps in a single screening visit as the principal criterion to determine colon cancer prevention. Thus, the ACS report favors

screening technologies with superior single screening detection characteristics over less sensitive tests that have demonstrated efficacy with repeated screening.

#### **Adenoma Size and Risk of Dysplasia**

A critical issue in the evaluation of CT colonography is the underlying risk of lesions smaller than 10 mm in size. Because CT colonography is generally recognized to be less sensitive for lesions smaller than 10 mm (and lesions smaller than 5 mm are not even to be reported), the risk of missing or not removing such lesions should be considered. Studies vary in their estimate of the prevalence of such lesions. This prevalence would affect the indirect causal chain supporting the effectiveness of CT colonography. If the prevalence is high, CT colonography would not be as effective as optical colonoscopy in preventing colon cancer. The following section highlights some of the variation in the literature and indicates some uncertainty on this issue.

A study by Kim et al. (2007a) found that only 3.4% (7/205) of 6- to 9-mm adenomas were considered advanced neoplastic lesions, using criteria of either high-grade dysplasia or greater than 25% villous histology. Other studies have shown a much higher prevalence of advanced neoplastic features in polyps in this size range. O’Brien et al. (1990) analyzed data from the National Polyp Study, a randomized trial of polyp surveillance to assess the risk of dysplastic features among polyps of various sizes. In this study, using a definition of high-grade dysplasia alone as an advanced lesion, they found that 4.4% of polyps between 6–10 mm were advanced lesions. This definition of advanced lesion is different than the studies of Kim et al. (2007a). However, the study does contain data on the prevalence of adenomas with various grades of villous histology. Calculating from the proportions provided in the paper shows an approximate 13% of advanced neoplasia using the definition of high-grade dysplasia or greater than 25% villous histology. (The approximation is because the calculation has some error; cannot exactly reconcile the denominator of the rate).

The study by Gschwantler et al. (2002) analyzed data from their own institution in Austria on the histologic characteristics of adenomas removed from their patients. Using slightly broader categorization of polyp size, they found a 13.5% rate of high-grade dysplasia in polyps between

5–10 mm. This study also included information on the villous component of the adenoma, and also allows recalculation of advanced neoplasia according to the definition of Kim et al. (2007a). Using this definition, the rate of advanced neoplasia was 40%.

When using a similar definition of a high-risk lesion, these 3 studies show very different risks among patients who potentially might have their polyps missed by CT colonography (Table 1). However, there are many possible reasons for the differences. Age is an independent risk factor for advanced neoplasia, and may have differed systematically between studies. All studies excluded patients with prior cancer, polypectomy, and chronic abdominal disease, but the proportion with symptoms is not reported in the studies. The polyp size categories vary slightly between the studies—the inclusion of 1 mm larger size in two of the studies probably increases the prevalence of advanced lesions somewhat.

The risk of advanced neoplasia in small polyps appears to be very low. In a personal communication cited in the 2008 ACS guidelines (Levin et al. 2008), the prevalence of advanced neoplasia in patients whose largest polyp was 5 mm or smaller was 1.7%.

#### **CT Colonography**

CT colonography was first introduced in 1994, and since then has undergone rapid technological development in the areas of software development, criteria for interpretation, optimization of CT techniques, and other areas. Rapid development in several areas has resulted in lack of protocol standardization and the possibility of performance variability. However, there are 5 principal areas regarding the technique that may be important determinants of its performance.

**Type of Scanner.** Newer generation machines that have multiple detector rows can produce better images which can more accurately determine the location and size of lesions in the colon.

**Bowel Preparation.** An adequate bowel preparation is necessary in order to produce the clearest images and eliminate artifacts. Patients restrict their diets for a few days before the procedure and take laxative preparations. Optional techniques include ingestion of oral contrast to opacify fluid. The most

**Table 1.** Studies Showing the Risk of Dysplasia among Adenomas in the Range of Polyp Size 5–10 mm

Author	Definition of High-Risk Lesion	Polyp Size	Prevalence of Lesion	Notes
Kim et al. 2007a	>25% villous or high-grade dysplasia	6–9 mm n=205	7/205 (3.4%)	1/7 dysplasia, rest meet villous criteria
O'Brien et al. 1990	high-grade dysplasia	6–10 mm n=1,230	54/1,230 (4.4%)	published data
	>25% villous or high-grade dysplasia	6–10 mm n=1,230	155/1,230 (approx 13%)	data recalculated to same definition of Kim et al. (2007b)
Gschwantler et al. 2002	high-grade dysplasia or carcinoma	5–10 mm n=2,789	376/2,789 (13.5%)	published data
	>25% villous or high-grade dysplasia	5–10 mm n=2,789	1,106/2,789 (40%)	data recalculated to meet definition of Kim et al. (2007b)

advanced technique involves additional ingestion of contrast to opacify remaining stool in the colon (“stool tagging”), which can then be digitally subtracted from the CT images before interpretation.

**CT Technique.** The colon is distended with air or carbon dioxide via a small rectal tube. The patient is then scanned in the supine and/or prone positions. Patients must be able to hold their breath during the scan for 20–50 seconds, depending on the equipment used.

**Software.** Conversion of the axial CT images into 2- and 3-dimensional images suitable for interpretation is performed through dedicated software packages, which also allow recording, “navigation,” and alternative views of the colon. There are more than 20 such software packages available currently, but evidence comparing the performance of these packages is lacking.

**Interpretation.** There appears to be a steep learning curve, and evidence that only rigorously trained radiologists should interpret the study. Thus, performance may vary based on the training and experience of the radiologist. In 2005 (updated 2006), The American College of Radiology published practice guidelines for the performance of CT colonography in adults (American College of Radiology 2006).

### Evaluation of Diagnostic Performance of CT Colonography

There are many possible methods used in the literature to analyze the diagnostic performance of CT colonography. The 2 most common methods are referred to as a per-polyp analysis and a per-patient analysis. In the per-polyp analysis, the capability of CT to detect all polyps is calculated in terms of sensitivity relative to a reference standard, usually colonoscopy. Specificity cannot be calculated because there is no real denominator for the absence of a polyp. Although a per-polyp analysis gives some insight regarding the technical capability of CT, it is not as relevant as a per-patient analysis in determining its clinical utility.

Furthermore, in most studies, the per-polyp analysis gives a misleading estimate of sensitivity as it would be used clinically. The studies usually consider CT colonography to have “matched” a polyp seen on colonoscopy if the size of the polyp seen on CT is within 50% of the size determined on colonoscopy. For example, a polyp measured as 4 mm on CT is considered a positive finding for a polyp measured as 8 mm on colonoscopy. However, this should not be considered as a positive finding in a per-patient analysis, if the threshold for reporting or referral for colonoscopy is 5 mm.

Thus, the most relevant analysis for the purpose of assessing screening performance of CT colonography is a per-patient analysis.

A per-patient analysis uses the patient as the unit of analysis, and assesses the capability of CT colonography to detect or rule out a patient with at least one lesion of a particular minimum size. The per-patient analysis must specify the size threshold for referral, because in order to be efficient only patients with a specific minimum size polyp should have colonoscopy. Up until the 2008 ACS guidelines, there was no generally agreed on size threshold for a “positive” CT colonography. The guideline states that patients with polyps 6 mm or greater should be referred for colonoscopy.

Many studies were excluded from data abstraction for this Assessment because they only calculated per-patient sensitivity and specificity for detection of any polyp regardless of size, a strategy that refers a very high proportion of patients to colonoscopy. A few studies used clearly flawed methods in that different size thresholds were apparently used in the calculations of sensitivity and specificity. For example, in a study by Rex et al. (1999), a threshold of any polyp seen on CT, regardless of size, was used to calculate sensitivity to detect a patient with a polyp of 10 mm or larger. However, specificity was calculated based on whether CT showed a false-positive polyp larger than 10 mm. Other studies were excluded because it was unclear whether they used similar diagnostic thresholds for polyp size in the calculations of sensitivity and specificity.

It is also important to consider the reference standard in assessing the performance of CT colonography. Most studies use colonoscopy as the reference standard; although colonoscopy is imperfectly sensitive, it is highly likely to be close to 100% specific. To the extent that CT colonography detects some polyps that are missed by colonoscopy, these potentially true positives are instead classified as false positives. Thus, both the sensitivity and specificity of CT colonography are downwardly biased from their “true” values when colonoscopy alone is used as a reference standard.

A few studies used unblinded colonoscopy as the reference standard, where the CT colonography findings are sequentially revealed to the colonoscopist, who can then investigate all polyps thought to be seen with CT (Pickhardt et al. 2005; Cotton et al. 2004; Pineau et al. 2005). By rechecking areas of the colon that CT identified as having polyps, lesions that might be classified as false positive on CT can be

correctly reclassified as true positive if a polyp is seen on reexamination with colonoscopy. The diagnostic characteristics of the blinded colonoscopy examination can be compared to this unblinded colonoscopy reference standard. Although this method corrects initially false-positive CT findings, because it only allows for correction of findings detected by CT colonography, is now slightly biased against the blinded initial colonoscopy.

#### **Other Health-Related Aspects of CT Colonography not Related to Detection of Colon Cancer**

There is some concern over the long-term potential harms of the radiation exposure from CT exams. Brenner and Georgsson (2005) estimated that a CT colonography examination in a 50-year-old individual with an estimated dose of 7 to 13 mSV might add an additional 0.044% to the lifetime risk of colon cancer. Another analysis by Hall and Brenner (2008) states, “Summed over all of the organs at risk [including colon, kidney, liver, stomach, and leukemias], the estimated lifetime risk of cancer induction from a pair of [CT colonography] scans ... in a 50 year old is ~0.14%, approximately 1 in 700.” Estimated risks for cancer mortality would be less. These estimates are subject to wide confidence intervals due to uncertain effects of low-dose radiation. However, more individuals are undergoing numerous CT exams of various types, and CT colonography is expected to be repeated several times over a lifetime.

CT colonography produces images not only of the colon but of the surrounding internal organs. Various studies have reported the incidence of clinically significant extracolonic findings, and the reported range of such findings is 4.5% to 11% (Levin et al. 2008). Such findings may be beneficial, but they also entail further work up and diagnostic testing. At least one decision model has estimated a net health benefit due to detection and treatment of extracolonic findings found on CT colonography, particularly due to the early detection of abdominal aortic aneurysm (Hassan et al. 2008). Such benefit has not been directly assessed in clinical trials.

**FDA Status.** CT colonography may be performed using any CT scanner capable of producing helical (spiral) thin-section images ( $\leq 5$  mm). More recent studies have been conducted using commercially available

multidetector-row (multislice) helical CT scanners which facilitate faster image acquisition and thinner sections. The 2-dimensional cross-sectional CT images may be interpreted directly and software algorithms using 3-dimensional reformatting techniques may also be used to facilitate interpretation. Three-dimensional reformatting software may be cleared through the U.S. Food and Drug Administration (FDA) for this specific application. For example, the Viatronix V3D-Colon<sup>®</sup> CT colonography system (Viatronix, Inc., Stonybrook, NY) was cleared for marketing by the via the 510(k) process on April 19, 2004, for use as a screening tool in detecting colon cancer.

## Methods

### Search Methods

There are no studies of the use of CT colonography as a screening technique that report long-term patient outcomes. Studies are currently limited to cross-sectional studies evaluating the diagnostic performance of CT colonography, usually using colonoscopy as a reference standard. There is one nonrandomized study comparing the yield of significant lesions between CT colonography and colonoscopy. Studies of CT colonography were identified through search of the MEDLINE<sup>®</sup> database through October 2008. The search strategy included the terms “virtual colonoscopy,” “computed tomography colonoscopy OR colonography,” and “CT colonography.” Abstracts and review articles were reviewed in order to find additional references that met study criteria.

### Study Selection

Studies have been performed in populations of differing risk. To be most relevant to the question of colon cancer screening, the ideal population would be asymptomatic. Most studies evaluate the performance of CT colonography in symptomatic patients who are scheduled for colonoscopy, as they are a convenient research population. It is important to note that these are not patients who would usually be considered for screening with CT colonography. However, studies that only examined symptomatic patients were not initially eliminated. In fact, some patients with clinical indications for colonoscopy such as routine surveillance after polypectomy may have a lower prevalence of lesions than screening populations. The risk characteristics

of the patients in different studies can ultimately be characterized by the prevalence rates of lesions, which can be compared between studies.

Studies were included if they had the following characteristics:

1. Prospective enrollment of subjects undergoing both CT colonography and optical colonoscopy
2. Valid reference standard (usually colonoscopy, sometimes “unblinded colonoscopy”)
3. Valid per-patient analysis of CT colonography allowing calculation of both sensitivity and specificity at a specific polyp size threshold, and adequate data to calculate prevalence rates of polyps and referral rates (test-positive rates)
4. Minimum sample size of 50 patients

### Medical Advisory Panel Review

This Assessment was first reviewed by the Blue Cross and Blue Shield Association Medical Advisory Panel (MAP) on June 10, 2008, and tabled until full publication of the ACRIN trial (Johnson et al. 2008). A revised draft was submitted to the Panel for electronic review and vote in October 2008. In order to maintain the timeliness of the scientific information in this Assessment, literature searches were performed subsequent to the Panel’s review (see “Search Methods”). If the search updates identified any additional studies that met the criteria for detailed review, the results of these studies were included in the tables and text where appropriate.

## Formulation of the Assessment

### Patient Indications

Patients are those who are at average risk for colon cancer and who are undergoing colorectal cancer screening. Such patients will generally be asymptomatic, in the age range that initial screening for colon cancer is recommended, which is age 50.

### Technologies to be Compared

A strategy of CT colonography followed by optical colonoscopy with polypectomy for those considered to be positive for adenomatous polyps (with at least one polyp 5 mm or larger) will be compared to optical colonoscopy. The follow-up colonoscopy with polypectomy

as needed should be considered part of the screening procedure. Diagnostic test performance or yield of significant cancer precursors will be compared to optical colonoscopy.

### Health Outcomes

The ultimate health outcome of interest is reduction in colon cancer mortality. Effective screening would reduce colon cancer mortality in exchange for the cost, discomfort, and adverse effects of screening and associated medical interventions. However, no direct evidence exists for these health outcomes for either optical colonoscopy or CT colonography.

Reviewing studies that examine sensitivity and specificity of the 2 tests at one point in time do not directly answer the question of effectiveness in preventing colon cancer mortality. Outcomes for colon cancer prevention between the 2 strategies may not be comparable even if the 2 methods are identically sensitive for detecting polyps. The clinical strategies differ between the 2 screening techniques. CT colonography is intended to be used more frequently than optical colonoscopy (every 5 years versus every 10 years after a negative study). Referral for polypectomy only occurs if a polyp larger than 5 mm is found, whereas all polyps of any size are routinely removed during a screening optical colonoscopy.

In addition to this essential difference in clinical strategy, other factors vary between the 2 tests in terms of very low probability adverse events or benefits that complicate the comparison between the 2 procedures. These include the probability of perforation during colonoscopy, risks of sedation from colonoscopy, risks from radiation exposure from CT colonoscopy, and net risk or benefit from work up and treatment of extracolonic findings found on CT. Any estimate of the net risk or benefit from all these factors would be speculative and uncertain. However, patients might find some of these outcomes more important to them than others, and they should be fully informed of the differences between the screening techniques regarding short-term effects and potential long-term effects. A summary of these differences is shown in Table 2.

### Specific Assessment Questions

Because of absence of direct evidence regarding capability of CT colonography or optical colonoscopy to prevent colon cancer,

the principal assessment question that can be answered from the literature is:

1. What is the diagnostic performance of CT colonography compared to colonoscopy for detection of adenomatous polyps?

And then, based on an indirect chain of logic,

2. Will the diagnostic performance of CT colonography translate to improved health outcomes comparable to effective methods of cancer screening?

## Review of Evidence

### What is the diagnostic performance of CT colonography compared to colonoscopy for the detection of adenomatous polyps?

**Overview of Studies.** Descriptive characteristics of the studies are shown in Table 3. These studies all enrolled patients who were referred for elective colonoscopy and agreed to also have CT colonography performed. Pickhardt et al. (2003) and the ACRIN trial (Johnson et al. 2008) enrolled asymptomatic patients and thus are the only studies truly representing screening populations; however, when the prevalence of lesions is calculated, other studies were not too remarkably different in terms of the risk characteristics of the enrolled patients. The study by Fletcher et al. (2000) is an outlier in that an extremely high percentage of patients, 53%, had polyps larger than 10 mm. There appear to be minor variations in the bowel preparation used, with the exception of the Pickhardt et al. (2003) study and the ACRIN trial (Johnson et al. 2008), which are the only studies that used a stool tagging technique to eliminate stool artifacts from the images. There is wide variation in the qualifications and experience of the persons interpreting the test. The study by Cotton et al. (2004) is notable in that the study was performed in multiple centers with a requirement that the radiologists have a minimum experience of only 10 CT colonographic exams.

**Per-patient Detection of Polyps at 10-mm Size Threshold.** A 10-mm size polyp is considered clinically important to detect. All included studies reported sensitivities and specificities for detection of polyps at this size threshold. Results of performance of CT colonography are reported in Table 4.

**Table 2.** Differences Between CT Colonography and Optical Colonoscopy

Listed Under the Screening Technique that Provides the Potential Advantage (or Both, if Unclear)

CT Colonography	Optical Colonoscopy
<b>Prevention of colon cancer through detection and removal of adenomas</b>	
	Higher sensitivity for polyps 10 mm or smaller
	Removal of all detected polyps regardless of size
More frequent screening interval (5 years) may improve polyp detection, detect interval polyps	
<b>Complications of screening</b>	
Lower perforation rate of screening procedure itself	
Lower perforation rate due to lower polypectomy rates	
No risks from sedation	
<b>Comfort, pain, other convenience factors</b>	
No sedation needed	Sedation during procedure may make it more comfortable than CT colonography
Shorter time for exam	
Shorter recovery from exam, no chaperone needed	
Avoid colonoscopy if test is negative.	Only one procedure needed. Only one bowel prep needed if CT colonography cannot be followed up by same day colonoscopy
	Longer 10-year interval after negative study
<b>Health outcomes other than polyp detection and colon cancer detection</b>	
	No radiation exposure
Extracolonic disease may be detected and treated	False-positive or incidental extracolonic diseases not detected avoiding unnecessary workups

**Table 3.** Characteristics of Studies Assessing Diagnostic Performance of CT Colonography

Author	Study Size	Study Population	Bowel Preparation	CT Technique, Image Type, etc.	Interpretation
Johnson et al. 2008 (ACRIN trial)	2,531	Asymptomatic patients scheduled for colonoscopy, without risk factors	Stool-tagging regimen	>50% of studies performed on 64-detector row scanners, minimum 16-detector row	500 cases prior experience or 1.5 day training course
Pickhardt et al. (2003)	1,233	Asymptomatic, average-risk patients and patients with family history	90 mL laxative 500 mL barium stool tagging oral contrast for luminal fluid	1.25-2.5 mm slice width 1-mm reconstruction int 3D views interpreted	6 radiologists, minimum 25 prior studies, 2 with >100 experience
Rockey et al. (2005)	614	Positive fecal blood test, anemia, family history	90 mL laxative	2.5-mm slice width 4-8 multidetector CT	>50 prior study experience or training class
Johnson et al. (2003)	703	Prior family history, prior polyp, or iron deficiency	Golytely and bisacodyl tablets	5-mm slice width 3-mm reconstruction int	3 radiologists, >150 experience, double reading
Cotton et al. (2004)	615	Elective colonoscopy patients, age older than 50, including symptomatic patients	45 mL laxative X 2	2.5-5 mm slice width 1.5-1 mm reconstruction int 2D views interpreted	16 radiologists, 9 centers minimum experience of 10 prior exams
Hara et al. (2001)	237	History of polyps, family history, or iron deficiency	Golytely and bisacodyl tablets Glucagon	Single-Detector Row 5-mm slice width 3-mm reconstruction int Multidetector Row 5-mm slice width 3-mm reconstruction int	3 radiologists, unstated prior experience
Pineau et al. (2003)	205	Elective colonoscopy patients, age older than 35, including symptomatic patients	90 mL laxative oral contrast glucagon	5-mm slice width 1-mm reconstruction int	Single blinded reader
Fletcher et al. (2000)	180	Prior history or suspected polyps	Golytely and bisacodyl tablets ½ randomized to oral contrast Glucagon	5-mm slice width 3-mm reconstruction int	3 radiologists with CT colonography experience

**Table 3.** Characteristics of Studies Assessing Diagnostic Performance of CT Colonography (cont'd)

Author	Study Size	Study Population	Bowel Preparation	CT Technique, Image Type, etc.	Interpretation
Bruzzi et al. (2004)	82	Patients with prior polyps, family history of colon cancer	Various methods	Only axial images produced, no 3D images produced	2 radiologists using axial images only
Morrin et al. (2000)	81	Symptomatic patients referred for elective colonoscopy	Fleets BaE preparation or Golytely Glucagon	3-mm slice width 1.5-mm reconstruction int	2 radiologists with 18 months' experience
Wong et al. (2002)	71	Symptomatic patients referred for elective colonoscopy	45 mL Fleet's IV contrast	3.75-mm slice width 1.25-mm reconstruction int	Single radiologist with GI interest
Hara et al. (1997)	70	35 patients with positive barium enema or sigmoidoscopy, 35 patients surveillance colonoscopy	Golytely and bisacodyl tablets Glucagon	5-mm slice width 3-mm reconstruction int	2 radiologists with minimal training
Pescatore et al. (2000)	50	Clinically indicated elective colonoscopy, no screening patients	3 L Golytely spasmolytic agent	5-mm slice width 2.5-mm reconstruction int	Radiologist + GI team, experience not noted

**Table 4.** Diagnostic Performance of CT Colonography for Detection of Patients with Lesions 10 mm or Larger

Study	Sensitivity (n/N)		Specificity (n/N)		Prevalence of Lesions
<b>Unblinded colonoscopy as reference standard</b>					
Pickhardt et al. 2003					
CT colonography	94%	45/48	96%	1,138/1,185	4%
Colonoscopy	92%	42/48	100%	by def	
Cotton et al. 2004					
CT colonography	55%	23/42	96%	535/558	7%
Colonoscopy	100%	42/42	100%	by def	
Rockey et al. 2005					
CT colonography	59%	37/63	96%	529/551	10%
Colonoscopy	98%	62/63	99.6%		
Pineau et al. 2003 (CT colonography only)					
	90%	18/20	95%	165/175	10%
<b>Colonoscopy only as the reference standard</b>					
Johnson et al. 2008 (ACRIN trial)					
	90%	98/109	86%	2,083/2,422	4.3%
Johnson et al. 2003					
Reviewer 1	38%	16/42	97%	524/543	7%
Reviewer 2	35%	8/23	98%	367/374	
Reviewer 3	72%	21/29	98%	387/394	
Hara et al. 2001					
Single-det row	100%	5/5	90%	65/72	6%
Multi-det row	78%	7/9	93%	140/151	6%
Fletcher et al. 2000					
Supine images	70%	67/96	93%	78/84	53%
Supine+prone	85%	82/96	93%	78/84	
Bruzzi et al. 2004					
	100%	2/2	100%	72/72	3%
Morrin et al. 2000					
	86%	12/14	100%	67/67	17%
Wong et al. 2002					
	88%	7/8	100%	63/63	10%
Hara et al. 1997					
	75%	9/12	91%	53/58	17%
Pescatore et al. 2000					
Team 1	37%	NR	74%	NR	NA
Team 2	62%	NR	74%	NR	

The studies by Pickhardt et al. (2003), Cotton et al. (2004), and Pineau et al. (2003) used a reference standard of sequentially unblinded colonoscopy as the reference standard, which is a more sensitive reference standard than colonoscopy alone. However, since all polyps are actually eventually visualized on colonoscopy, this reference standard still leaves colonoscopy with a specificity of 100%. These 3 studies showed great variability in the calculated sensitivity of CT colonography. Pickhardt et al. (2003) showed a sensitivity of 94%, Pineau et al. (2003) showed a sensitivity of 90%, and Cotton et al. (2004) showed a sensitivity of only 55%. The specificities were all similar between the studies at 95% to 96%. Two of the studies also calculated sensitivities for colonoscopy (before unblinding of the CT colonography results): Pickhardt et al. (2003) reported a sensitivity of colonoscopy of 92%, whereas Cotton et al. (2004) reported a sensitivity of 100%.

The remaining studies all reported CT colonography diagnostic performance using a reference standard of colonoscopy alone. Recall that this biases both the sensitivity and specificity of CT colonography downward. With the exception of the ACRIN trial (Johnson et al. 2008), these studies tend to have smaller sample sizes than the other studies. Differences between CT techniques and different interpreters are explored within some of the studies. The ACRIN trial is notable for its use of latest generation scanners (minimum 16-row detector), stool-tagging protocol, and high standards for interpretation. The ACRIN trial showed a high sensitivity of 90% for detection of 10 mm or greater size polyps and a specificity of 86%; positive and negative predictive values were 23% and 99%, respectively. Sensitivities varied widely between the other studies, as low as 35% for one reviewer in the study by Johnson et al. (2003), up to 100% for Hara et al. (2001) and Bruzzi et al. (2004). The sensitivity values for the other studies tended to be between 70 and 90%. Specificity values were more consistent between studies, with the exception of Pescatore et al. (2000), which reported very poor specificities of 74%, all the other studies reported specificities in the 90% to 100% range.

Several of the studies reported sensitivity and specificity for a smaller size threshold for polyp detection, either 5 mm or 6 mm. This corresponds to the size threshold for referral recommended in the 2008 ACS guidelines.

These results are reported in Table 4. Note that this calculation includes detection of patients who have polyps from the minimum size and including polyps greater than 10 mm, not just between 5 mm and 10 mm. Specificity is based on patients who do not have any polyps that are at least 5 mm in size. For the studies that used unblinded colonoscopy as the reference standard, sensitivity for polyps 5 mm or larger was lower than that for polyps 10 mm or larger. Pickhardt et al. (2003) reported a sensitivity of 89%, Cotton et al. (2004) reported a sensitivity of 39%, Rockey et al. (2005) reported a sensitivity of 55%, and Pineau et al. (2003) reported a sensitivity of 83%. The study by Pickhardt et al. (2003) also reports the sensitivity of colonoscopy in the same patients, which at 92% is very similar to CT colonography. Specificities in these 3 studies were also less than those reported for the 10 mm or larger threshold, ranging from 80% to 91%.

In the 4 remaining studies that used colonoscopy alone as the reference standard, sensitivity for detecting patients with 5 mm or larger lesions ranged from 53% to 88%, which were all lower values than the corresponding value for each study compared to the value for detecting patients with 10 mm or larger lesions. Specificities were also lower at this size threshold, ranging from 58% to 94%.

The prevalence of lesions 5 mm or larger is much greater than the prevalence of lesions 10 mm or larger, and is reflected in the prevalence values shown in Table 5. Combined with the lower specificity of CT colonography at this size threshold, the proportion of patients that would be referred for colonoscopy is quite substantial. If the study by Cotton et al. (2004) is discounted because the low referral rate is due to poor sensitivity and the study by Fletcher et al. (2000) is discounted because of the inordinately high proportion of polyps, the referral rates at this size threshold range from 17% to 51%. Findings in the ACRIN trial would have resulted in a 17% referral rate. The positive predictive value for detection of a 10 mm or larger polyp was 0.23, meaning that about one-fourth of follow-up colonoscopies detected at least one polyp 10 mm or larger at a population prevalence of such polyps of 4.3%. Thus, at this size threshold, in a population with this prevalence of polyps, very high proportions of patients are subjected to colonoscopy. At lower population prevalences of polyps, positive predictive values would be even lower, resulting in a higher

proportion of negative colonoscopies. However, the prevalence of 10 mm or larger polyps in the ACRIN study may be representative of the prevalence in a screening population. The only other study that enrolled an asymptomatic screening population (Pickhardt et al. 2003) had a similar prevalence of such lesions (4%).

### **Importance of ACRIN National Colonography Trial**

The ACRIN Trial addresses many of the gaps identified in the prior assessments of CT colonography (Johnson et al. 2008). Important features of the trial include large population (n=2,600), multiple institutions (n=15), minimum 16-slice CT scanner, stool tagging, and comparison of 3 commonly used bowel preparation regimens. As described in the trial protocol (ClinicalTrials.gov Identifier NCT00084929), the primary aim of the trial was to evaluate the sensitivity of CT colonography, compared to optical colonoscopy, for detecting individuals with a clinically significant large lesion, defined as 10 mm or larger. Secondary aims were detecting polyps from 5–10 mm, and for detecting signal characteristics (i.e., high-grade dysplasia, invasive carcinoma, and/or villous features) of polyps 5 mm or larger. Of practical importance, the trial evaluates inter-observer variability in accuracy of CT colonography examination interpretation. Additional descriptive data that will contribute to assessing effectiveness of CT colonography include patient acceptance, prevalence and distribution of flat lesions, prevalence and clinical significance of extracolonic findings, and differences in interpretation techniques.

The news item summarizing the preliminary ACRIN results (Barnes 2007) also included comments from the principal investigator of the trial, citing the importance of adequate training and credentialing of CT colonography readers for the effectiveness of the technique. This suggests the need to credential providers who perform this procedure, at least in the initial phase of dissemination. According to the ACRIN trial (Johnson et al. 2008):

“Each participating radiologist was required to submit confirmation of having interpreted at least 500 CT colonographic examinations or having participated in a specialized 1.5-day training session on CT colonography. 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 2008 guideline on colon cancer screening, a joint guideline of the American Cancer Society, the U.S. Multi-Society Task Force on Colorectal Cancer, and the American College of Radiology (ACR; Levin et al. 2008) notes that following the publication of the results of the ACRIN trial, the 2006 *ACR Practice Guidelines for Performance of Computed Tomography (CT) Colonography in Adults* (American College of Radiology 2006) will be updated. The ACR Guidelines address “the techniques, quality control, clinical uses, training, and communication of results for [CT colonography].” The joint guideline also notes that the ACR is piloting quality metrics for CT colonography, has begun construction of an interactive training facility, and is evaluating “a process for individual certification and proficiency.” Standards for training of gastroenterologists performing CT colonography were also published by the American Gastroenterological Association in 2007 (Rockey et al. 2007).

### **Comparative Yield of Neoplasia, CT Colonography versus Optical Colonoscopy**

Kim et al. (2007b) published a nonrandomized comparative study of CT colonography versus optical colonoscopy for the detection of advanced neoplasia (Table 6). Unlike studies in which CT colonography and optical colonoscopy were done in the same patients, allowing comparisons of diagnostic performance, performance of the tests in separate populations only allows a comparison of the yields of the test. Under the unobservable assumption that the study groups have the same underlying prevalence of advanced neoplasia, then equal diagnostic yield rates are consistent with equivalent sensitivity. However, because there is no reference standard, diagnostic test characteristics cannot be calculated.

The number of patients undergoing optical colonoscopy after detection of polyps during CT colonography, the referral rate, would be a function of the prevalence of disease, the threshold polyp size for referral, and the specificity of CT colonography. However, the outcome of this study, advanced neoplasia, is only a subset of polyps that show dysplastic features on pathology or have a substantial (>25% ) villous component, features that cannot be determined from CT colonography.

**Table 5.** Diagnostic Performance for Detection of Patients with Lesions 5 mm and Larger or 6 mm and Larger

Study	Sensitivity		Specificity		Prevalence of Lesions	Referral Rate True positives plus false positives
<b>Studies using sequentially unblinded colonoscopy as reference standard</b>						
Pickhardt et al. 2003						
CT colonography	89%	149/168	80%	848/1,065	14%	30%
Colonoscopy	92%	155/168	100%	by def		
Cotton et al. 2004						
CT colonography	39%	41/104	90.5%	449/496	17%	15%
Colonoscopy	99%	103/104	100%	by def		
Rockey et al. 2005						
CT colonography	55%	85 /155	89%	408/459	25%	36%
Colonoscopy	99%	153/155	99.6%	457/459		
Pineau et al. 2003						
CT colonography only	84%	38/45	83%	133/160	22%	32%
<b>Studies using colonoscopy alone as reference standard</b>						
Johnson et al. 2008 (ACRIN trial)	65%	183/282	89%	2,001/2,249	11%	17%
Fletcher et al. 2000					72%	
Supine images	75%	97/130	80%	40/50		59%
Supine+prone	88%	114/130	72%	36/50		71%
Wong et al. 2002	53%	9/17	94%	51/54	24%	27%
Hara et al. 1997						
observer A*	68%	17/25	58%	26/45	36%	51%

\* Results for one of 2 observers, roughly similar to the other observer

**Table 6.** Diagnostic Yield of CT Colonography and Optical Colonoscopy Screening (Kim et al. 2007b)

Variable	CT Colonography	Optical Colonoscopy	p value
n	3,120	3,163	
use of optical colonoscopy	246 (7.9)*	all (100)	
polyps removed	561*	2,434	
advanced adenomas			
≥10 mm	103	103	0.92
6–9 mm	5*	11	0.14
≤5 mm	1	3	0.32
invasive carcinoma			
no. carcinoma	14	4	0.02
no. patients	12 (0.4)	4 (0.1)	0.04
total advanced neoplasia			
no. neoplasm	123	121	0.81
no. patients	100 (3.2)	107 (3.4)	0.69

\*Does not include 193 polyps in 158 patients with polyps 6-9 mm who did not undergo colonoscopy, but elected CT colonography surveillance

Thus, it is expected that many more patients would be referred for colonoscopy than would actually have advanced neoplasia. The referral rate, however, does provide a sense of the “efficiency” of using CT colonography. If a substantial proportion of patients require referral to colonoscopy, then the advantage of the less-invasive screening test is overcome by having large numbers of patients having to undergo two tests.

The study shows roughly equivalent rates of detection of advanced adenomas. It should be noted that the number of subjects referred for colonoscopy, 7.9%, would have been substantially higher had not some patients elected to have CT colonography surveillance instead of immediate optical colonoscopy. Adding the 158 patients would have resulted in a 13% referral rate for colonoscopy. There is probably some number of missed advanced adenomas between 6–9 mm among the 193 polyps that were not assessed with colonoscopy. The authors estimated that 60% of polyps 6–9 mm would be adenomatous, and that approximately 3% of those adenomas would have advanced histologies, resulting in 3 to 4 additional advanced adenomas.

Although the study is not randomized, under the assumption that the underlying rate of advanced neoplasia is equivalent between the two groups, the study is consistent with roughly equivalent sensitivity of CT colonography and optical colonoscopy for the detection of advanced neoplasia. The expected deficit of advanced adenomas between 6 and 9 mm is not numerically large enough in a study of this size to be statistically significant.

**Does the diagnostic performance of CT colonography translate to evidence that it will improve health outcomes compared to effective methods of cancer screening?**

Taking the data from comparisons of diagnostic sensitivity and specificity and translating that information into projections of health benefit requires several assumptions, only some of which are known with precision. Based on the understanding of the indirect causal chain that supports the use of optical colonoscopy as an effective screening test for prevention of colon cancer, if CT colonography has similar sensitivity for polyps larger than 10 mm, it is likely that it would produce similar benefits as colonoscopy. However, it is difficult to know the aggregate

net benefits or harms of all the additional factors (listed in Table 2), and whether they would meaningfully add to or subtract from the relative benefit of one procedure versus the other. Some of the factors favor colonoscopy, some of the factors favor CT colonography.

If CT colonography is less sensitive than optical colonoscopy for polyps larger than 10 mm, then given that colonoscopy is thought to be one of the more effective accepted methods of colon cancer screening (based on inference from indirect evidence), then it is still possible that it is still an effective screening test. CT colonography may be more effective than proven methods for cancer screening detection (e.g., fecal occult blood testing). Or, when there is good compliance with follow-up colonoscopy and polypectomy, may be more effective than sigmoidoscopy, an alternative for preventive screening, which has declined substantially with wider use of colonoscopy.

Technical improvements in scanning technology and improved standards for interpretation make it likely that the results of the ACRIN trial (Johnson et al. 2008), which are similar to that of Pickhardt et al. (2003), in which the sensitivity of CT colonography for polyps 10 mm or larger is around 90%, represent what is currently attainable if similar equipment and interpretation standards are available in the community.

Insight into how differences in sensitivity, specificity, screening intervals, and other factors relevant to these tests translate into overall effectiveness in preventing colon cancer may be achieved by examining some of the results of published cost-effectiveness analyses. Several cost-effectiveness analyses of CT colonography have been published. Although the studies vary in numerous aspects, they share a similar decision structure. Most of the studies assumed that CT colonography was less sensitive than optical colonoscopy. The studies all estimated that CT colonography was close, but slightly less effective than optical colonoscopy in preventing colon cancer mortality. For example, in the study by Pickhardt et al. (2007), assuming a sensitivity of 85% for polyps 10 mm or larger for CT colonography, CT colonography screening produced a 35% population reduction mortality in colorectal cancer, whereas optical colonoscopy produced a 39% reduction in population mortality. Another study by the same set of authors produced a

very similar relative effectiveness (Hassan et al. 2008). However, this study additionally modeled effects of detection of extracolonic findings, and found that adding in the benefits of detection of abdominal aortic aneurysm produced dominance (better outcomes at lower cost) for CT colonography. This study also incorporated other extracolonic findings detectable with CT, radiation exposure effects, and complications of polypectomy, and found that these effects contributed very little to the overall findings.

Decision analysis and cost-effectiveness analysis are not direct evidence, but a formal method of integrating data from many different sources to provide an estimate of benefit. Optical colonoscopy has been supported as an effective screening test through informal and formal integration of this type of information. Central to this conclusion is the high sensitivity of optical colonoscopy for detection of adenomatous polyps greater than 10 mm in size. If CT colonography approaches the sensitivity of optical colonoscopy for the detection of these polyps, and all other effects are relatively small in magnitude, then formal decision models should also demonstrate colon cancer prevention in a similar order of magnitude to optical colonoscopy.

## Discussion

The conclusions of this Assessment rely on the generalizability of the ACRIN trial to general screening populations and community radiologists. This trial constitutes the most important and substantively new evidence available since the prior TEC Assessment, which was published in July 2004. The prior TEC Assessment concluded that CT colonography did not meet the TEC criteria. Overall, sensitivity reported in the literature was quite variable among studies. Interpreter experience and technical factors were suggested to be likely explanations for the observed variability in performance. The 2004 Assessment also noted that clear criteria needed to be established for size polyp size threshold for removal and for frequency of screening in order to estimate the effectiveness of CT colonography.

The ACRIN trial addressed many of the gaps identified in the prior Assessment. Important features of the trial include a large population (n=2,600), multiple institutions (n=15), minimum 16-slice CT scanner, stool tagging,

and comparison of 3 commonly used bowel preparation regimens. As described in the trial protocol (ClinicalTrials.gov Identifier NCT00084929), the primary aim of the trial was to evaluate the sensitivity of CT colonography, compared to optical colonoscopy, for detecting individuals with a clinically significant large lesion, defined as larger than 10 mm. Secondary aims were sensitivity for detecting polyps from 5–10 mm and for detecting signal characteristics (i.e., high-grade dysplasia, invasive carcinoma, and/or villous features) of polyps 5 mm or larger. Of practical importance, the trial evaluated interobserver variability in accuracy of CT colonography examination interpretation. Additional descriptive data that will contribute to assessing effectiveness of CT colonography include patient acceptance, prevalence and distribution of flat lesions, prevalence and clinical significance of extracolonic findings, and differences in interpretation techniques.

## Summary of Application of the Technology Evaluation Criteria

Based on the available evidence, the Blue Cross and Blue Shield Association Medical Advisory Panel made the following judgments about whether CT colonography for colon cancer screening meets the Blue Cross and Blue Shield Association Technology Evaluation Center (TEC) criteria.

### 1. The technology must have final approval from the appropriate governmental regulatory bodies.

CT colonography may be performed using any CT scanner capable of producing helical (spiral) thin-section images ( $\leq 5$  mm). More recent studies have been conducted using commercially available multidetector-row (multislice) helical CT scanners that facilitate faster image acquisition and thinner sections. The 2-dimensional cross-sectional CT images may be interpreted directly and software algorithms using 3-dimensional reformatting techniques may also be used to facilitate interpretation. Three-dimensional reformatting software may be cleared through the U.S. Food and Drug Administration (FDA) for this specific application. For example, the Viatronix V3D-Colon<sup>®</sup> virtual colonoscopy system (Viatronix, Inc., Stonybrook, NY) was cleared for marketing by the FDA via the 510(k) process on April 19,

2004, for use as a screening tool in detecting colon cancer.

**2. The scientific evidence must permit conclusions concerning the effect of the technology on health outcomes.**

No direct evidence is available on health outcomes. An inference of effectiveness must be made based on a chain of logic that starts with the diagnostic sensitivity and specificity of CT colonography. The ACRIN study, a large trial of a screening population, using the latest scanners and techniques for bowel preparation and image interpretation, showed a 90% sensitivity of CT colonography for detection of polyps 10 mm or larger and a specificity of 86%; positive and negative predictive values were 23% and 99%, respectively.

**3. The technology must improve the net health outcome; and**

**4. The technology must be as beneficial as any established alternatives.**

Given the chain of logic and other underlying evidence that support the practice of accepted colon cancer screening techniques such as optical colonoscopy, a 90% sensitivity of CT colonography for detection of polyps 10 mm or larger is consistent with an improvement in health outcomes due to detection and removal of precancerous lesions. The 86% specificity of CT colonography would result in some false-positive tests, which, in turn, would result in some unnecessary follow-up colonoscopies. However, compared with optical

colonoscopy, there are several other types of health outcomes that may differ in terms of convenience, cost, detection of unrelated health problems, and radiation exposure. These are difficult to quantify, and are probably small in magnitude compared to the health benefit of identifying and removing cancer precursors.

**5. The improvement must be attainable outside the investigational settings.**

The results of the ACRIN trial were dependent on the technical standards required for performance of the test and the training and skill of the interpreters of the test. Each participating radiologist was required to submit confirmation of having interpreted at least 500 CT colonographic examinations or having participated in a specialized 1.5-day CT colonography 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. If these practices can be replicated in the community, then it is likely that improved health outcomes can be achieved outside investigational settings. Standards of performance and interpretation of CT colonography consistent with those reported in the ACRIN trial will be necessary for CT colonography to be an effective screening test.

Based on the above, CT colonography for the purpose of colon cancer screening meets the TEC criteria.

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