



**TITLE:** Computed Tomographic Colonography (Virtual Colonoscopy) for  
Colorectal Cancer Screening in Average Risk Individuals

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# COMPUTED TOMOGRAPHIC COLONOGRAPHY (VIRTUAL COLONOSCOPY) FOR COLORECTAL CANCER SCREENING IN AVERAGE RISK INDIVIDUALS

*A Technology Assessment*

## INTRODUCTION

The California Technology Assessment Forum was requested to review the scientific evidence for the use of computed tomographic colonography (CTC) as a screening test for average risk asymptomatic patients. This review was prompted by reports that there are new trials published since this topic was evaluated by the California Technology Assessment Forum in June 2004<sup>1</sup>.

## BACKGROUND

Colorectal cancer (CRC) is the thirteenth most common cancer among men and women and the second leading cause of death from cancer in the United States, with an estimated 154,000 new cases and 52,000 deaths in 2007. CRC screening clearly reduces mortality yet many individuals are not being screened<sup>2, 3</sup>.

The vast majority of colorectal cancers arise from colorectal adenomas. Adenomas are very common with a prevalence of 25-50% in individuals aged 50 and over<sup>4</sup>. Adenomas can progress to carcinoma, but do so slowly. The time that it takes for an adenoma to progress to a cancer ("dwell time") is believed to be ten years<sup>5</sup>.

Polyps can be either hyperplastic or adenomatous. Hyperplastic polyps hardly ever undergo malignant transformation. Adenomatous polyps can either be tubular (85-90%), tubulovillous or villous. All can undergo malignant transformation although the vast majority remain benign<sup>6</sup>. It is estimated that 95% of colorectal cancers arise from polyps and removal of these polyps can *prevent* colorectal cancer and can save lives. The goal of colorectal cancer screening tests is to identify either early cancers or polyps.



Screening for colorectal cancer is currently recommended for all men and women aged 50 and over. There are several different screening options for CRC. Currently available and commonly used tests endorsed by all organizations that recommend screening included fecal occult blood testing (FOBT), sigmoidoscopy (SIG) and colonoscopy (COL). Although CRC screening rates are increasing, they are still low. In 2004, only 27% of eligible adults had an FOBT in the past two years and only 53% had ever had a SIG or COL.

There are many patient barriers to receiving CRC screening. These include embarrassment, concern about discomfort, concern about the preparation, distaste with encountering stool, and being too busy. Since patient compliance with CRC screening is a problem, it has been suggested that tests that are easier to do than conventional COL might improve patient compliance.

CTC is a non-invasive radiological technique that permits visualization of the entire colon. The patient must undergo bowel preparation similar to that required for conventional COL, although there is ongoing research for a “prep-less” technique that does not require bowel cleansing<sup>7, 8</sup>.

In contrast to COL, the patient is not sedated. The colon must be distended throughout its length with carbon dioxide or air using a rectal tube to enhance imaging<sup>9</sup>. The patient must lie both supine and prone to be scanned. In addition, the patient must hold their breath for between 20 and 50 seconds, depending on whether a single or a multi-detector CT scanner is used. The radiation dose is approximately that of a barium enema<sup>10, 11</sup>. The images are then transferred to a computer workstation for interpretation by a radiologist. The radiologist can display multiple views (axial, coronal and sagittal) and can also display a three dimensional endoluminal view that simulates a COL. Although primary 3-D fly by reading can be used, usually, two dimensional views are used to identify the lesions and the 3-D views can be used when a specific area of concern is identified. When the 2-D and 3-D lesions are used together, it is possible to differentiate between retained stool, complex haustral folds and polyps<sup>12</sup>. When polyps are identified, the patient then must undergo conventional COL so that the polyps can be removed.

Reviews of the images can take from 15 to 40 minutes, depending on the experience of the radiologist. Interpretation of the CTC is very operator dependent, but how much experience is needed for optimal performance is not known.



Similar to conventional COL, CTC allows visualization of the entire colon. Although preparation is still required, there is no sedation and there is a much lower risk of perforation or bleeding. A potential advantage is the identification of extra-colonic findings, some of which may be clinically significant. Risks include radiation exposure and the identification of extra-colonic findings which are not clinically significant but require additional testing. Finally, the insufflation, in addition to the preparation, contributes to patient discomfort. Because of these reasons, CTC has not been consistently preferred to conventional colonoscopy by patients<sup>13-15</sup>

## **TECHNOLOGY ASSESSMENT (TA)**

**TA Criterion 1:           The technology must have final approval from the appropriate government regulatory bodies.**

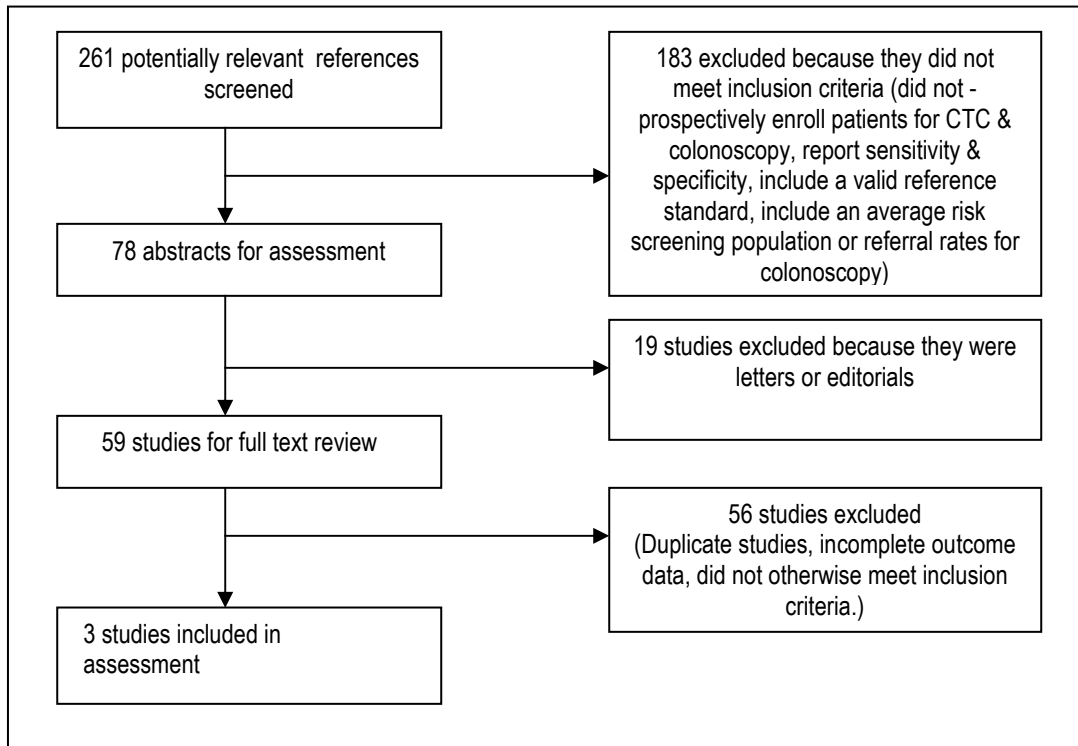
There are several manufacturers of CT machines including Philips, Siemens, General Electric and Toshiba. These machines are approved by the FDA through the 510(k) process. In addition, there are several manufacturers of 3D reconstruction/image processing software. These include Philips, iCAD and Vital Images Inc. to name a few. These software applications are approved by the FDA through the 510(k) process.

TA Criterion 1 is met.

**TA Criterion 2:           The scientific evidence must permit conclusions concerning the effectiveness of the technology regarding health outcomes.**

Search Methods: We searched Medline, the Cochrane clinical trials database, Cochrane reviews, database and the Database of Abstracts of Reviews of Effects (DARE) using the search terms of colorectal neoplasms, CT colonography or virtual colonoscopy cross referenced with accuracy or diagnostic performance or sensitivity or predictive value. In addition, we searched the bibliographies of the identified articles and other reviews to identify primary data sources and search strategies to ensure a complete

review of the relevant literature. The abstracts of citations were reviewed for relevance and all potentially relevant articles were reviewed in full. We used the same inclusion criteria as the recent TEC review. [TEC CT colonography “virtual colonoscopy for colon cancer screening <http://www.bcbs.com/blueresources/tec/press/ct-colonography-virtual.html>] Studies were included if they were studies of screening asymptomatic average risk individuals with CTC, they prospectively enrolled patients receiving both CTC and optical colonoscopy, they included a valid reference standard (colonoscopy), and if they included adequate information to calculate sensitivity and specificity for detection of particular size polyps and allowed the calculation of prevalence rates and rates of referral for colonoscopy. In addition, all included studies had to be published in English as a peer reviewed article. We also included all articles published but not yet indexed in Medline.



Ideally, a study of screening CTC would assess whether or not screening CTC reduces CRC mortality. The only screening test for CRC that has been evaluated in a clinical trial is FOBT. FOBT done annually to biennially has been shown to reduce CRC mortality in three randomized controlled trials<sup>16-18</sup>. SIG has been associated with a reduction in CRC mortality in case control studies<sup>19</sup>, but not in randomized controlled

trials (RCTs). COL has never been assessed in a clinical trial, but was an integral part of the FOBT trials, in that individuals who had positive FOBT tests underwent colonoscopy. Based on this, the efficacy of COL in reducing CRC mortality is assumed.

Since CRC screening is clearly effective and since additional RCTs of new screening modalities are unlikely to be performed, it has been recommended that new screening tests only need to demonstrate that they have equal or better performance characteristics in order to be considered for CRC screening<sup>5</sup>. Since a RCT of CTC is unlikely to be performed, the question is whether or not CTC is as good as optical COL. Thus, studies that compare the diagnostic performance of CTC with optical COL can indirectly determine whether CTC is as effective as optical COL.

Many of the early studies of CTC focused on individuals at high risk for cancer or adenomas and or used older technologies. The focus of the current review is on the accuracy of CTC using currently available technologies as a screening tool in individuals at average risk for CRC

Several of the studies of CTC used the technique of “segmental unblinding,” whereby the endoscopist is blinded to the results of the CTC during the introduction of the colonoscope. As the scope is withdrawn, the results are recorded. After that, the CTC results are revealed and re-examination can occur for any discrepancy<sup>15, 20</sup>. This enables the endoscopist to be initially blind to the CTC results but to have the opportunity not to miss any clinically significant findings. Although this can enhance the estimates of diagnostic accuracy, it is probably not representative of how colonoscopies are performed in the “real world.”

Before the recent publication of the ACRIN (American College of Radiology Imaging Network) trial, there were three large studies of CTC using currently available technology. One of these evaluated it as a screening test in average risk individuals, and the other two did not include a screening population. In the first of these, the study in a screening population, CTC performed quite well with a sensitivity for polyps >10 mm of 93.8% and a specificity of 86%<sup>15</sup>. However, this study used a 3-D technology that was not available everywhere and, in addition, used an extremely thorough bowel prep and the results were interpreted by academic specialists in a single medical center. A subsequent study that included patients who were

undergoing colonoscopy for clinical reasons, was done in multiple centers using a 2-D technology that is more commonly available. In this study, sensitivity was significantly lower - 55% for polyps  $\geq 10$  mm<sup>20</sup>. In a second study, which also did not include a screening population, all participants had air contrast barium enema (ACBE), CTC and COL, the sensitivity of CTC for polyps  $\geq 10$  mm was only 59%<sup>21</sup>. Thus the uses of CTC in “real world” settings were less promising than those performed in a more controlled academic environment.

The ACRIN study<sup>22</sup> is the largest multicenter screening study of CTC published to date. In this multi-institutional study, 2531 asymptomatic individuals underwent CTC and same day optical COL. The CTCs were done on scanners that were at least 16 slice scanners. The CTC preparation included stool tagging, laxatives and fluid tagging. Insufflation with carbon dioxide or room air was performed and glucagons were administered unless contraindicated or declined. COL was performed according to the standard clinical protocol at each of the sites. Endoscopy was performed without knowledge of the CTC results. CTC results were interpreted by radiologists who were extensively trained. If an abnormality was seen on CTC, but not on conventional COL, a follow up colonoscopy in 90 days was recommended. Tissue samples were all centrally reviewed for pathology.

The primary endpoint was detection of histologically confirmed large adenomas and adenocarcinomas (10 mm or larger) that had been detected by COL. Detection of smaller lesions (6-9 mm) was a secondary outcome. Per patient sensitivity, specificity, positive predictive value, negative value and area under the receiver operating characteristic (ROC) curve were calculated for each radiologist and then averaged across radiologists.

The per –patient sensitivity of CTC for lesions  $\geq 10$  mm was 90%, which means that only ten percent of lesions at least this size were missed. The specificity was 86%, which means that 14% of individuals without lesions were incorrectly classified as having them. In addition, they calculated the individual sensitivities for all the radiologists and they ranged from 0.67 to 1.00. Only three patients had complications- one had severe nausea and vomiting, one had hematochezia after snare polypectomy and one was hospitalized for E coli bacteremia. Over two thirds of individuals had extra-colonic findings; 16% required additional evaluation or urgent care.

The results of this study suggest that the accuracy of CTC in detecting significant colorectal abnormalities is relatively comparable to COL.

**Table 1: Studies Comparing CTC with Conventional Colonoscopy in Average Risk Individuals**

Study	N	Design	Reference Standard	Outcome
ACRIN, 2008 <sup>22</sup>	2531	Multicenter All received CTC with bowel prep, stool and fluid tagging and multi-detector row CT (16 or more rows)	Optical colonoscopy and histologic review. No segmental unblinding	Primary: Detection of histologically confirmed large adenomas and adenocarcinomas (10 mm or larger) that had been detected by colonoscopy Secondary: smaller (5-9 mm lesions)
Pickhardt, 2003 <sup>15</sup>	1233	Single center same date CTC and colonoscopy CTC included bowel prep, stool and fluid tagging Four or 8 channel CT scanner	Same day optical colonoscopy with "segmental unblinding"	Primary: Detection of polyps 6 mm or greater Secondary: Advanced neoplasia (adenoma 10 mm or greater, high grade dysplasia, prominent villous component or focus of cancer)

**Table 2: Diagnostic Accuracy of Studies Comparing CTC with Colonoscopy in Average Risk Individuals**

Study	N	Sensitivity	Specificity	Other
ACRIN, 2008 <sup>22</sup>	2531	0.90 per patient sensitivity for polyps $\geq 10$ mm 0.84 Per polyp sensitivity for large adenomas or cancer 0.78 per patient sensitivity for polyps $\geq 6$ mm	0.86 For polyps $\geq 10$ mm	Inter-observer reliability of radiologists also measured Sensitivity 0.67-1.00
Pickhardt, 2003 <sup>15</sup>	1233	.938 for polyps $\geq 10$ mm .887 for polyps $\geq 6$ mm	0.96 for polyps $\geq 10$ mm 0.796 for polyps $\geq 6$ mm	Segmental unblinding used; Sensitivity of optical colonoscopy before unblinding: 0.875 for polyps $\geq 10$ mm 0.915 for polyps $\geq 8$ mm 0.923 for polyps $\geq 6$ mm

Level of Evidence: 3

TA Criterion 2 is met

**TA Criterion 3:           The technology must improve net health outcomes.**

### **Potential Benefits**

A potential benefit of CTC is that it can detect small polyps, which can then be removed to prevent the development of CRC. Its accuracy approaches that of COL in detecting polyps  $\geq 10$  mm. In addition, the procedure complication rate is significantly less than that with optical COL<sup>22</sup>. Another potential benefit is that it is less invasive than other screening tests such as SIG or COL.

A third potential benefit is that it may be more acceptable to patients than more invasive screening tests such as SIG or COL. Studies about its acceptability have been mixed- in some studies, patients describe it as more acceptable, but in others they describe it as less acceptable than conventional COL<sup>13, 14</sup>. In the Pickhardt screening study, patients recalled greater discomfort with CTC than with optical COL, but this may have been related to receiving sedation with optical COL<sup>15</sup>. In this study, more patients found CTC more acceptable with respect to overall convenience, and slightly more (50% vs. 41%) would prefer CTC for future screening<sup>15</sup>. However, a limitation of acceptability is that many individuals with abnormalities found on CTC then must go on to COL so that the polyp can be removed.

### **Potential harms:**

**Radiation exposure:** There are potential long term harms from CT colonography-related radiation exposure. No studies have directly measured harms caused by low dose radiation exposure from CT. However, models have been used to estimate the lifetime risk for cancer related to radiation received. Total radiation exposure ranges from 1.6 to 24.4 mSv for dual positioning (prone and supine) with a median dose estimate of 8.8 mSv to 10.2 mSv per CT examination<sup>23, 24</sup>. It has been estimated that one individual per thousand could develop a solid cancer or leukemia with exposure to 10 mSv above background<sup>25</sup>.

**Procedure related harms:** Six cohort studies of CTC have reported on adverse effect of CTC and have found relatively few procedure related harms.<sup>15, 22, 26-29</sup> In two large studies of screening CTC, there were no perforations<sup>22, 27</sup>. In one study, one out of 2531 individuals who had CTC and COL was hospitalized for bacteremia.

Perforation rates are slightly higher among individuals undergoing diagnostic (vs. screening) CTC. Among 11,870 individuals undergoing screening and diagnostic CTC, one in the screening group and six in the diagnostic group had a perforation<sup>27</sup>.

**Identification of extra-colonic findings:** Because CTC obtains images of structures outside the colon, the potential implications of identifying these extra-colonic findings must be considered. Extra-colonic findings are quite common and occur in 27% to 69% of individuals undergoing CTC<sup>30</sup>. These extracolonic findings have been classified into varying levels of clinical significance. Those of “high “ clinical significance typically require surgical or medical treatment or intervention or further investigation, those of “moderate” clinical significance typically might require further investigation or future treatment but not immediate medical attention) and those of “low” clinical significance would not require further investigation or treatment. Extracolonic findings of high importance (e.g. solid organ mass or abdominal aortic aneurysm) occur in 4.5-11% of the population, those of moderate importance (renal calculi or small adrenal mass) occurred in up to 27% of individuals. Overall, approximately 7% to 16% of individuals undergoing CTC underwent additional evaluation for extracolonic findings, although very few of these abnormalities ultimately required definitive treatment. An important limitation of all of these studies is their relatively limited follow up, the longest being only two years.

Although it is possible that early detection of these abnormalities may lead to improved outcomes, it is also possible that there will be additional unnecessary medical testing of these abnormalities with associated anxiety.

In summary, there are several potential benefits of CTC. Including that it is less invasive, is associated with fewer procedure related complications and may be more acceptable to some people. However, there are also several potential harms, including radiation exposure, some procedure related harms and the

identification of extra-colonic findings, which require additional anxiety and additional testing, and may not prove to be of clinical importance. Although the accuracy of CTC approaches that of optical COL, and thus has potential benefit, it is not known whether the potential harms (radiation exposure, extracolonic findings and procedure related complications) are outweighed by the potential benefits or not. Assessing the impact of the potential harms would take a longer duration of study.

TA Criterion 3 is not met.

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

There are currently three major screening tests universally recommended as screening tests for CRC. These include stool tests (FOBT or fecal immunochemical tests), SIG and COL. Double contrast barium enema has been advocated, although it is rarely used as a screening test for CRC. The efficacy of FOBT has been established in clinical trials, that of SIG in case control studies. COL has never been studied as a screening test, but its efficacy has been assumed since it was an integral part of the FOBT trials. COL, although imperfect, is generally considered the gold standard for CRC screening, and studies of CTC compare its accuracy to COL.

With the results of the ACRIN trial, CTC has now been shown to have a diagnostic test accuracy almost as good as COL. Thus, it is probably almost as good as COL at identifying lesions  $\geq 10$  mm which could ultimately progress to cancer. Thus, with respect to its ability to identify worrisome lesions, it appears to be comparable to COL. However, controversy remains about the importance of detecting smaller lesions, many of which will not progress clinically.

Whether or not CTC is as “beneficial” as established alternatives depends not only on its diagnostic accuracy but on how its overall risks and benefits compare with those of the other screening tests. The potential risks of CTC include radiation exposure and the identification of extra-colonic findings, many of which require additional evaluation but are ultimately clinically insignificant. Since, if performed, CTC would be done repeatedly (the Multisociety Task force recommends five year intervals), which would lead to increases in cumulative radiation exposure and more opportunities to identify extracolonic findings. The



current length of follow up of CTC studies is not long enough to determine the impact of these potential risks.

Thus, currently, there is not evidence that CTC is as beneficial as any established alternatives.

TA Criterion 4 is not met.

**TA Criterion 5:           The improvement must be attainable outside of the investigational setting.**

Several features of the ACRIN study make it generalizable to the non-investigational setting. First, it was a multi-institutional study. Second, it included three methods of bowel preparation. Third, there were multiple radiologist interpreters and the trial evaluated inter-observer variability in CTC interpretation. In addition, in order to be sure that the COL experience reflected that seen in clinical practice, endoscopists did not receive any advanced training, beyond what they would require for usual credentialing. In particular, the techniques used in prior studies such as segmental unblinding, were not used to make the COL be more like usual practice. The radiologists in the trial did undergo extensive training. First, they had to either confirm that they had interpreted at least 500 CTCs and or participated in a 1.5 day training course. Second, they had to achieve at least a 90% detection rate for lesions  $\geq 10$  mm in a reference image set. Finally, of 20 radiologists who originally met the inclusion criteria, the 15 who achieved the top scores on the qualifying examination were invited to participate in the study.

In summary, the particular improvement seen in the ACRIN trial (improved diagnostic accuracy) is potentially attainable outside the investigational setting, with the caveat being that highly trained radiologists are available to interpret the CTC. However, although improved diagnostic accuracy can be seen outside the investigational setting, there are still the potential risks of radiation exposure and high rates of extra-colonic findings. Thus whether CTC leads to an *improvement* in health outcomes has not been shown outside the investigational setting.

Criterion 5 is not met.



## **CONCLUSION**

CTC is a non-invasive technology for CRC screening. The recent results of the ACRIN trial have shown that CTC has diagnostic accuracy comparable to that of optical COL and importantly that this level of diagnostic accuracy can be achieved in the “real world.” The ACRIN study was done in multiple institutions, using multiple bowel preparations and COL procedures in place at the participating institutions, thereby increasing its generalizability. However, the radiologists were highly trained in how to interpret CTC results. Despite the exciting results of the ACRIN trial, several important questions remain before it 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 extra-colonic 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.

## **RECOMMENDATION**

It is recommended that CTC *does not meet* CTAF TA criteria 3, 4 or 5 as a screening test for CRC in average risk individuals.

### **March 11, 2009**

Previous CTAF assessments of CTC were conducted in June 2004 and February 2003.

*The California Technology Assessment Forum panel voted to accept the recommendation as presented.*



## RECOMMENDATIONS OF OTHERS

### **Blue Cross Blue Shield Association (BCBSA)**

The BCBSA Technology Evaluation Center (TEC) reviewed this technology in 2008. To date, the full report has not been published.

### **Centers for Medicare and Medicaid Services (CMS)**

In a Proposed Decision Memo for Screening Computed Tomography Colonography (CTC) for Colorectal Cancer (CAG-00396N) dated February 11, 2009, CMS has concluded “the evidence is inadequate to conclude that CT colonography is an appropriate colorectal cancer screening test.....” This document is available at:

<https://www.cms.hhs.gov/mcd/viewdraftdecisionmemo.asp?from2=viewdraftdecisionmemo.asp&id=220&>

### **United States Preventive Services Task Force (USPSTF)**

The most current USPSTF Screening for Colorectal Cancer Recommendation Statement “concludes that the evidence is insufficient to assess the benefits and harms of computed tomographic colonography and fecal DNA testing as screening modalities for colorectal cancer”

<http://www.ahrq.gov/clinic/uspstf08/colocancer/colors.htm>

### **American Cancer Society, the US Multi-Society Task Force on Colorectal Cancer and the American College of Radiology**

These organizations published Screening and Surveillance for the Early Detection of Colorectal Cancer and Adenomatous Polyps, 2008: A Joint Guideline in 2008. The guideline is available at

<http://caonline.amcancersoc.org/cgi/content/full/CA.2007.0018v1>. A representative of the American Cancer Society provided testimony in support of the use of this technology.



### **California Radiological Society (CRS)**

A representative of the CRS provided testimony in support of this technology.

### **American Gastroenterological Association (AGA)**

An AGA representative attended the meeting and provided an opinion.

### **American Society of Gastrointestinal Endoscopists (ASGE)**

An ASGE representative provided an opinion in support of the recommendation.

### **ABBREVIATIONS USED IN THIS REVIEW**

CTC	Computed tomographic colonography
CRC	Colorectal cancer
FOBT	Fecal occult blood testing
SIG	Sigmoidoscopy
COL	Colonoscopy
DARE	Database of Abstracts of Reviews of Effects
RCTs	Randomized controlled trials
ACRIN	American College of Radiology Imaging Network
ACBE	Air contrast barium enema
ROC	Receiver operating characteristic

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